Document Number:		**c29377542-04**
EudraCT No.	2018-002344-81	
BI Trial No.	1381-0009	
BI Investigational Medicinal Product(s)	Ezabenlimab (BI 754091 [anti-PD-1]) BI 836880 (anti-VEGF/Ang2)	
Title	An open-label, Phase II trial evaluating the safety and efficacy of BI 836880 in combination with ezabenlimab in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy.	
Lay Title	Platform trial module evaluating safety and efficacy of BI 836880 in combination with ezabenlimab in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced/metastatic solid tumours.	
Clinical Phase	Phase II	
Clinical Trial Leader	[redacted] Phone: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted]	
Status	Final Revised Protocol (based on Global Amendment 3)	
Version and Date	**Version: 4.0**	**13 JUN 2023**

CLINICAL TRIAL PROTOCOL SYNOPSIS MODULE C (EZABENLIMAB + BI 836880)

Company name	Boehringer Ingelheim
Name of finished product :	N.A.
Name of active ingredient :	Ezabenlimab (BI 754091) and BI 836880
Protocol date	23 April 2020
Revision date	13 JUN 2023
BI trial number	1381-0009
Title of trial	An open-label, Phase II trial evaluating the safety and efficacy of BI 836880 in combination with ezabenlimab in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy.
Coordinating Investigator	[redacted] Phone: [redacted]
Trial site(s)	This multicentre trial will be conducted in North America and the United Kingdom.
Clinical phase	Phase II
Trial rationale	Refer to Master protocol.
Trial objective(s)	The main objective of this treatment-specific Module is to assess the antitumour response of ezabenlimab combined with BI 836880 in patients with advanced and/or metastatic solid tumours.
Trial endpoints	Refer to Master protocol.
Trial design	Open-label, multicentre, Phase II, Master design with treatment-specific Modules. Both Module C and the Master protocol must be followed. Where there are differences in stringency or cut-off values between the Master protocol and specific module, the specific module takes precedence.
Total number of patients randomised	Not applicable
Number of patients on each treatment	Approximately 150 patients are planned for Module C.

Diagnosis	Cohort 1 GEC: Patients with locally advanced, unresectable or metastatic gastric adenocarcinoma or gastro-oesophageal adenocarcinoma with ≥1 prior systemic treatment, excluding prior anti-PD-1 or anti-PD-L1 based treatment. Cohort 2: Patients with secondary resistance to anti-PD-1 or anti-PD-L1 based therapy: Any advanced or metastatic solid tumour (excluding non-squamous non-small cell lung cancer [NSCLC] and all melanoma) with previous anti-PD-1 or anti-PD-L1 based treatment which progressed after achieving benefit (at least stable disease [SD] with a minimum duration of benefit of 4 months and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 based treatment without experiencing disease progression during that period). Cohort 3: Patients with primary resistance to anti-PD-1 or anti-PD-L1 based therapy: Select advanced or metastatic solid tumour types with previous anti-PD-1 or anti-PD-L1 based treatment without achieving benefit (RECIST v1.1 SD <4 months or progressive disease in <4 months while on previous anti-PD-1 or anti PD-L1 based treatment). Cohort 4 CRC: Locally advanced, unresectable or metastatic second line or greater, microsatellite stable (MSS) colorectal cancer with no prior anti-PD-1 or anti-PD-L1 based treatment. Cohort 5 Endometrial: Patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and who have documented disease progression following one line of chemotherapy and are not candidates for curative surgery or radiation and have not been treated previously with anti-PD1 or anti-PDL1. Hormonal monotherapy does not count as a line of therapy. Patients may have received up to one additional line of chemotherapy if given in the neoadjuvant or adjuvant treatment setting. Patients who have just received one line of chemotherapy in the neoadjuvant or adjuvant treatment setting and progressed without subsequent treatment are also eligible.
Main in- and exclusion criteria	Abbreviated Inclusion Criteria 1. At least one measurable lesion according to RECIST v1.1 2. Patient must agree to pre- and on-treatment tumour biopsies. If archived tumour tissue is available from the last treatment failure, sections may be supplied instead of a pre-treatment biopsy.

	Abbreviated Exclusion Criteria 1. Any exclusion criteria listed in the Master protocol. 2. Unresolved, Grade >1 toxicity before the start of treatment with the study drug except for hair loss (alopecia) and hypothyroidism that requires thyroid hormone supplements but is asymptomatic under therapy. 3. Significant cardiovascular/cerebrovascular diseases (i.e. uncontrolled hypertension, unstable angina, history of infarction within past 6 months, congestive heart failure > New York Heart Association [NYHA] II). 4. Uncontrolled hypertension defined as: blood pressure in rested and relaxed condition ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic (with or without medication) measured in triplicate, taken 2-5 minutes apart and averaged. 5. History of severe haemorrhagic or thromboembolic event in the past 12 months (excluding central venous catheter thrombosis and peripheral deep vein thrombosis). 6. Known inherited predisposition to bleeding or to thrombosis in the opinion of the Investigator.
Test product(s)	Ezabenlimab will be co-administered with BI 836880.
dose(s)	Ezabenlimab: a fixed dose of 240 mg once every 3 weeks BI 836880: 720 mg once every 3 weeks
method and route of administration	Ezabenlimab: by intravenous infusion BI 836880: by intravenous infusion
Comparator product(s)	Not applicable.
dose	Not applicable.
method and route of administration	Not applicable.
Duration of treatment	Treatment may continue until progression of disease (PD), unacceptable toxicity, withdrawal of patient consent, or 53 cycles [approximately 3 years] from the start of first treatment administration, whichever occurs first. Patients will be allowed to stay on treatment in case of initial radiological PD, until progression is confirmed or 53 cycles from the start of first treatment administration if the Investigator considers that the treatment is beneficial for the patient
Statistical methods	Refer to Master Protocol

FLOW CHART MODULE C BI 1381-0009

			Trial Treatment Days[a,b] Cycle = 21 Days							Post-Treatment Days	
	Informed consent, tumour assessment, and screening with 28-day window	Screening with 14-day window[c]	Cycle 1				Cycles 2-4	Cycles 5-11	Cycles 12-53	End-of-Treatment (EOT) Visit	30-Day Safety Follow-up
Assessments (Days)	**-28 to -1**	**-14 to -1**	**1**	**2**	**8 (±1)**	**15 (±1)**	**1 (±2)**	**1 (±2)**	**1 (±2)**	**(within 7 days of EOT)**	**(+2)**
Informed Consent[b]	X										
Inclusion/Exclusion Criteria	X										
Medical History and Demographics[d]		X									
Physical Examination[c, d, e]		X	X			X	X	X	X	X	X
ECOG Performance Status[c, d, e]		X	X				X (C2, 3)	X (C5, 7, 9, 11)	X (C13, 15)	X	X
Vital Signs[c, d, k]		X	X	X	X	X	X	X	X	X	X
Triplicate BP and Pulse		X	X	X	X	X	X	X	X	X	X
12-Lead Digital Electrocardiogram[c, d, f]		X	X				X	X	X	X	(X)
Echocardiogram	X[m]		If clinically indicated							X	
Infectious Screening[l]	If clinically indicated										

			Trial Treatment Days[a,b] Cycle = 21 Days							Post-Treatment Days	
	Informed consent, tumour assessment, and screening with 28-day window	Screening with 14-day window[c]	Cycle 1				Cycles 2-4	Cycles 5-11	Cycles 12-53	End-of-Treatment (EOT) Visit	30-Day Safety Follow-up
Assessments (Days)	**-28 to -1**	**-14 to -1**	**1**	**2**	**8 (±1)**	**15 (±1)**	**1 (±2)**	**1 (±2)**	**1 (±2)**	**(within 7 days of EOT)**	**(+2)**
Haematology and Clinical Chemistry Labs[c, d]		X	X		X	X	X	X	X	X	X
Urinalysis[c, d]		X	X		X		X	X	X	X	
Pregnancy Test for Women of Child-Bearing Potential[c, d, g]		X	X				X	X	X	X	
Concomitant Medications[c]	X		X	X	X	X	X	X	X	X	X
Adverse Events[c]	X		X	X	X	X	X	X	X	X	X
SAEs/AESIs considered related to study drug(s) and cancer of new histology											
Tumour Assessments[c, d, h]	X		X	Can be performed according to institutional practices and SOC from the acknowledgement of the amendment							
Patient status											X
Ezabenlimab Infusion[i,j]			X				X	X	X		
BI 836880 Infusion[i,j]			X				X	X	X		

Flow Chart Footnotes:

a All cycles are 3 weeks (21 days) in duration. Days are calculated as calendar days. **The date of an assessment is considered Day 1 of the window.** Patients will continue treatment with the study drugs until disease progression (PD) by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and/or immune-related RECIST (iRECIST), withdrawal of patient consent, an unacceptable toxicity occurs, or 1 year of treatment is completed, whichever occurs first. Patients will be allowed to stay on treatment in the case of initial radiological PD, if the Investigator feels that it is in the patient's best interest. In addition, patients without PD may stay on trial beyond 1 year on a case-by-case basis after discussion with the Medical Monitor and the Sponsor. A new informed consent will be required if the patient remains on study with radiological PD. Day 1 of Cycle 1 is defined as the first day when the combination of BI 836880 and ezabenlimab is administered.

b Informed consent for Module C must be obtained ≤28 days prior to the initiation of treatment. **The date of the assessments is considered Day 1 of the window.**

c Screening assessments required in the Master protocol and the Module obtained ≤14 days prior to Cycle 1 Day 1 do not need to be repeated unless otherwise noted.

d Safety laboratory assessments including haematology, serum biochemistry, and urinalysis will be performed locally. The screening medical history and demographics, physical examination and Eastern Cooperative Oncology Group (ECOG) performance status, vital signs (BP to be conducted in triplicate, taken 2-5 minutes apart and averaged), haematology (including reticulocytes), clinical chemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, albumin, total protein, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin [indirect and direct], lactate dehydrogenase, serum glucose, troponin [only at screening, C1D1, C1D8, C1D15, C2D1, C3D1, C4D1 and anytime creatine phosphokinase (CPK) is elevated], haptoglobin, CPK [if CPK is elevated, then CPK-muscle/brain (CPK-MB), troponin, and myoglobin should be reactively tested], serum urea nitrogen [or urea], serum uric acid, and thyroid panel [thyroid stimulating hormone (TSH), free T4, and free T3]), urinalysis, and screening pregnancy test should be done ≤14 days prior to initiation of treatment. **The date of the assessments is considered Day 1 of the window.** Additionally, amylase and lipase should be analysed in case of symptoms of pancreatitis. If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of the ECOG performance status, an abbreviated physical examination, vital signs (pre- and post-infusion), and a single ECG required prior to first trial dose. Baseline programmed cell death ligand 1 (PD-L1) expression level, microsatellite instability, and tumour mutation burden information will be collected in the electronic case report form (eCRF), if locally available. Refer to the Master protocol for additional details. Vital signs are checked at every visit.

e Physical examinations will be done at screening, on Day 1 of each treatment cycle, at the end of treatment (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) on Cycle 1 Day 15. ECOG performance status will be done at screening, on Day 1 of Cycles 1 and 2, on Day 1 of every other cycle beginning with Cycle 3, at the EOT visit, and at the 30-day follow-up visit.

f Single digitalised ECGs must be done. Pre ECGs are to be done before blood work or other procedures after 5 minutes of rest at screening, on Day 1 of every cycle, at the EOT visit, and whenever the Investigator deems it necessary. 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 (see Master protocol).

g Women of child-bearing potential must have a serum beta human chorionic gonadotropin (β-HCG) pregnancy test at screening. Thereafter, this test can be done in either serum or urine on Day 1 of each cycle, and at the EOT visit. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. (see Master protocol).

h Tumour assessments should be done according to RECIST v1.1 and iRECIST, and should include computed tomography/positron emission tomography (CT/PET) 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/PET scan or magnetic resonance imaging [MRI]). Tumour assessments (scans) should be performed ≤28 days prior to initiation of treatment and copies may be collected by the Sponsor or designee. The same radiographic procedure must be used throughout the trial. Assessments will be performed by the Investigator at screening and afterwards can be performed according to institutional practices and standard of care (SOC) form the acknowledgement of this protocol forward every 2 cycles (6 weeks ±3 days) for the first 6 months of treatment, once every 3 cycles (9 weeks ±3 days) thereafter, at the EOT visit (if not performed within the previous 4 weeks), and at the discretion of the Investigator, and copies will be collected by the sponsor or designee.

i Dosing of BI 836880 and ezabenlimab is described in Module C Section 4.1.

j If the decision is made to permanently discontinue study treatments during a scheduled visit, both ezabenlimab and BI 836880 should be discontinued together and the EOT visit should be performed instead of the scheduled visit.

k See Appendix 10.7 for BP and HR management and see Appendix 10.6 for the BP monitoring and study drug administration guidelines. BP and HR should be measured before and after study drugs have been administered. BP and HR should be measured in triplicate, taken 2-5 minutes apart and averaged.

l Hepatitis B surface antigen (HBsAg; qualitative), hepatitis B core antibody (anti-HBc; qualitative), Hep B DNA, hepatitis C antibodies (Anti-HCV; qualitative), Hep C DNA, hepatitis D antibodies (Anti-HDV; qualitative), human immunodeficiency virus (HIV)-1 and HIV-2 antibody performed at the discretion of the Investigator where clinically indicated.

m Echocardiogram must be collected ≤28 days prior to the initiation of treatment.

n As of 01 June 2021, [redacted] samples are no longer collected.

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ABBREVIATIONS

[redacted]	[redacted]
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANG2	Angiopoietin-2
AUC	Area under the Curve
BHM	Bayesian Hierarchical Model
BI	Boehringer Ingelheim
C_{max}	Maximum Plasma Drug Concentration After a Single Dose
CRC	Colorectal Cancer
CRF	Case Report Form, paper or electronic
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DBP	Diastolic Blood Pressure
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
EudraCT	European Clinical Trials Database
FFPE	Formalin Fixed and Paraffin Embedded
GEC	Gastro-oesophageal Adenocarcinoma
IB	Investigator's Brochure
ICF	Informed Consent Form
IHC	Immunohistochemistry
irAE	Immune-Related Adverse Events
iRECIST	Immune-Related Response Evaluation Criteria in Solid Tumours
ISF	Investigator Site File
i.v.	Intravenous
[redacted]	[redacted]
LAG-3	Lymphocyte-Activation Gene 3
mAb	Monoclonal Antibody
MDSC	Myeloid-Derived Suppressor Cell

MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
MSS	Microsatellite Stable
NSCLC	Non-Small-Cell Lung Cancer
ORR	Overall Response Rate
p.o.	*per os* (Orally)
PD	Progression of disease
PD-1	Programmed Cell Death 1 (receptor)
PD-L1	Programmed Cell Death Ligand 1
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetics
[redacted]	[redacted]
qw	Every Week
q3w	Every 3 Weeks
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable Disease
SBP	Systolic Blood Pressure
SOC	Standard of Care
TNFα	Tumour Necrosis Factor-Alpha

[redacted]

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Refer to the Master protocol document to review the medical background information.

1.2 DRUG PROFILE

1.2.1 BI 836880

Angiogenesis is the formation of new blood vessels from pre-existing vasculature and is a key process in tumour growth. The Ang2/Tie2 and the vascular endothelial growth factor (VEGF)/VEGFR2 pathways have been identified as key pathways mediating tumour angiogenesis (R13-0448). Multiple studies have described increased VEGF levels in a variety of human cancers, and VEGF expression levels have been correlated with poor survival (R15-1720). The VEGF neutralising monoclonal antibody bevacizumab has demonstrated anti-tumour activity in clinical trials and is currently approved for several indications and settings, mainly in combination with standard chemotherapy regimens (R15-1222).

Studies in mice have shown that Ang2, a ligand of the Tie2 receptor, controls vascular remodelling by enabling the functions of other angiogenic factors, such as VEGF (R12-3593). Ang2 is primarily expressed by endothelial cells and strongly induced by hypoxia and other angiogenic factors, and has been demonstrated to regulate tumour vessel plasticity, allowing vessels to respond to VEGF and fibroblast growth factor 2 (FGF2) (R12-3834).

VEGF-A induces accumulation of myeloid-derived suppressor cells (MDSCs), immature dendritic cells, Tregs and tumour-associated macrophages. MDSCs are able to control activation of T-cell and natural killer (NK) cells. Anti-VEGF treatment significantly enhances dendritic cell maturation (R17-4036, R17-4037), and decreases T-regs either by inhibiting the accumulation of MDSCs and immature dendritic cells in the tumour environment or directly through VEGF/VEGFR pathway inhibition of Tregs (R17-4038, R17-4039).

The Nanobody® technology was originally developed following the discovery that camelidae (camels and llamas) possess fully functional antibodies that lack light chains. These heavy chain antibodies contain a single variable domain (VHH) and two constant domains (CH3). The cloned and isolated VHH domain is a stable polypeptide harbouring the full antigen-binding capacity of the original heavy-chain antibody. These newly discovered VHH domains form the basis of a new generation of therapeutic antibodies named Nanobodies (R15-1719).

BI 836880 is a genetic fusion protein of one VEGF-A-binding antibody (VHH) and one Ang2-binding single domain antibody (Nanobody®). The two single domain antibody moieties are linked via a human serum albumin-binding Alb11 domain, serving as half-life extension, and glycine-serine linkers between the domains. The protein has a molecular mass of 40.7 kDa.

BI 836880 is highly selective for VEGF-A and Ang2, as the molecule did not bind to the related growth factors VEGF-B, -C, -D, placental growth factor (PlGF), and angiopoietin 1

(Ang1). BI 836880 is highly potent and showed *in vivo* monotherapy efficacy (tumour growth inhibition) in several tumour xenografts representing colon cancer (CXF 243), non-small-cell lung cancer (NSCLC; LXFE 211, LXFE 1422), mammary cancer (MAXF 401), ovarian cancer (OVXF 1353), pancreatic cancer (PAXF 546), and renal cell cancer (RXF 1220).

A 13-week repeat dose administration of BI 836880 was performed in cynomolgus monkeys. BI 836880 was well tolerated up to the highest dose of 60 mg/kg. No mortality was attributed directly to BI 836880 administration. BI 836880 did not demonstrate any effects on neurological, renal, or cardiovascular functions including electrocardiograms (ECGs). In a monkey presenting the immunogenic reaction, membrano-proliferative glomerulopathy in the kidney was observed. This finding was considered a secondary response to immune complex deposition in the glomeruli and not directly related to BI 836880 administration.

At the time of data cut off for the last IB version (17 Aug 2021), 421 patients had been treated with BI 836880 in 5 clinical trials, either as a monotherapy (n = 62) or in a combination therapy (n = 359). The combination therapy trials evaluate BI 836880 in combination with ezabenlimab, an anti-PD-1 monoclonal antibody, administered every 3 weeks (1336-0011, 1336-0012 Part 2, 1381-0009 Module C). Of the 359 patients exposed to combination therapy so far, 347 patients have been treated with the recommended Phase II dose (RP2D).

The most frequent adverse events (AEs) in patients treated with BI 836880 monotherapy were hypertension (54.8%), asthenia (48.4%), vomiting (29.0%), nausea (27.4%), diarrhoea (25.8%), and constipation (25.8%). One patient (1.6%) was reported with an AE requiring dose reduction and 13 patients (21.0%) with AEs leading to treatment discontinuation. There were 43.5% of patients with on-treatment SAEs; hypertension and pleural effusion (3 patients [4.8%] each) were the only SAEs reported for more than 2 patients.

After evaluating all available PK, PD, efficacy, and safety data, the dose of 720 mg BI 836880 every 3 weeks (q3w) was determined as a RP2D. The most common AEs reported for this dosing regimen were hypertension (73.9%), asthenia (43.5%), vomiting (34.8%), and nausea (39.1%). Hypertension (34.8%) was also the most frequently reported Grade 3 event. Two patients (8.7%) were reported with a Grade 4 AE; these AEs were neutropenia and dyspnoea. One patient in this dose group was reported with fatal AEs resulting from disease progression: metastases to liver and hepatic failure.

Data pooled from the combination trials showed that 326 patients (90.8%) treated so far have been reported with at least 1 AE. The most common individual AE (by preferred term) has been hypertension (20.3%), followed by asthenia (17.5%), diarrhoea (17.3%), nausea (16.7%), fatigue (15.3%), decreased appetite (12.8%), peripheral oedema (12.3%), and vomiting (10.3%). Six patients (1.7%) have been reported with AEs requiring dose changes; 25 patients (7.0%) had an AE leading to treatment discontinuation. Hypertension (8.4%) has been the most frequently reported Grade 3 event. Adverse events of Grade 4 have been reported for 13 patients (3.6%); each Grade 4 AE has been reported for a single patient. There have been 22 patients (6.1%) with AEs resulting in death; sepsis and general physical health deterioration (3 patients each, 0.8%) as well as respiratory failure (2 patients, 0.6%) have been the only fatal AEs reported for more than 1 patient. Adverse events under the SMQ haemorrhages occurred in 28 patients (7.8%), with 4 patients (1.1%) presenting AEs of

Grade 3 and 3 patients (0.8%) presenting a Grade 5 AE. There have been 59 patients (16.4%) reported with immune-related AEs according to investigators judgement; 7 patients (1.9%) had Grade 3 AEs and 6 patients (1.7%) had Grade 4 AEs.

The pharmacokinetics, pharmacodynamics and immunogenicity of BI 836880 were investigated based on data from the monotherapy Phase I studies. Maximum plasma concentrations were reached shortly after the end of infusion. BI 836880 plasma concentration remained around the maximum for up to 8 h and started to decline afterwards slowly. Cmax and AUC increased in a dose-proportional manner over the entire dose range. As expected for a nanobody, the clearance was low, resulting in a terminal half-life of ~275 h (~11 days). The volume of distribution was also low and in the range of the average blood volume. An accumulation ratio of 1.11 to 1.54 was observed, showing slight accumulation of BI 836880 after multiple dosing. A PopPK/PD model showed that the preliminary results of the combination of BI 836880 and ezabenlimab are consistent with PK results from the BI 836880 monotherapy studies.

Free Ang2 and free VEGF-A plasma concentrations were measured as target engagement biomarkers. Free VEGF-A and free Ang2 were already depleted at the first post-dose sampling point (8 h) and remained depleted over entire Cycle 1 and also over all subsequent cycles. The depletion was independent of the dose administrated for free VEGF-A, and it was observed for doses ≥360 mg for free Ang2.

Pre-existing anti-drug antibodies (ADAs) were detected in approximately half of patients, and an additional 33.3% of the patients developed ADAs during treatment. There was no dose dependency observed in the development of treatment-induced BI 836880 ADAs. The PK was not influenced by the development of ADAs.

After evaluating all available PK, PD, efficacy, and safety data, a dose of 720 mg BI 836880 every 3 weeks in combination with 240 mg ezabenlimab was determined as the recommended Phase II dose (RP2D), and this was endorsed by the Safety Monitoring Committee.

The Residual Effect Period (REP) is the period after the last administration of study drug with measurable drug levels and/or pharmacodynamics effects still likely to be present. The REP of BI 836880 and ezabenlimab is up to 30 days.

For a more detailed description of the BI 836880 profile please refer to the current Investigator's Brochures (IBs) (c02353883-09).

1.2.2 Ezabenlimab (BI 754091)

Ezabenlimab is a mouse derived; monoclonal IgG4Pro antibody (mAb) targeted to the human programmed cell death 1 (PD-1) immune checkpoint inhibitor. Ezabenlimab is extensively humanized and potently blocks PD-1/PD-L1 and PD-1/PD-L2 interactions *in vitro*. The mAb is devoid of Complement Dependent Cytotoxicity (CDC) and Antibody-Dependent Cell-mediated Cytotoxicity (ADCC) activities.

At the time of data cut off for the last IB version (01 Nov 2021), 117 patients with advanced/metastatic solid tumours have been treated with single agent ezabenlimab, 111 of these patients were treated with the 240 mg q3w recommended phase II dose (RP2D). Additionally, 881 patients have been treated with the RP2D of ezabenlimab in combination with other agents. Three hundred and ninety four patients treated in combination with BI 754111 (anti-LAG-3 mAb), 381 patients were treated in combination with BI 836880 (VEGF/Ang-2 inhibitor), 37 patients were treated in combination with BI 891065 (SMAC mimetic) and 11 patients were treated in combination with BI 754111 and BI 907828 (MDM2-p53 antagonist).Six patients were treated with the combination of ezabenlimab and BI 907828 (MDM2 inhibitor), 5 patients were treated with the combination of ezabenlimab and BI 1387446 (STING agonist), 20 patients were treated with the combination of ezabenlimab plus BI 765063 (SIRPαantagonist), and 27 patients were treated with the combination of ezabenlimab plus BI 3018078 (anti-tumour vaccine).

The currently available ezabenlimab clinical data demonstrate that it is well tolerated. The most common AEs reported in patients treated with ezabenlimab monotherapy were fatigue (39.3%), nausea (29.9%) and decreased appetite (21.4%). There were no Grade 5 or treatment related Grade 4 events reported in patients treated with ezabenlimab monotherapy. Immune-related AEs (irAEs) were reported in 32 patients (27.4%) on ezabenlimab monotherapy, the vast majority were Grade 1 and 2. There were no Grade 4 or Grade 5 irAEs and no infusion related reaction of any grade reported in patients treated with ezabenlimab monotherapy.

Preliminary efficacy analysis shows overall objective response rate in 111 patients receiving 240 mg ezabenlimab monotherapy to be 16.2% (15 patients with confirmed partial response [PR] and 3 patients with complete responses [CR]) (95% CI 9.4, 23.2). All 3 patients with CRs and 8 of the 15 patients with PR were still on treatment at the time of last data cut-off. Tumour responses were seen in diverse cancer types.

The available PK data show that ezabenlimab has a (at least) bi-phasic distribution. The volume of distribution ranged between 4.63 L and 5.88 L. The systemic clearance of ezabenlimab ranged between 0.00971 L/h (80mg dose) and 0.0119 L/h (400mg dose) (i.e. approx. 0.0237 - 0.0286 L/day) resulting in gMean half-life estimates of 13.8 to 17.8 days. Volume of distribution ranged from 4.63L to 5.88 L. The small total volume of distribution is consistent with a limited extravascular disposition as expected for a therapeutic antibody.

For a more detailed description of the ezabenlimab profile please refer to the current Investigator's Brochures (IBs) (c07895879-06) and the Master protocol.

[redacted]

research efforts are now focusing on achieving clinical benefit using a combination therapy approach.

It is well established that pro-angiogenic factors (e.g., VEGF-A) have an immunosuppressive effect in the tumour microenvironment. Preclinical data showed modulation of immunosuppressive cells by an anti-VEGF treatment and enhancement of the antitumour effect of the combination of VEGF and PD-1 inhibition. Furthermore, internal Boehringer Ingelheim (BI) preclinical data showed an additive effect of angiopoietin inhibition to the dual VEGF and PD-1 inhibition (BI 836880 IB).

This scientific rationale and preclinical data support a combination trial of the triple inhibition of VEGF, Ang-2 and PD-1 inhibition. This trial will evaluate the tolerability of the combination of BI 836880 and ezabenlimab and the effect of triple inhibition in patients with advanced solid tumours including CRC and GEC. This will allow a decision on further development of this combination in these patients and the start of a dedicated Phase II program. The therapeutic benefit or specific AEs in patients cannot always be anticipated during the trial setup. Later on, there may be new scientific knowledge about biomarkers and other factors contributing to diseases or the action of a drug. In order to be able to address future scientific questions, patients will be asked to voluntarily donate bio-specimens for banking. If the patient agrees, banked samples may be used for future drug development.

As of January 2022, a total of 134 patients have been treated in this ongoing Phase II trial. Clinical activity was observed across all cohorts.

DECISION TO TERMINATE THE TRIAL

Although a preliminary assessment of the available data from the ongoing clinical program for the ezabenlimab + BI 836880 combination exhibit signs of antitumour activity and a manageable safety profile for an overall positive benefit risk ratio, careful review of the full data set performed in the context of the current standards of care for the indications under study has led to the decision taken by the sponsor in December 2021 to discontinue recruitment in study 1381-0009, and terminate further expansion of the study.

An important consideration in the review process was whether the investigational combination treatment under study, namely BI 836880 plus ezabenlimab, had demonstrated benefit that delivered clear improvement over the current standards of care, some of which had evolved over the course of the study. The measure used to evaluate efficacy was the Objective Response Rate (ORR) which was the primary efficacy endpoint of the trial. It is important to note that at the time of this evaluation all cohorts had completed planned enrolment, and sufficient data had been collected to support a well-informed decision. Based on this evaluation, the efficacy observed in the different indications did not show clear improvement over the standards of care relative to published efficacy results in the different indications, with the one possible promising result in the 2L Endometrial carcinoma cohort. Given the evolution of the standard of care for 2L Endometrial carcinoma to combination treatment with immune checkpoint inhibitor plus an tyrosine kinase inhibitor (KEYNOTE-775), it was determined that this setting does no more present an opportunity for further development moving forward. Based on this evaluation, the decision was taken to terminate the trial.

As a part of this decision, for patients still under active treatment, treatment with BI 836880 plus ezabenlimab may continue until disease progression, undue toxicity, withdrawal of patient consent, or 53 cycles [approximately 3 years] from the start of first treatment administration, whichever occurs first (see Section 4.2.8, 'Treatment duration' for full details).

1.4 BENEFIT - RISK ASSESSMENT

Both BI 836880 and ezabenlimab are currently being tested in early phase clinical trials.

As of 17 Aug 2021, 62 patients with solid tumours had been treated with BI 836880 monotherapy in 3 Phase I clinical trials testing either an every-3-week schedule (1336-0001, 1336-0012 Part 1) or a weekly schedule (1336-0006).

Overall, dose-limiting toxicities (DLTs) were reported for 6 patients: there was 1 patient with a DLT in Trial 1336-0001 and 5 patients with DLTs in Trial 1336-0006. Based on the safety profile and PK/PD data of these 2 trials, q3w dosing was chosen to be taken forward for the monotherapy and combination trials. The dose of 720 mg q3w was determined as the recommended Phase II dose (RP2D) for monotherapy and was later confirmed for the combination therapy with ezabenlimab.

Additional 359 patients with solid tumours received BI 836880 in combination with a checkpoint inhibitor ezabenlimab in Part 2 of a Phase I trial (1336-0012), in a Phase Ib trial (1336-0011), and in a Phase II trial (1381-0009, Module C); 347 of these patients have been treated at the recommended Phase II dose (RP2D) for the combination therapy.

After completing a dose escalation phase and determination of RP2D, ezabenlimab is currently used in an expansion phase evaluating the preliminary efficacy of the compound in several tumour types including NSCLC. Three doses of ezabenlimab (80, 240 and 400 mg) were tested in the dose escalation part of the phase I trial in 9 patients with solid tumours. No dose-limiting toxicities (DLTs) or drug-related serious AEs (SAEs) were observed during the maximum tolerated dose (MTD) evaluation period at any dose level. The most common reported AEs were nausea, fatigue, decreased appetite, constipation and arthralgia. Based on this dose escalation data, the dose of 240 mg is recommended for further development in monotherapy or as a starting dose in combination trials.

The combination of an immune checkpoint inhibitor with a [redacted] blocker has previously been tested in a phase I trial combining atezolizumab with bevacizumab in patients with renal cell carcinoma. This combination was well tolerated with most AEs reported as mild or moderate in severity. The only Grade 3-4 reported event was hypertension. Other reported AEs included check-point inhibitor related events such as fatigue, chills, diarrhoea, rash and pruritus and other AEs related to [redacted] blockade (fatigue, hypertension, and epistaxis).

Based on the mode of action of ezabenlimab and BI 836880, published and internal preclinical data and available clinical data, it is expected that the combination will increase

the anti- tumour efficacy resulting in an increase in response rate with prolonged duration of response as compared to each monotherapy.

Despite the positive safety profile reported for both drugs, patients should be advised of the potential risk of side effects from these investigational drugs. Furthermore, patients with uncontrolled hypertension or history of severe haemorrhage or thromboembolism are not allowed to participate to this study. Other side effects may be rare and unknown with irreversible and/or life-threatening effects.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety (see also Section 5.2.2, adverse events of special interest [AESIs]).

A Safety Review Committee will be responsible for the continuous assessment of the trial data to ensure the overall safety of the patients treated. They will also provide the Investigators and the Sponsor with advice about the conduct of the trial and the integrity of the data.

In summary, considering the unmet medical need for new treatment option in patients with advanced or metastatic cancer, the anti-tumour activity of a [redacted] blockade or PD-1 inhibition, the safety profiles of BI 836880 and ezabenlimab monotherapy, and the existing data suggesting that a combination of PD-1 blockade with [redacted] blockade is a promising therapeutic strategy, the benefit-risk assessment for patients enrolled into this trial is considered to be favourable.

Even so, patients should be advised of the potential risks of side effects from investigational trial treatments (e.g., relatlimab and nivolumab reports of a few cases of myocarditis). While some may be anticipated, others may be rare and unknown with irreversible and/or life-threatening effects. Patients should also be advised that there are other unknown risks associated with participation in a clinical trial.

1.4.1 COVID-19 Related Risks

To date, there is no evidence suggesting a link between susceptibility to COVID-19 infections and the inhibition of VEGF-A and Ang2 targeted by BI 836880. Also, there is no evidence suggesting a link between susceptibility to COVID-19 infections and the inhibition of PD-1/PDL-1 by ezabenlimab. Available non-clinical and clinical data from completed clinical trials have not shown an increased risk of infections with BI 836880 and ezabenlimab.

Considering the limited and sparse data on immune activation and the role of inflammation as well as other underlying factors that may increase the severity and mortality from COVID-19 infection, there may be some factors representing the risk for using inhibitors of VEGF/Ang2 or PD1 that are currently still unknown. The information about the risk factors, the severity and the activity of immune response in patients with COVID-19 infections will be constantly monitored as it evolves.

2. TRIAL OBJECTIVES AND ENDPOINTS

Refer to the Master protocol for a complete list of objectives and endpoints for the trial.

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this treatment-specific Module is to assess the antitumour response of ezabenlimab combined with BI 836880 in patients with advanced and/or metastatic solid tumours.

2.1.2 Primary endpoint

Refer to the Master protocol document for the primary endpoint.

2.1.3 Secondary endpoints

Refer to the Master protocol document for a list of the secondary endpoints.

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase II, open-label, non-randomised, multicentre trial of BI 836880 administered in combination with ezabenlimab to patients in one of five cohorts shown below.

- Cohort 1 GEC: Patients with locally advanced, unresectable or metastatic gastric adenocarcinoma or gastro-oesophageal adenocarcinoma with ≥1 prior systemic treatment, who have failed standard treatment, for whom no further therapy of proven efficacy exists, and with no prior anti-PD-1 or anti-PD-L1 based treatment.
- Cohort 2: Patients with secondary resistance to anti-PD-1 or anti-PD-L1 based therapy: Any advanced or metastatic solid tumour (excluding NSCLC and all melanoma) with previous anti-PD-1 or anti-PD-L1 based treatment which progressed after achieving benefit (at least stable disease [SD] with a minimum duration of benefit of 4 months and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 based treatment without experiencing disease progression during that period.

- Cohort 3: Patients with primary resistance to anti-PD-1 or anti-PD-L1 based therapy: Select advanced or metastatic solid tumour types with previous anti-PD-1 or anti-PD-L1 based treatment without achieving benefit (RECIST v1.1 SD <4 months or progressive disease in <4 months while on previous anti-PD-1 or anti PD-L1 based treatment).
- Cohort 4 CRC: Locally advanced, unresectable or metastatic second line or greater, microsatellite stable (MSS) colorectal cancer with no prior anti-PD-1 or anti-PD-L1 based treatment.
- Cohort 5 Endometrial: Patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and who have documented disease progression following one line of chemotherapy and are not candidates for curative surgery or radiation and have not been treated previously with anti-PD1 or anti-PDL1. Hormonal monotherapy does not count as a line of therapy. Patients may have received up to one additional line of chemotherapy if given in the neoadjuvant or adjuvant treatment setting. Patients who have just received one line of chemotherapy in the neoadjuvant or adjuvant treatment setting and progressed without subsequent treatment are also eligible.

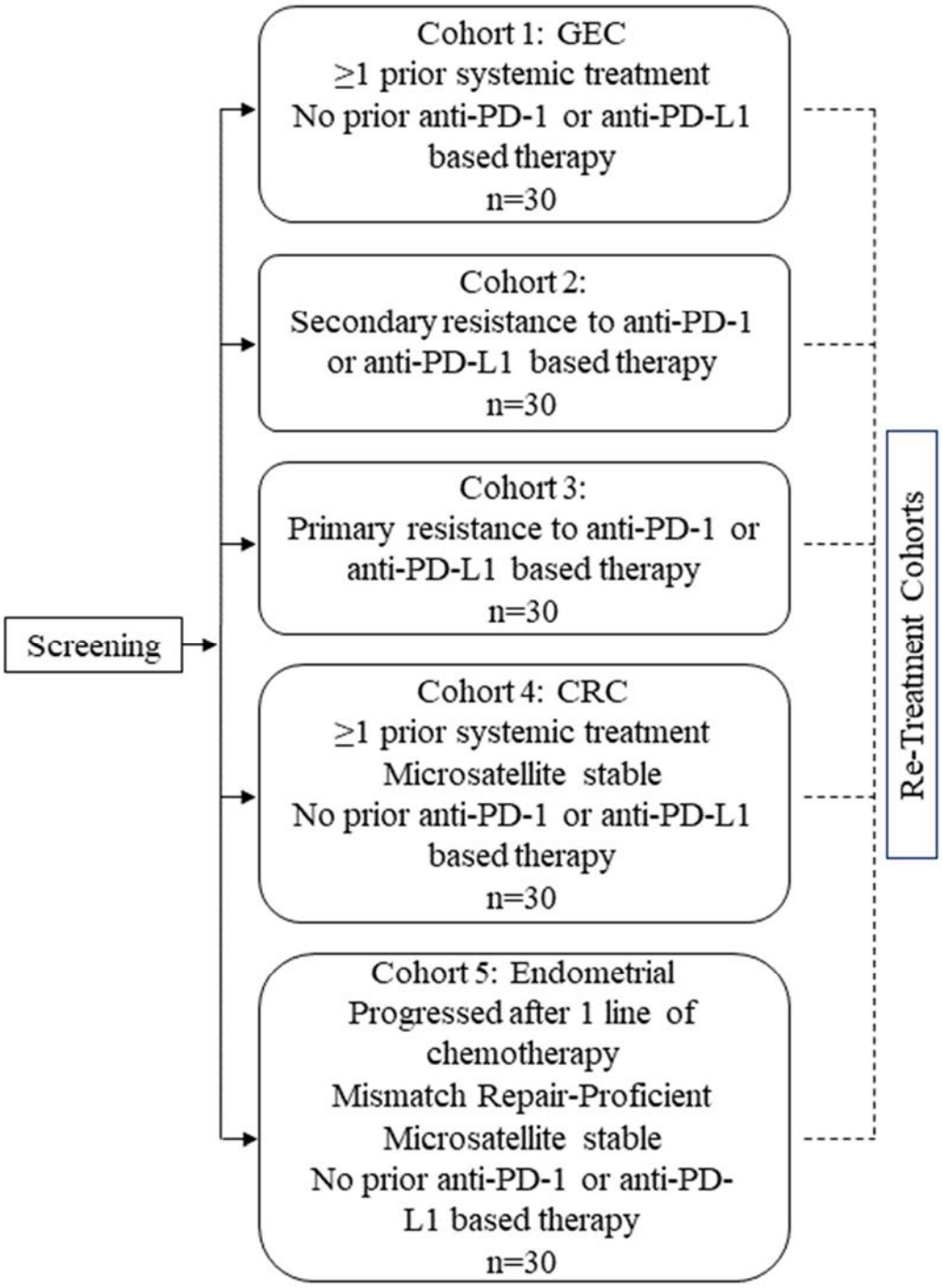


Figure 3.1: 1 Study schema

Patients in this Module of the clinical trial will receive ezabenlimab and BI 836880 by i.v. infusion after signing the Master and Module informed consent forms (ICFs) and completing the screening processes. Treatment cycles will be 3 weeks (21 days). Safety laboratory assessments will be performed locally according to the Flow Chart (see Module C flow chart). Both Module C and the Master protocol must be followed. Where there are differences

in stringency or cut-off values between the Master protocol and specific module, the specific module takes precedence.

Tumour assessments will be performed using RECIST v1.1 and/or Immune RECIST (iRECIST) at screening and afterwards can be performed according to institutional practices and SOC after acknowledgement of this protocol amendment using the same radiographic procedure.

Patients will continue study treatment until disease progression (PD) according to RECIST v1.1 or iRECIST, withdrawal of patient consent, an unacceptable toxicity occurs, or 53 cycles [approximately 3 years] from the start of first treatment administration, whichever occurs first. Patients will be allowed to stay on treatment in the case of initial radiological PD, until progression is confirmed or up to 53 cycles from the start of the first treatment duration if the Investigator considers that it is in the patient's best interest (see Section 4.2.8, "Treatment duration" for full details).

A new informed consent will be required if the patient remains on study with radiological PD.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

Not applicable.

3.3 SELECTION OF TRIAL POPULATION

Screening of patients for this Module of the trial is competitive, i.e. screening for this Module of the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this Module of the trial.

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

If a patient is enrolled in error (e.g., 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

Please refer to Section 8.3.1 (Source Documents) in the Master protocol for the documentation requirements pertaining to the inclusion and exclusion criteria. Patients must have one of the tumour types described in item number 2, Section 3.3.2.

3.3.2 Inclusion criteria

For inclusion in the Module, patients must fulfil all of the following criteria in addition to the inclusion criteria described in the Master protocol.

1. Patient must have completed the screening process according to the Master protocol. Provision of signed and dated written ICF prior to any trial-specific procedures, sampling, or analyses (Master ICF and Module ICF).
2. Histologically confirmed diagnosis of one of the following cohorts:
    - Cohort 1 GEC: Locally advanced, unresectable or metastatic gastric adenocarcinoma or GEC.
        - Must have had no prior anti-PD-1/PD-L1 based therapy
        - Patients who have failed standard treatment or for whom no further therapy of proven efficacy exists
        - Patients must have been treated with at least one prior systemic treatment
    - Cohort 2: Patients with secondary resistance to anti-PD-1 or anti-PD-L1 based therapy: Any advanced or metastatic solid tumour (excluding NSCLC and all melanoma) with previously anti-PD-1 or anti-PD-L1 based treatment which progressed after achieving benefit.
        - Must have had ≥1 line of prior systemic anticancer treatment; only one prior anti-PD-1/PD-L1 based therapy with the exception of BI PD-1 investigational agent allowed. Prior anti-PD-1 or anti-PD-L1 secondary resistance is defined as a minimum duration of benefit (i.e., at RECIST v1.1 SD) of 4 months and minimum treatment duration of 2 months on the previous anti-PD-1 or anti-PD-L1 based treatment without experiencing disease progression during that period.
    - Cohort 3: Patients with primary resistance to anti-PD-1 or anti-PD-L1 based therapy: Select advanced or metastatic solid tumour types with previous anti-PD-1/PD-L1 based treated tumour without achieving benefit.
        - Must have had ≥1 line of prior systemic anticancer treatment; only 1 prior anti-PD-1/PD-L1 based therapy with the exception of BI PD-1 investigational agent allowed.
        - Anti-PD-1 or anti-PD-L1 with primary resistance is defined as RECIST v1.1 stable disease (SD) less than 4 months or progressive disease in less than 4 months while on previous anti-PD-1 or anti-PD-L1 based treatment.
        - Included tumour types:
            - Previously treated CRC
            - Merkel cell carcinoma
            - Squamous cell skin carcinoma
            - Other squamous cancers: head and neck, cervical, anal, penile, oesophageal and vulvar
            - Other gastrointestinal (GI) cancers: biliary tract, gastric, oesophageal, GIST
            - Other thoracic cancers: small cell lung cancer (SCLC), mesothelioma
            - Urothelial cancers, renal cell carcinoma
            - Neuroendocrine tumours, soft-tissue sarcomas, thyroid cancer
            - Gynaecological tumours: Ovarian, endometrial and cervical
            - Other tumour types for which no therapy of proven efficacy exists, or which are not amenable to standard therapies and where anti-PD-1/PD-L1 therapy may be considered in exceptional cases upon discussion with the Medical Monitor.

- Cohort 4 CRC: Locally advanced, unresectable or metastatic second line or greater, microsatellite stable (MSS) colorectal cancer.
  - Must have had no prior anti-PD-1/PD-L1 based therapy
  - Recurrence within 6 months after completion of adjuvant therapy is considered as a line in the metastatic setting
  - Must have microsatellite stable disease (identified using any validated test)

- Cohort 5 Advanced Endometrial cancer: Endometrial carcinoma that is pMMR (Mismatch Repair-Proficient)/MSS and is advanced, recurrent, or persistent and has relapsed or is refractory to curative therapy.
  - Documented disease progression following one line of chemotherapy and may have received up to one additional line of chemotherapy if given in the neoadjuvant or adjuvant treatment setting. Hormonal monotherapy does not count as a line of therapy.
  - Must have not been treated previously with anti-PD1 or anti-PDL1
  - Patients who have just received one line of chemotherapy in the neoadjuvant or adjuvant treatment setting and progressed without subsequent treatment are also eligible.
  - Must have microsatellite stable disease (identified using any validated test)

3. All patients must have at least one measurable lesion according to RECIST v1.1. Tumour lesions that have been irradiated at least ≥4 weeks before the start of treatment, and have subsequently had documented progression, may be chosen as target lesions only in the absence of measurable lesions that have not been irradiated.
4. Patient must agree to pre- and on-treatment tumour biopsies. If archived tumour tissue is available from the last treatment failure, sections may be supplied instead of a pre-treatment biopsy.

3.3.3 Exclusion criteria

Patients must not enter the trial if any of the following exclusion criteria are fulfilled:

1. Any exclusion criteria listed in the Master protocol.
2. Unresolved, Grade >1 toxicity before the start of treatment with the study drug except for hair loss (alopecia) and hypothyroidism that requires thyroid hormone supplements but is asymptomatic under therapy.
3. Significant cardiovascular/cerebrovascular diseases (i.e. uncontrolled hypertension, unstable angina, history of infarction within past 6 months, congestive heart failure > New York Heart Association [NYHA] II):
   - Uncontrolled hypertension is defined as: blood pressure in rested and relaxed condition ≥ 140 mmHg, systolic or ≥ 90 mmHg diastolic (with or without medication), measured in triplicate, taken 2-5 minutes apart and averaged according to Appendix 10.7.
   - Patients with personal or family history of QT prolongation and/or long QT syndrome, or prolonged QTcF at baseline (> 470 ms).
   - LVEF < 50%
4. History of severe haemorrhagic or thromboembolic event in the past 12 months (excluding central venous catheter thrombosis and peripheral deep vein thrombosis).

5. Known inherited predisposition to bleeding or to thrombosis, in the opinion of the investigator.
6. Patients who require full-dose anticoagulation (according to local guidelines). Only LMWH and ASA at doses for prevention/prophylaxis are allowed.
7. Prior anti-angiogenic therapy (with the exception of CRC Cohort [Cohort 4]).
8. Known hypersensitivity to the trial drugs or their excipients or risk of allergic of anaphylactic reaction to drug product according to Investigator judgement (e.g. patient with history of anaphylactic reaction or autoimmune disease that is not controlled by nonsteroidal anti-inflammatory drugs [NSAIDs], inhaled corticosteroids, or the equivalent of ≤ 10 mg/day prednisone).

3.3.3.1 Withdrawal of patients from treatment or assessments

Refer to the Master protocol for withdrawal of patients from treatment or assessments guidance.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

4.1.1.1 BI 836880

Details of the drug product, BI 836880, are presented in Table 4.1.1.1: 1. Additional details are presented in the BI 836880 IB and the Module C Pharmacy Manual.

Table 4.1.1.1: 1 BI 836880

Substance:	BI 836880
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg/mL (vials with 10 mL)
Posology	Infusion on Day 1 of each 3-week cycle
Route of administration:	i.v. infusion
Duration of use:	Until progression, unacceptable toxicity, or up to a maximum of 53 cycles

4.1.1.2 Ezabenlimab

Details of the drug product ezabenlimab are presented in Table 4.1.1.2: 1 and Table 4.1.1.2: 2. Additional details are presented in the ezabenlimab IB and the Module C Pharmacy Manual.

Table 4.1.1.2: 1 Ezabenlimab – CMC 1

Substance:	Ezabenlimab (BI 754091)
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	20 mg/mL (vial with 15 mL filling volume)
Posology:	Infusion on Day 1 of each 3-week cycle
Route of administration:	i.v. infusion
Duration of use:	Until progression, unacceptable toxicity, or up to a maximum of 53 cycles

Table 4.1.1.2: 2 Ezabenlimab – CMC 2

Substance:	Ezabenlimab (BI 754091)
Pharmaceutical formulation:	Concentrate for solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	20 mg/mL (vial with 12 mL filling volume)
Posology:	Infusion on Day 1 of each 3-week cycle
Route of administration:	i.v. infusion
Duration of use:	Until progression, unacceptable toxicity, or up to a maximum of 53 cycles

4.2 SELECTION OF DOSES IN THE TRIAL

Ezabenlimab and BI 836880 will be diluted and administered separately via i.v. infusion once every three weeks according to the details in the Module C ‘Instructions for Pharmacist’ Manual.

4.2.1 BI 836880

The selected dose of BI 836880 to be used in combination with ezabenlimab 240 mg is 720 mg administered via i.v. infusion once every 3 weeks. This dose of BI 836880 in combination with the selected dose of ezabenlimab 240 mg was selected based on the dose escalation data obtained in the ongoing trial 1336-0011 (refer to the BI 836880 Investigator’s Brochure [IB]).

4.2.2 Ezabenlimab

The selected dose of ezabenlimab to be used in combination with other agents is 240 mg every 3 weeks. This dose was selected by using the most recent clinical information from the ongoing trial BI 1381.1, administering ezabenlimab monotherapy to patients with advanced solid tumours. PK data were collected and clinical response was observed during the conduct of trial BI 1381.1, providing a basis to investigate a combination approach (Ezabenlimab Investigator Brochure).

4.2.3 Method of assigning patients to treatment groups

After assessment of all inclusion and exclusion criteria, each eligible patient will be assigned to the applicable open cohort. Site personnel will enter the medication number in the case report form (CRF).

4.2.4 Blinding and procedures for unblinding

Not applicable in this open-label trial.

4.2.5 Packaging, labelling, and re-supply

Refer to the Master protocol for this information.

4.2.6 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.

4.2.7 Drug accountability

Refer to the Master protocol for this information.

4.2.8 Dose administration and modifications

The two study drugs will be prepared and handled according to the ‘Instruction for Pharmacists’ Manual which will be filed in the ISF. Upon notification that a patient entered the study; the pharmacy will prepare the study drug in the assigned dosage for administration to the patient.

Ezabenlimab and BI 836880 will be given every 3 weeks as 2 separate, consecutive intra-venous infusions by authorized site staff in a specialized unit where emergency care can be provided (e.g., intensive care unit available, medical personnel trained in advanced life support) according to ‘Instruction for Pharmacists’. The planned infusion time is 60 minutes (+/- 10 minutes) for ezabenlimab and 60 minutes (+/- 10 minutes) for BI 836880; Ezabenlimab will be administered first, then 15 minutes (+/- 10 min) after the end of the ezabenlimab infusion, BI 836880 will be administered. Infusion of BI 836880 should not be prolonged to more than 6 hours. Appropriate drugs and medical equipment to treat

anaphylactic reactions must be immediately available and study personnel must be trained to recognize and treat anaphylaxis.

In the event of an infusion-related reaction ≤ Grade 2, treat the symptoms accordingly with antihistamine or corticosteroids if needed. Steroids, if used to manage an infusion-related reaction, are to be limited to prednisone 10 mg qd or equivalent. The infusion rate of study drug(s) 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, study drug(s) will be permanently discontinued (refer to the safety section in the Master protocol) and adequate therapy should be initiated to treat the AE.

Infusion rate and premedication for further treatment cycles should be adapted according to Investigator decision, but adaption of administration scheme needs to be agreed with by the Sponsor.

Premedication:
No premedication will be required for BI 836880 or ezabenlimab infusions. If a patient expresses signs of infusion reaction at any BI 836880 treatment, premedication will be considered for all subsequent treatment infusions (dosage and schedule according Investigator's decision), comparable to the following scheme:

- Acetaminophen/Paracetamol 650-1000 mg by mouth (p.o.), or equivalent
- Antihistamine p.o. or i.v., equivalent to diphenhydramine 50 mg i.v.

Pre-treatment should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect.

Drug re-administration criteria during Cycle 1
Before initiating a new treatment cycle the health status of the patient will be assessed according to the Module C flow chart. To continue treatment with further cycles, all of the following criteria must be met:

1. Pre-infusion SBP (measured in triplicate, taken 2-5 minutes apart, and averaged) should be < 140 mmHg and pre-infusion DBP should be < 90 mmHg; study drug administration of both study drugs should be temporarily delayed until BP < 140/90 mmHg. Please see Table 10.7:1 in Appendix 10.7, which describes the guidelines for BP management and study drug administration.
2. QT interval corrected per Fridericia's formula (QTcF) ≤470 ms
3. Echocardiography if clinically indicated (based on Investigator's judgment) with Left Ventricular Ejection Fraction (LVEF) ≥ 50%

Acceptable tolerability (in case of an adverse event at the planned start of a treatment cycle patients may continue therapy only after recovery to a level which would allow further therapy in the opinion of investigator).

Drug re-administration criteria after the first cycle has been completed

Before initiating a new treatment cycle the health status of the patient will be assessed according to the Module C flow chart. To continue treatment with further cycles, all of the following criteria must be met:

1. Pre-infusion SBP (measured in triplicate, taken 2-5 minutes apart and averaged) should be < 160 mmHg and pre-infusion DBP should be < 100 mmHg; study drug administration of both study drugs should be temporarily delayed until BP < 160/100. Please see Table 10.7:1 in Appendix 10.7, which describes the guidelines for BP management and study drug administration.
2. QT interval corrected per Fridericia's formula (QTcF) ≤470 ms Echocardiography if clinically indicated
3. Echocardiography if clinically indicated (based on investigators judgment) with Left Ventricular Ejection Fraction (LVEF) ≥ 50%
4. Acceptable tolerability (in case of an adverse event at the planned start of a treatment cycle patients may continue therapy only after recovery to a level which would allow further therapy in the opinion of investigator).

In case the above mentioned criteria 2, 3, and 4 are not fulfilled the patient should be re-evaluated as needed. Any case of a delay in treatment cycle should be communicated to the Medical Monitor. The investigator in agreement with the Medical Monitor and Sponsor will decide about further treatment of individual patient, based on known risk/benefit of BI 836880 and ezabenlimab.

Dose reduction guidelines

Dose escalations of BI 836880 or ezabenlimab in any patient is not allowed.
Dose reductions are not allowed for ezabenlimab in any patient.
Dose reductions are allowed only for BI 836880.

Dose reduction recommendations for BI 836880:

BI 836880 received dose	BI 836880 reduced dose
720 mg	480 mg

A dose reduction of BI 836880 from 720 mg to 480 mg is allowed, if investigator can attribute the AE unequivocally to the BI 836880 (for e.g., hypertension). If the reduced dose is still intolerable, the dose may be delayed (please see below the sub-section "Delay of treatment"). If the reduced dose is tolerable, and where deemed in the best interest of the patient, the investigator should re-escalate to the originally assigned dose of 720 mg of BI 836880 as soon as deemed clinically appropriate.

Delay of treatment:

During combination therapy, if treatment is held or discontinued, both BI 836880 and ezabenlimab will be held or discontinued together. If treatment is to be restarted, preferably both BI 836880 and ezabenlimab must be started together.

In some cases, in discussions with the Sponsor, treatment with one of the two investigational drugs can be allowed if there is an AE reported which can be clearly attributed to one of the

two drugs and further warrants a temporary discontinuation of this drug in the interest of the patient.

Treatment duration:
Treatment with BI 836880 plus ezabenlimab may continue until disease progression, undue toxicity, withdrawal of patient consent, or 53 cycles [approximately 3 years] from the start of first treatment administration, whichever occurs first. Patients will be allowed to stay on treatment also in the case of initial radiological PD, until progression is confirmed or up to 53 cycles from the start of first treatment administration if the investigator considers that the treatment is beneficial for the patient.

Investigators may consider discontinuing BI 836880 and continue therapy with ezabenlimab for up to 53 cycles from the start of the first treatment administration if the patient has been on therapy ≥ 6 months, has achieved at least SD by RECIST 1.1 and can tolerate the therapy, and if the investigator considers this to be in the best interest of the patient.

For any patient still on treatment with the investigational combination of BI 836880 plus ezabenlimab for 53 cycles from the start of the first treatment administration, treatment extension will be considered on a case-by-case basis upon request by the investigator for a maximum additional 6 cycles, to complete no later than 30 April 2025, if the investigator considers this to be in the best interest of the patient. After this date treatment with the investigational combination BI 836880 plus ezabenlimab will no longer be available.

Investigators are requested to prepare for discontinuation of patients from the current investigational treatment of BI 836880 plus ezabenlimab and to switch them to alternative available treatment options outside of the current protocol no later than by the final availability date of 30 April 2025.

4.3 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.3.1 Other treatments and emergency procedures

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

4.3.2 Restrictions

4.3.2.1 Restrictions regarding concomitant treatment

Concomitant therapy, with reasons for the treatment, must be recorded in the electronic case report form (eCRF) during the screening and treatment periods, starting at the date of signature of ICF and ending at the 30-day follow-up visit. After the 30-day follow up, only concomitant therapy indicated for treatment of a related AE has to be reported. If a new anti-cancer treatment is started, it will be documented in the eCRF, on a separate page of follow-up therapy, different from the concomitant therapies pages.

4.3.2.2 Permitted concomitant medications

- If medically feasible, patients taking regular medication should be maintained on it throughout the trial.
- To reduce the risk of infusion related reactions, patients may be pre-treated with an antihistamine and acetaminophen or paracetamol. Pre-treatment should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect.
- Supportive care and other medications that are considered necessary for the patient's well-being may be given at the discretion of the Investigator. This includes medications for the management of nausea, diarrhoea, and vomiting for which the patient must be treated according to institutional standards.
- Blood or cell packet transfusions are allowed at any time after the start of the trial, except to meet inclusion criteria. There must be at least 4 weeks between a patient's last transfusion and their screening laboratory assessment. Exceptions to this will be considered by the Sponsor on a case-by-case basis.
- Patients already receiving erythropoietin at the time of screening for the trial may continue it, provided they have been receiving it for more than one month at the time trial treatment is started. Prophylactic erythropoietin should not be started during the 4 weeks before the start of treatment and during the first 3 weeks of any cohort, but may be started thereafter.

4.3.2.3 Restricted concomitant medications

- Previous anti-cancer therapy must have been discontinued before first administration of trial drug and the patient must have recovered from all clinically relevant reversible toxicities.

- Concomitant anti-cancer therapy is not allowed.

- Full-dose anticoagulation (according to local guidelines) is not allowed during the trial conduct; only low-molecular-weight heparin (LMWH) or ASA at prevention/prophylaxis doses are allowed.

- Any concomitant medication known to prolong the QT interval is not allowed.

- The following caveats apply for 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 (TNFα) blockers are prohibited. Use of immunosuppressive medications for the management of investigational product-related AEs (except irAEs from prior anti-PD-1/anti-PD-L1 therapy) or in patients with contrast allergies is acceptable, and does not necessarily warrant immediate treatment discontinuation. In addition, use of inhaled, topical, or 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 Medical Monitor.
    - For the treatment of [redacted] release syndrome (CRS), supportive therapy including steroids and/or interleukin 6 receptor (IL6R) antagonists (R15-0031) may be used as clinically indicated.

- Other restrictions on concomitant medications are:
    - Live attenuated vaccines are prohibited during the trial through 30 days after the last dose of investigational product.
    - Herbal preparations/medications are not allowed throughout the trial 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.
    - Granulocyte colony stimulating factors should not be used prophylactically during the first 3 weeks of treatment. Thereafter, prophylactic colony stimulating factors may be used according to institutional standards.
    - Palliative radiotherapy is not allowed during the first cycle for any lesion. Palliative radiotherapy is allowed only for non-target lesions, following discussion with the Medical Monitor, 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 assessment of the non-target lesions and the overall assessment. Unless in emergency situations, the Medical Monitor should be contacted prior to the administration of palliative radiotherapy in the expansion phase.

4.3.2.4 Restrictions on diet and life style

No restrictions.

4.3.2.5 Contraception requirements

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

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    - oral
    - intravaginal
    - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral

  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
  - provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
- Sexual abstinence
  - defined as refraining from heterosexual intercourse during the entire period (stated above) of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

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

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

4.4 TREATMENT COMPLIANCE

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

4.4.1 Ezabenlimab

Refer to the Master protocol Section 4.3.

4.4.2 BI 836880

BI 836880 will be administered by i.v. infusion at the sites by the investigator and/or trained site personnel, and dosing will be recorded in the eCRF. Therefore, actual dosing is expected to precisely follow the prescribed drug regimen. Missed or interrupted doses will be recorded in the eCRF with the associated reasons. The methods of collecting dosing information assure that total exposure can be calculated programmatically taken into account any missing doses.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

To review the section on assessing efficacy according to RECIST v1.1 (R09-0262) and iRECIST (R17-0923) refer to the Master protocol.

As of the decision of Boehringer Ingelheim in December 2021 no additional patients will be included to this trial. From the acknowledgement of this amendment forward tumour assessment can be performed according to institutional practices and SOC; and not required to follow master protocol specified schedule.

5.2 ASSESSMENT OF SAFETY

The safety of ezabenlimab and BI 836880 will be assessed by a descriptive analysis of incidence and severity of AEs graded according to CTCAE (version 5.0), laboratory data, and results of physical examinations. Safety will be assessed in a descriptive way without confirmatory analysis.

Refer to the Master protocol for descriptions of the safety assessments (physical examination, laboratory parameters, and ECGs).

For Module C, on days of study drug administrations, blood pressure (in triplicate, taken 2-5 minutes apart and averaged) and heart rate will be evaluated at two time points:

1. Pre-dose (-60 min. to -5 min.), before infusion of ezabenlimab; the results should be assessed using the BP management and study drug administration guidelines in Appendix 10.7.
2. 5 to 10 minutes after infusion of BI 836880.

In case of an infusion-related reaction, the Investigator should decide whether to intensify or prolong monitoring of vital signs of the patient.

Frequency of blood pressure measurements at each time point
Systolic and diastolic blood pressure as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after 5 minutes of rest in the seated position.

In addition to the laboratory safety samples described in the Master protocol, indirect and direct bilirubin, haptoglobin, and reticulocytes will be measured.

Screening for infections will also be conducted. HIV-1 and HIV-2 antibody (qualitative, as per applicable local regulations, at the discretion of the Investigator where clinically indicated). Hepatitis B serology (HBsAg, anti-HBc qualitative) and Hepatitis C serology (anti-HCV qualitative) for screening active Hepatitis B and Hepatitis C.

5.2.1 Other safety parameters

Not applicable.

5.2.2 Adverse events of special interest (AESI)

Adverse events of special interest are listed within Section 5.2.6.1.3 of the Master protocol and in addition for Module C, the event described below in Section 5.2.2.1.

5.2.2.1 Persistent Hypertension Unresponsive to Treatment

A hypertensive episode will be considered an AESI if:

- Systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg which persists longer than 2 days despite either initiation of antihypertensive agent(s) in a patient without prior history of hypertension, or intensification/addition of new antihypertensive agents in a patient with prior history of hypertension.

5.2.3 All other AEs

Refer to the Master protocol for assessment of AEs.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

As of the decision of Boehringer Ingelheim in December 2021 no additional blood samples for pharmacokinetics will be collected.

Blood for PK analysis of ezabenlimab and BI 836880 will be collected at the visits specified in the Module C flow chart and in Appendix 10.4.

Pre-dose plasma concentrations shortly before the start of infusion and plasma concentrations after end of infusion of ezabenlimab and BI 836880, will be evaluated descriptively according to BI internal Standard Operating Procedure (SOP) (001-MCS-36-472_RD-01 [2.0] and Venn Life Sciences SOP 'SOP-1.PKA.03 Non-compartmental PK/PD Analysis').

Sampling in the study will be limited to sparse sampling to primarily support an exploratory model based analysis. The plasma concentrations observed in study 1381-0009 will be pooled with data from other studies for a pooled model based analysis. The model based analysis will be planned and documented separately according to internal and external guidelines and BI SOP.

5.3.2 Methods of sample collection

Blood samples should not be obtained from the arm used for infusion. In case a central venous access is used for infusion, the blood samples can be collected from either forearm or central line. The actual sampling date and time (24-hour time clock) for each sample has to be recorded accurately.

For quantification of analyte plasma concentrations, blood will be drawn for both ezabenlimab and BI 836880 at the time points specified in the PK time schedule in Appendix 10.4.

Samples may be used for further methodological investigations (e.g., stability testing). 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 [redacted] or biomarkers for PK if

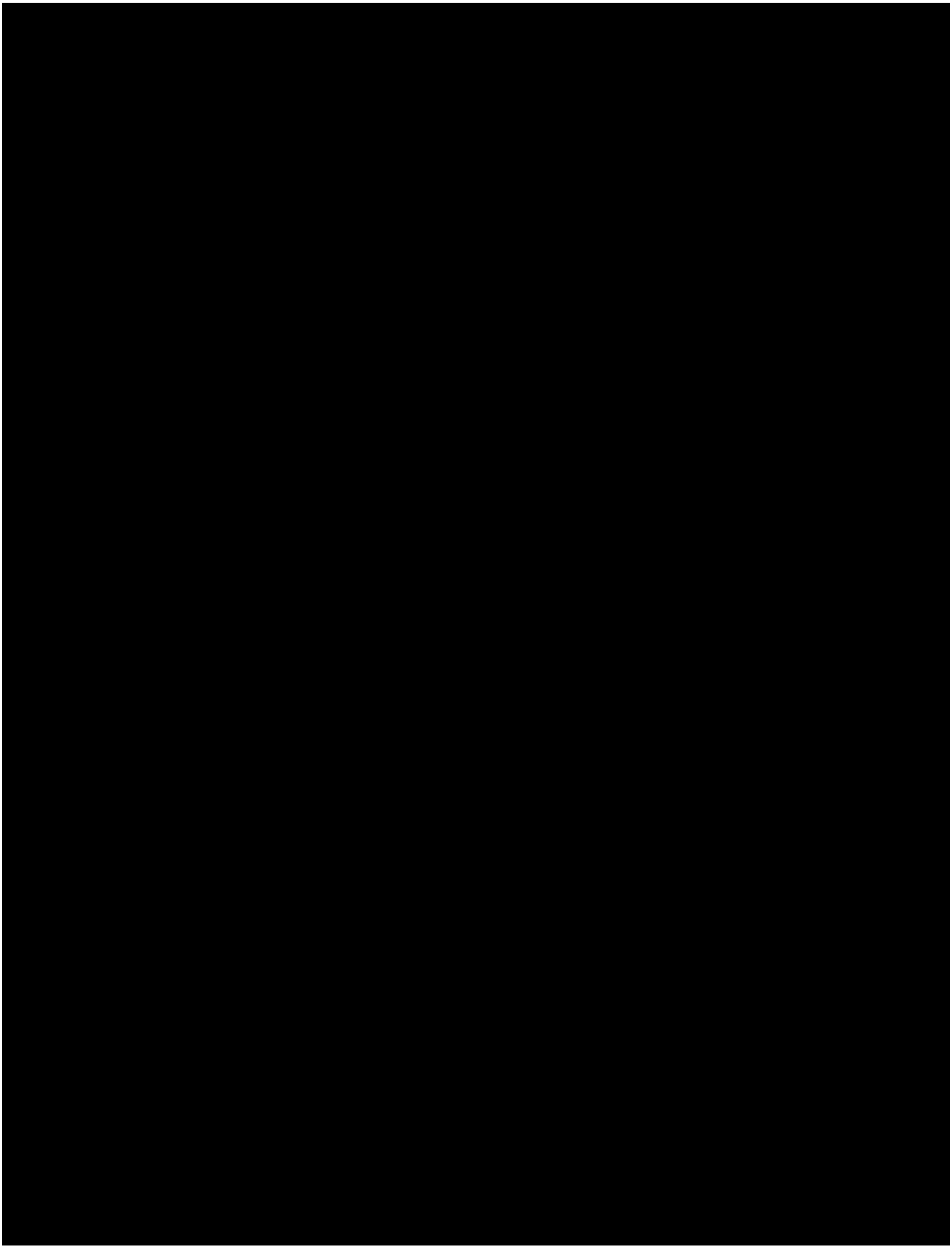
sample volume allowed). The trial samples will be discarded after completion of the additional investigations.

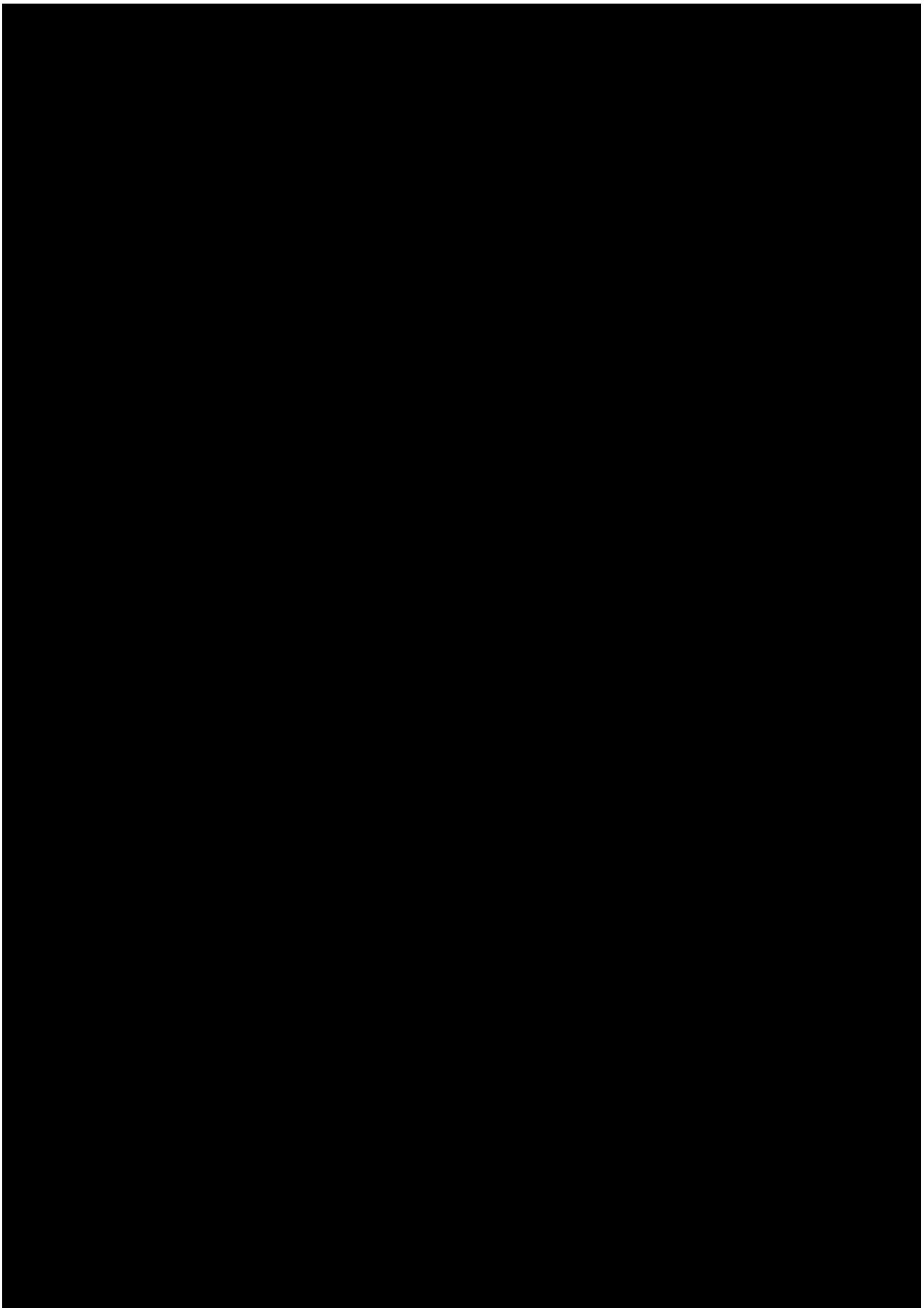
Details on sample collection for BI 836880 and ezabenlimab characteristics, processing, handling, and shipment are provided in the Module C Laboratory Manual.

If only 1 of the 2 drugs has been administered at the time of the PK sample collection, it should be noted. See the laboratory manual for further instructions.

5.3.4 Pharmacokinetic – pharmacodynamic relationship

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





[redacted]

5.5 BIOBANKING

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

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 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, including an audit trail for clinical data and samples to identify and destroy such samples according to the ICF, is in place.
- A fit-for-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 consent.

The leftovers of biopsied samples as specified in Module C Section 5.4.2.3 may be banked.

[redacted]

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients meeting the inclusion and exclusion criteria for the Master and Module C and who have signed a written ICF (Master and Module C) are eligible for participation in this Module. Patients will visit the clinical site at the time points specified in the flow chart (see Module C flow chart). 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.

Once the decision is made for any reason for a patient to stop the treatment with the combination of BI 836880 plus ezabenlimab, an EOT visit must occur as soon as possible (preferably within 7 days). After the EOT visit, the patient must undergo a follow-up evaluation 30 (+2) days after the last administration of study therapy.

The trial will be conducted according to the principles of good clinical practice (GCP).

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The procedures required at each trial visit in both portions of the trial are presented in the flow chart of this protocol (Module C flow chart). The key procedures required include:

- Reporting of all AEs occurring from signing the ICF onwards until 30 days or the end of residual effect period (REP).
- Baseline and on-treatment blood biomarker and immunogenicity assessments.
- Tumour assessments (based on CT/positron emission tomography [PET] and/or magnetic resonance imaging [MRI] scans) according to RECIST v1.1 and iRECIST will be performed according to institutional practices and SOC from the acknowledgement of this protocol amendment forward.

6.2.1 Screening period

The screening period may occur over a period of 28 days (period within the trial and before the first intake of BI 836880 and ezabenlimab). For the detailed description of the tests to be performed during this period and their timing, please refer to the appropriate flow chart.

6.2.2 Treatment period

Please refer to the Module C flow chart for a detailed presentation of each visit during the treatment period.

6.2.3 Follow-up period and trial completion

6.2.3.1 End-of-treatment visit

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

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

The intent is to complete the EOT as soon as the decision is to remove the patient from treatment. The decision can occur at a scheduled visit, or in between visits. If it happens on a scheduled visit, the site is to complete the EOT visit assessments for that day. If it happens in between visits, they should have patient return within 7 days of last dose (if possible) and complete EOT instead of what that next scheduled visits would have been.

6.2.3.2 30-day post-treatment safety visit

The safety follow-up visit is performed 30 (+2) days after the decision to discontinue the trial medication. The information collected at this visit must include all new AEs that occurred after the EOT visit, and a follow-up of AEs ongoing at EOT.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

Refer to the Master protocol for the description of a Bayesian hierarchical model (BHM) approach, which effectively uses the information from different patients' cohorts in the assessment of the efficacy.

Prior distribution
A non-informative normal distribution with mean 0 and standard deviation of 2 is specified for the mean μ. For the inter-cohort heterogeneity parameter τ, a half normal distribution with parameter 1 is used which is a very conservative assumption regarding between-cohort variability and hence leads to only little borrowing of data across patient cohorts because there is little prior information on the strength of the correlation between the treatment effects across cohorts

7.2 NULL AND ALTERNATIVE HYPOTHESES

This is an exploratory trial. No formal hypothesis testing is planned in this trial.

7.3 PLANNED ANALYSES

7.3.1 Primary endpoint analyses

Refer to the Master protocol.

7.3.2 Secondary endpoint analyses

Refer to the Master protocol.

[redacted]

7.3.4 Safety analyses

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

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards.

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

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

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

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

7.3.5 Pharmacokinetic and pharmacodynamic analyses

Please refer to Section 5.3.1.

7.4 INTERIM ANALYSES

Refer to the Master protocol.

An interim futility analysis will be performed for each cohort in the Module, if applicable. Until any decision from the futility analysis is made, the enrolment of further patients will not be stopped. The two-stage design is planned to stop further recruitment of patients if the defined efficacy boundary (see Table 7.7: 1) is not met at the first stage.

The interim analyses will be conducted when:

- After the 15th patient in each cohort has completed the third on-treatment imaging assessment (i.e. end of cycle 6).

If the 15th patient in any cohort discontinues earlier than the third on-treatment imaging, the interim futility analysis will be triggered at approximately 4 months after the first administration of that patient.

If the cohort completes the recruitment when the time point for interim analyses reaches, the futility analyses will not be performed.

In addition, interim analyses may be performed as each cohort is finished. Subsequent upon the decision of Boehringer Ingelheim in December 2021 that no additional patients will be included in this trial, no interim analyses will be performed.

7.5 HANDLING OF MISSING DATA

Refer to the Master protocol.

7.6 RANDOMISATION

For general aspects please refer to the Master protocol.

7.7 DETERMINATION OF SAMPLE SIZE

For cohort 1, around 10% ORR with anti-PD-1 antibody monotherapy is assumed. In KEYNOTE-059 (R17-3847) which is a phase II trial with pembrolizumab in patients with advanced gastric or esophagogastric junction adenocarcinoma, the ORR in cohort 1 (pembrolizumab monotherapy in previously treated patients) was 11.2% [95%CI, 7.6-15.7] (N=259).

For cohorts 2, 3, and 4, no literature is available for the target patients. As there are no treatments of proven efficacy for this population, ORR is assumed to be around 5% (cohort 2) and 0% (cohorts 3 and 4) respectively with anti-PD-1 antibody monotherapy.

For cohort 5, it is assumed that the ORR with standard of care is around 10%. In a phase II study of oxaliplatin as second-line chemotherapy in endometrial carcinoma (R20-0809), the ORR was 13.5% (N=52). In a phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer (R20-0810), the ORR was 9.5% [95%CI, 2.7-22.6] (N = 42). In a phase II study evaluating docetaxel in the treatment of recurrent or persistent endometrial carcinoma (R20-0811), the ORR was 7.7% (N=26). In a phase II study of topotecan in patients with advanced, persistent, or recurrent endometrial carcinoma (R20-0812), the ORR was 9% (N=22).
The futility boundary and early stopping probability for each cohort is described in Table 7.7: 1.

About 30 patients each will be included in each cohort. Different homogeneous scenarios and heterogeneous scenarios as well as different sample sizes are considered in the simulations to assess the frequentist operating characteristics of the BHM approach. The simulation results as shown in Table 7.7: 2 below show that, with the proposed cohort size, the BHM approach has reasonable probability of reaching the pre-specified response rate under a wide range of scenarios.

Table 7.7: 1 Early stopping probabilities at interim based on observed ORR under different scenarios

Scenario (ORR (%) in each patient cohort)	Early stopping criterion (observed ORR (%)	Early stopping probability
(30, 25, 15, 20, 30)	(<15, <10, <5, <5, <15)	12%,9%,9%,3%,14%
(20, 15, 7.5, 10, 20)		42%,32%,33%,20%,38%
(10, 5, 0, 0, 10)		82%,86%,100%,100%,78%
(10, 25, 15, 0, 10)		82%,10%,10%,100%,82%
(30, 25, 0, 20, 30)		11%,7%,100%,4%,12%
(30, 5, 0, 5, 30)		12%,83%,100%,48%,14%
(10, 5, 15, 0, 10)		82%,82%,8%,100%,81%

Table 7.7: 2 Operating characteristics of the Bayesian Hierarchical Modelling approach for final analysis under different scenarios after continuing at the interim

Sample Size	Scenario (ORR (%) in each patient cohort)	Probability of shrinkage estimator of the ORR(%) ≥ (25, 20, 10,15,25) in at least one cohort at final	Probability of shrinkage estimator of the ORR(%) ≥ (25, 20, 10, 15,25) in each cohort at final	Probability of shrinkage estimator of the ORR(%) ≥ (30, 25, 15, 20,30) in at least one cohort at final	Probability of shrinkage estimator of the ORR(%) ≥ (30, 25, 15, 20,30) in each cohort at final
(30, 30, 30, 30,30)	(30, 25, 15, 20, 30)	99%	82%,85%,90%,92%,79%	80%	52%,50%,51%,51%,51%
	(20, 15, 7.5, 10, 20)	39%	11%, 13%, 24%, 13%,12%	7%	2%,2%,1%,1%,1%,3%
	(10, 5, 0, 0, 10)	0%	0%,0%,0%,0%,0%,0%	0%	0%,0%,0%,0%,0%
	(10, 25, 15, 0, 10)	77%	1%,56%,63%,0%,1%	41%	0%,27%,25%,0%,0%
	(30, 25, 0, 20, 30)	97%	76%,80%,0%,88%,77%	72%	45%,46%,0%,44%,47%
	(30, 5, 0, 5, 30)	75%	57%,0%,0%,4%,59%	49%	30%,0%,0%,0%,34%
	(10, 5, 15, 0, 10)	49%	0%,0%,49%,0%,0%	19%	0%,0%,19%,0%,0%

Number of simulations = 1000

Therefore, a total sample size of approximately 150 patients is expected.

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

Refer to Section 8 in the Master protocol for this information.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

Refer to the Master protocol.

8.2 DATA QUALITY ASSURANCE

Refer to the Master protocol.

8.3 RECORDS

Refer to the Master protocol.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

Refer to the Master protocol.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Refer to the Master protocol.

8.6 TRIAL MILESTONES

Refer to the Master protocol.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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9.2 UNPUBLISHED REFERENCES

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10. APPENDICES

10.1 IMMUNE-RELATED ADVERSE EVENTS OF SPECIAL INTEREST

Refer to the Master protocol Appendix 10.1.

10.2 MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

Refer to the Master protocol Appendix 10.2.

10.3 PHARMACOKINETIC METHODS AND ANALYSES

Not applicable.

10.4 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

10.4.1 Schedules for PK, [redacted] and [redacted] blood sampling

According to Section 4.2.8 of the protocol, the infusion time may be adapted for BI 836880. PKs are timed from the start of ezabenlimab infusion. In this case, the PK sampling referring to the 'end' time of the infusion should be performed shortly after the end of infusion including flushing of the tubes, no matter the duration of the infusion. The subsequently requested PK sampling should be drawn as planned. Do not adapt the time because of the variation of the duration of the infusion schema.

Table 10.4.1:1 Time schedule for PK, [redacted] and [redacted] blood sampling in Cycle 1

Day	Time Point [hh:min]/ event	CRF Time /PTM	PK[a] BI 836880	PK[a] Ezabenlimab	[redacted] Ezabenlimab and [redacted] BI 836880	[redacted]	[redacted] and [redacted]	[redacted]	[redacted]
1	Just before drug infusion	-0:05	X	X	X	X	X	X	X
	Ezabenlimab infusion	0:00							
	BI 836880 infusion	1:15							
	After end of BI 836880 infusion	2:15	X	X					
2	24:00	24:00	X	X		X	X		
8		168:00	X			X	X	X	
15		336:00	X	X	X	X	X	X	

[redacted] BI = Boehringer Ingelheim; CRF = Case Report Form; PTM = planned time; MDSC = myeloid-derived suppressor cells; [redacted]

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

- Predose samples (PTM -0:05): within 1 hour before ezabenlimab infusion
- On Day 1 (PTM 2:15): After end of BI 836880 infusion
- On Day 2 (PTM 24:00): within ±2 hours of designated time
- On Day 8 and 15 (PTM 168:00 and 336:00): within ±24 hours of designated time

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

b As of 01 June 2021, [redacted] samples are no longer collected.

From December 2021 on, no further blood samples should be obtained for central lab shipments.

Table 10.4.1: 2 Time schedule for PK, [redacted] and [redacted] blood sampling from Cycle 2 onwards

Cycle	Day	Time Point [hh:min]/ event	CRF Time /PTM	PK[a] BI 836880	PK[a] Ezabenlimab	[redacted] Ezabenlimab and [redacted] BI 836880	[redacted]	[redacted] and [redacted]	[redacted]	[redacted]
2, 4, 8	1	Before start of infusion	-0:05	X	X	X (C4 & C8)	X (only cycle 2 and 4)	X (only cycle 2 and 4)	X (only cycle 2 and 4)	
		Ezabenlimab infusion	0:00							
		BI 836880 infusion	1:15							
		After end of BI 836880 infusion	2:15	X	X					
5, 6		Before start of infusion	-0:05	X	X					
3, 12, 16		Before start of infusion	-0:05	X	X	X				X (only cycle 3)
EOT				X	X	X				
30-Day FU				X	X	X				

[redacted] BI = Boehringer Ingelheim; CRF = Case Report Form; PTM = planned time; EOT = end of treatment; FU = follow up; MDSC = myeloid-derived suppressor cells; [redacted]

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

- Predose samples (PTM -0:05): within 1 hour before next ezabenlimab infusion
- Postdose samples (PTM 2:15): After end of BI 836880 infusion

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

b As of 01 June 2021, [redacted] samples are no longer collected.

From December 2021 on, no further blood samples should be obtained for central lab shipments.

10.5 TRIAL BIOMARKER PLAN

Biomarker collections are included in Appendix 10.4.1.

10.6 BLOOD PRESSURE MEASUREMENT PROCEDURE

Blood pressure measurements should be performed on the same arm and, if possible, by the same person. The machines or devices to be used for blood pressure measurement should be certified. The same method and device must be used throughout the trial for a patient i.e. if a patient receives the first blood pressure measurement for example with an electronic device, the same method and device should be used throughout the study for this patient (without switching to manual blood pressure measurement). On the other hand, inter-patient variability is acceptable, i.e. a study site is allowed to consistently use an electronic device to measure the blood pressure in a given patient throughout the study and a manual technique in another patient. After patients have rested quietly, in the seated position for five minutes, three blood pressure and pulse measurements will be taken 2-5 minutes apart and all three results have to be entered in the eCRF. The average of the 3 readings must meet criteria.

In case of a suspected “white coat effect” it is recommended to repeat the measurement in a pleasant condition after sufficient rest. Values from self-blood pressure measurements (SBPM) communicated from patient to investigator are not considered valuable for study related decisions.

10.7 BLOOD PRESSURE MANAGEMENT AND STUDY DRUG ADMINISTRATION GUIDELINES

Table 10.7:1 BP management and study drug administration guidelines following completion of Cycle 1, based on pre-infusion SBP and DBP measured on study drug administration visits. Prior to Cycle 2, BP guidelines follow inclusion/exclusion criteria.

Pre-infusion clinic BP (mmHg) on pre-planned infusion visits	**SBP <160 and DBP <100**	**SBP 160-179 or DBP 100-109**	**SBP≥180 or DBP≥110**	**Hypertensive crisis****
Action to be taken with BI 836880 and ezabenlimab	Proceed with study drug administration as scheduled / re-start.	Temporarily delay administration of both study drugs until BP < 160/100.	Delay administration of both study drugs until next pre-scheduled study drug administration.	Discontinue both study drugs.
Antihypertensive treatment	As deemed necessary by the investigator.*	Wait 10-15 minutes and ensure patient is relaxed, and re-measure BP: If BP <160/100 on re-assessment, administer both study drugs; If SBP remains 160-179 or DBP 100-109, initiate / modify antihypertensive regimens, delay administration of both study drugs, and re-assess within 12-48 hours of antihypertensive agent initiation/modification. After 12-48 hours: If BP <160/100, administer both study drugs. If BP remains ≥160/100, repeat after 10-15 minutes; if BP remains ≥160/100 hold study drug administration until next pre-planned infusion visit, and initiate / modify antihypertensive regimens.	Initiate / modify antihypertensive regimens, and re-assess at the next scheduled infusion visit.	Emergency admission for in-patient care

* Investigators should consider initiating / modifying antihypertensive regimens if SBP < 160 mmHg or DBP > 90 mmHg if their medical assessment is that lowering BP further is clinically indicated (for example, patient has cardiovascular risk factors), and discontinuing or modifying antihypertensive agents if there are symptoms /signs of hypotension.

** Hypertensive crisis defined as patients with significantly elevated blood pressure with signs or symptoms of acute, ongoing target-organ damage.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

Date of amendment		14 Jul 2021
EudraCT number **EU number**		2018-002344-81
BI Trial number		1381-0009
BI Investigational Medicinal Product(s)		Ezabenlimab (BI 754091 [anti-PD-1]) BI 836880 (anti-VEGF/Ang2)
Title of protocol		An open-label, Phase II trial evaluating the safety and efficacy of BI 836880 in combination with ezabenlimab in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		BI Investigational Medicinal Products
Description of change		**Ezabenlimab (**BI 754091 **[**~~(~~anti-PD-1**])**~~)~~ BI 836880 (anti-VEGF/Ang2)
Rationale for change		Ezabenlimab is the new name for BI 754091.
Section to be changed		Title
Description of change		An open-label, Phase II trial evaluating the safety and efficacy of BI 836880 in combination with **ezabenlimab**~~BI 754091~~ in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy

Rationale for change		Ezabenlimab is the new name for BI 754091.
Section to be changed		Lay Title
Description of change		Platform trial module evaluating safety and efficacy of BI 836880 in combination with **ezabenlimab**~~BI 754091~~ in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced/metastatic solid tumours.
Rationale for change		Ezabenlimab is the new name for BI 754091.
Section to be changed		Coordinating Investigator
Description of change		[redacted]
Rationale for change		[redacted] will replace [redacted] as the coordinating investigator.
Section to be changed		Synopsis Trial design
Description of change		Open-label, multicentre, Phase II, Master design with treatment-specific Modules. **Both Module C and the Master protocol must be followed. Where there are differences in stringency or cut-off values between the Master protocol and specific module, the specific module takes precedence.**
Rationale for change		To clarify that the Module values take precedence over the Master protocol.
Section to be changed		Synopsis Diagnosis and Section 3.1 Overall Trial Design and Plan and Section 3.3.2 Inclusion criteria
Description of change		Cohort 2: Patients with secondary resistance to anti-PD-1 or anti-PD-L1 based therapy: Any advanced or metastatic solid tumour (excluding non-squamous non-small cell lung cancer ~~(~~**[**NSCLC**]**~~)~~ and **all** melanoma)… Cohort 5…. **Hormonal monotherapy does not count as a line of therapy.**
Rationale for change		To clarify criteria for the trial cohorts.
Section to be changed		Synopsis Main in- and exclusion criteria and Section 3.3.2 Inclusion criteria
Description of change		Patient must agree to pre- and on-treatment tumour biopsies. If archived tumour tissue is available from the last treatment failure, sections may be supplied instead of a pre-treatment biopsy. ~~If the patient does not have an archival tumour tissue sample and is not biopsiable~~

		~~because of a safety concern the patient could be considered for study after discussion with the Medical Monitor to allow for a tumour type of interest.~~
Rationale for change		To clarify which patients are eligible for enrolment.
Section to be changed		Synopsis Main in- and exclusion criteria
Description of change		2 ~~Persistent toxicity from previous treatments that has not resolved to ≤Grade 1 with the exception of alopecia~~**Unresolved, Grade >1 toxicity before the start of treatment with the study drug except for hair loss (alopecia) and hypothyroidism that requires thyroid hormone supplements but is asymptomatic under therapy.**
Rationale for change		To clarify exclusion criteria guidelines for toxicity related to prior treatment.
Section to be changed		Synopsis Main in- and exclusion criteria
Description of change		4 Uncontrolled hypertension defined as: blood pressure in rested and relaxed condition ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic (with or without medication) **measured in triplicate, taken 2-5 minutes apart and averaged**.
Rationale for change		To clarify BP exclusion criteria for the Module.
Section to be changed		Flow Chart Module C BI 1381-0009
Description of change		Added a new column to separate assessments to be done within 28 days and within 14 days
Rationale for change		To clarify the time window for screening and baseline assessments.
Section to be changed		Flow Chart Module C BI 1381-0009
Description of change		Added triplicate BP and pulse to the flow chart
Rationale for change		To highlight BP and pulse measurements during the trial.
Section to be changed		Flow Chart Module C BI 1381-0009 footnotes a, b, and d
Description of change		**The date of an assessment is considered Day 1 of the window.**
Rationale for change		To highlight the assessment time window.
Section to be changed		Flow Chart Module C BI 1381-0009 footnote d

Description of change		**(BP to be conducted in triplicate, taken 2-5 minutes apart and averaged),** ~~electrocardiogram (ECG)~~
Rationale for change		To highlight and clarify BP measurement methods.
Section to be changed		Flow Chart Module C BI 1381-0009 text moved from footnote d to i.
Description of change		**Tumour assessments (scans) should be performed ≤28 days prior to initiation of treatment and copies may be collected by the Sponsor or designee.**
Rationale for change		To provide tumor assessment information in the appropriate location.
Section to be changed		Flow Chart Module C BI 1381-0009 footnote m
Description of change		Patients enrolling in a**nother open** ~~second~~ Module will be required to provide pre- and on-treatment tumour biopsy samples. In addition, an optional biopsy should be taken after treatment discontinuation, if possible.
Rationale for change		To clarify that patients may enrol on another Module in the trial.
Section to be changed		Flow Chart Module C BI 1381-0009 footnote n
Description of change		See Appendix 10.7 for BP and HR management and **see Appendix 10.6 for** the BP monitoring and study drug administration guidelines. BP and HR should be measured before and after study drugs have been administered. **BP and HR should be measured in triplicate, taken 2-5 minutes apart and averaged.**
Rationale for change		To highlight and clarify BP measurement methods.
Section to be changed		Flow Chart Module C BI 1381-0009 footnote o
Description of change		human immunodeficiency virus (HIV)-1 and HIV-2 antibody **performed at the discretion of the Investigator where clinically indicated**~~(at the discretion of the Investigator where clinically indicated) will be performed~~.
Rationale for change		To clarify guidance for HIV antibody testing criteria for patients.
Section to be changed		Flow Chart Module C BI 1381-0009 footnote p
Description of change		**Echocardiogram must be collected ≤28 days prior to the initiation of treatment.**

Rationale for change		To clarify when screening echocardiograms should be taken.
Section to be changed		Flow Chart Module C BI 1381-0009 footnote q, Section [redacted]
[redacted]		
Section to be changed		Section 1.2.1 BI 836880
Description of change		At the time of data cut-off for this protocol (**17 Aug 2020**~~11 Nov 2019~~), at total of **143**~~68~~ patients with solid tumours have been exposed to BI 836880. Of these, ~~5~~6**2** patients had been treated with BI 836880 monotherapy in 3 Phase I clinical trials testing either an every-3-week schedule or a weekly schedule, and **81**~~12~~ additional patients with **solid tumours**~~NSCLC~~ received BI 836880 in combination with the checkpoint inhibitor BI 754091 in a Phase Ib trial **(1336-011)**. In the ~~part-A~~ Part A of 1336-0011 t~~i~~r**i**al, 3 patients each were dosed at 360 mg and 500 mg dose while 6 patients were dosed at 720 mg dose in combination with 240 mg of BI 754091 in the q3w regimen. **720 mg q3w of BI 836880 and 240 mg of BI 754091 was chosen as the recommended phase 2 dose and this dose was additionally tested in the expansion cohorts of different indications in the Part B of the trial**. For patients treated with BI 836880 monotherapy, the most frequent adverse events (AEs) were hypertension (5**4**~~5~~.**8**~~4~~%, including 2**4**~~5~~.**2**~~0~~% of Grade 3), asthenia (**48**~~53~~.**4**~~6~~%, including ~~10~~**9**.7% of Grade 3), nausea (**27**~~30~~.4%, including **1 case [**1.**6**~~8~~%] of Grade 3), vomiting (2**7**~~8~~.**4**~~6~~%, including **1 case [**1.**6**~~8~~%] of Grade 3), **diarrhoea (25.8%, including 4.8% of Grade 3),** constipation (2**4**~~6~~.**2**~~8~~%; no AEs of Grade ≥3), ~~diarrhoea (26.8%, including 5.4% of Grade 3),~~

		and increased AST (2~~5~~.**6**~~0~~%, including **4**~~5~~.**8**~~4~~% of Grade 3 and **1 case [**1.8%**]** of Grade 4). **Few patients were reported with AEs requiring dose reductions or with AEs leading to treatment discontinuation. Infusion−related reactions and corresponding symptoms were reported for 5 patients (8.1%). Adverse events under the Standard MedDRA Query (SMQ) haemorrhages occurred in 9 patients (14.5%), with 1 patient (1.6%) presenting an AE of Grade 3. Serious AEs (SAEs) were reported for 27 patients (43.5%) and the most frequently reported SAEs were hypertension and pleural effusion, with 3 patients each (4.8%).** For patients treated with BI 836880 in combination with BI 754091, the most frequent adverse events (AEs) were hypertension (**19**~~58~~.**8**~~3~~%, including **8**~~25~~.**6**~~0~~% of Grade 3), followed by **Grade 1 or 2 nausea (12.3%), and Grade 1 or 2 Cough and diarrhoea (11.1%). No patients were reported with AEs requiring dose changes; 3 patients (3.7%) had an AE leading to treatment discontinuation. Infusion-related reactions and corresponding symptoms were reported in 8 patients (9.9%), with no AEs being higher than Grade 3. Adverse events under the SMQ haemorrhages occurred in 4 patients (4.9%), with 2 patients (2.5%) presenting AEs of Grade 3 and 1 patient presenting a Grade 5 AE. Eleven patients (13.6%) were reported with immune-related AEs according to investigator's judgement; 1 AE was of Grade 3 and 1 was of Grade 4.** ~~vomiting (41.7%; no AEs of Grade ≥3), nausea (33.3%, no AEs of Grade ≥3), asthenia (33.3%, no AEs of Grade ≥3), cough (25.0%, no AEs of Grade ≥3), and dyspnoea (25%, including 8.3% of Grade 3). Peripheral oedema was reported in 1 patient (8.3%). One patient (8.3%) was reported with an infusion-related reaction of hypertension (Grade 3). Bleeding AEs occurred in 2 patients (16.7%). Five patients (41.7%) were reported with immunerelated AEs according investigator's judgement; all of them were of Grade 1 or 2.~~

		~~There was no dose-dependent increase in the frequency of any AEs, SAEs, AEs of worst CTCAE Grade ≥3, or AEs of special interest. No patients were reported with AEs requiring dose changes; 1 patients had an AE leading to treatment discontinuation. Hypertension, was reported for two-thirds of patients in the lower dose groups (360 mg or 500 mg every 3 weeks) and for half of patients in the highest dose group (720 mg every 3 weeks). Based on laboratory values in all conducted trials, 5 patients were reported with AST/ALT >3x ULN simultaneous with ALKP <2x ULN, but none of those events met Hy's law criteria.~~**Laboratory values from all conducted trials did not show any event that met Hy's law criteria.**
Rationale for change		To provide updated clinical safety data for BI 836880.
Section to be changed		Section 1.2.1 BI 836880
Description of change		~~The pharmacokinetics, pharmacodynamics and immunogenicity of BI 836880 were investigated based on data from the monotherapy Phase I study 1336.0001 with a every 3 weeks dosing scheme. Maximum plasma concentrations were reached shortly after the end of infusion. BI 836880 plasma concentration remained around the maximum for up to 8 h and started to decline afterwards slowly. C_{max} and AUC increased in a dose-proportional manner over the entire dose range. As expected for a nanobody, the clearance was low, resulting in a terminal half-life of ~275 h (~11 days). The volume of distribution was also low and in the range of the average blood volume. An accumulation ratio of 1.11 to 1.54 was observed, showing slight accumulation of BI 836880 after multiple dosing. A PopPK/PD model showed that the preliminary results of the combination of BI 836880 and BI 754091 are consistent with PK results from the BI 836880 monotherapy studies.~~ [redacted]

		[redacted] ~~Pre-existing [redacted] were detected in approximately half of patients, and an additional 33.3% of the patients developed [redacted] during treatment. There was no dose dependency observed in the development of treatment-induced BI 836880 [redacted]. The PK was not influenced by the development of [redacted].~~ ~~After evaluating all available PK, PD, efficacy, and safety data, a dose of 720 mg BI836880 every 3 weeks in combination with 240 mg BI 754091 was determined as the recommended Phase II dose (RP2D), and this was endorsed by the Safety Monitoring Committee.~~ The Residual Effect Period (REP) is the period after the last administration of study drug with measurable drug levels and/or pharmacodynamics effects still likely to be present. The REP of BI 836880 and BI 754091 is up to 30 days. For a more detailed description of **the** BI 836880 ~~and BI 754091~~ profile~~s~~ please refer to the current Investigator's Brochures (IBs).
Rationale for change		To provide updated and abbreviated clinical PK information for BI 836880.
Section to be changed		Section 1.2.2 BI 754091 **(Ezabenlimab)**
Description of change		~~Refer to the Master protocol.~~**Ezabenlimab (BI 754091) is a mouse derived; monoclonal IgG4Pro antibody (mAb) targeted to the human programmed cell death 1 (PD-1) immune checkpoint inhibitor. Ezabenlimab is extensively humanized and potently blocks PD-1/PD-L1 and PD-1/PD-L2 interactions *in vitro*. The mAb is devoid of Complement Dependent Cytotoxicity (CDC) and Antibody-Dependent Cell-mediated Cytotoxicity (ADCC) activities.** **As of November 1st 2020, 117 patients with advanced/metastatic solid tumours have been**

		treated with single agent ezabenlimab, 111 of these patients were treated with the 240 mg q3w recommended phase II dose (RP2D). Additionally, 601 patients have been treated with the RP2D of ezabenlimab in combination with other agents. Three hundred and ninety three patients treated in combination with BI754111 (anti-LAG-3 mAb), 160 patients were treated in combination with BI 836880 (VEGF/Ang-2 inhibitor), 37 patients were treated in combination with BI 891065 (SMAC mimetic) and 11 patients were treated in combination with BI 754111 and BI 907828 (MDM2-p53 antagonist). **The currently available ezabenlimab clinical data demonstrate that it is well tolerated. The most common AEs reported in patients treated with ezabenlimab monotherapy were fatigue (39.3%), nausea (29.1%) and decreased appetite (21.4%). There were no grade 5 or treatment related Grade 4 events reported in patients treated with ezabenlimab monotherapy. Immunerelated AEs (irAEs) were reported in 34 patients (29.1%) on ezabenlimab monotherapy, the vast majority were Grade 1 and 2. There were no Grade 4 or Grade 5 irAEs and no infusion related reaction of any grade reported in patients treated with ezabenlimab monotherapy.** **Preliminary efficacy analysis shows overall objective response rate ezabenlimab monotherapy of 13.7% across all cohorts (14 patients with confirmed partial response [PR] and 2 patients with complete responses [CR]) (95% CI 8.0, 21.3). Both patients with CRs and 7 of the 14 patients with PR were still on treatment at the time of last data cut-off. Responding patients had the following tumour types: anal (2 patients) , breast cancer (2 patients), cervical cancer (2 patients), vulvar cancer (2 patients), angiosarcoma, oesophageal cancer, endometrial cancer, fallopian tube cancer, renal cancer, left supraclavicular nodal mesothelial cancer, and squamous cell carcinoma of the skin (1 patient each).**

		The available PK data show that ezabenlimab has a (at least) bi-phasic distribution. The volume of distribution ranged between 4.71 L and 5.88 L. The systemic clearance of ezabenlimab ranged between 0.00987 L/h (80mg dose) and 0.0119 L/h (400mg dose) (i.e. approx. 0.0237 - 0.0286 L/day) resulting in gMean half-life estimates of 13.8 to 17.8 days. Volume of distribution ranged from 5.29L to 5.88 L in BI 1381.1. The small total volume of distribution is consistent with a limited extravascular disposition as expected for a therapeutic antibody. Steady state exposure is estimated to be achieved after ~12-15 weeks (q3w, 4-5 cycles). **For a more detailed description of the ezabenlimab profile please refer to the current Investigator's Brochures (IBs) and the Master protocol.**
Rationale for change		To provide updated clinical safety and PK data for ezabenlimab.
Section to be changed		Section 1.4 Benefit-Risk Assessment
Description of change		In total, 6~~5~~ dose limiting toxicities were reported. In trial 1336-00011(q3w dosing) one patient treated on the highest dose level (1000 mg) experienced a pulmonary embolism. In trial 1336-0006 (q1w) **5**~~4~~ patients experienced DLTs (**2 patients each with** proteinuria and hypertension **and 1 patient each with sepsis** proteinuria, **and respiratory distress**~~, hypertension and respiratory distress one patient each).~~
Rationale for change		To provide updated benefit-risk information for the study.
Section to be changed		Section 1.4.1 COVID-19 Related Risks
Description of change		**COVID-19 Related Risks** **To date, there is no evidence suggesting a link between susceptibility to COVID-19 infections and the inhibition of VEGF-A and Ang2 targeted by BI 836880. Also, there is no evidence suggesting a link between susceptibility to COVID-19 infections and the inhibition of PD-1/PDL-1 by ezabenlimab. Available non-clinical and clinical data from completed clinical trials have not shown an**

		increased risk of infections with BI 836880 and ezabenlimab. **Considering the limited and sparse data on immune activation and the role of inflammation as well as other underlying factors that may increase the severity and mortality from COVID-19 infection, there may be some factors representing the risk for using inhibitors of VEGF/Ang2 or PD1 that are currently still unknown. The information about the risk factors, the severity and the activity of immune response in patients with COVID-19 infections will be constantly monitored as it evolves.**
Rationale for change		To provide benefit-risk information for the study as it related to COVID-19.
Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		**Both Module C and the Master protocol must be followed. Where there are differences in stringency or cut-off values between the Master protocol and specific module, the specific module takes precedence.**
Rationale for change		To clarify that the Module values take precedence over the Master protocol.
Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		**A new informed consent will be required if the patient remains on study with radiological PD.** ~~The patient will be required to sign a new ICF to continue treatment.~~
Rationale for change		To clarify that patients who receive treatment after an initial radiological PD, but not patients who continue to benefit from treatment after a year will need to provide further consent for treatment.
Section to be changed		Section 3.3.2 Inclusion criteria 2
Description of change		~~Patients must have had ≥ 1 line of prior systemic anticancer treatment in the metastatic setting~~
Rationale for change		To clarify inclusion criteria related to prior therapy.
Section to be changed		Section 3.3.2 Inclusion criteria 3
Description of change		**Tumour lesions that have been irradiated at least ≥4 weeks before the start of treatment,**

		and have subsequently had documented progression, may be chosen as target lesions only in the absence of measurable lesions that have not been irradiated.
Rationale for change		To clarify inclusion criteria related to target lesions.
Section to be changed		Section 3.3.3 Exclusion criteria 2
Description of change		~~Persistent toxicity from previous treatments that has not resolved to ≤Grade 1 with the exception of alopecia~~**Unresolved, Grade >1 toxicity before the start of treatment with the study drug except for hair loss (alopecia) and hypothyroidism that requires thyroid hormone supplements but is asymptomatic under therapy.**
Rationale for change		To clarify exclusion criteria related to toxicity associated with prior treatment.
Section to be changed		Section 3.3.3 Exclusion criteria 3
Description of change		Uncontrolled hypertension is defined as: blood pressure in rested and relaxed condition ≥ 140 mmHg, systolic or ≥ 90 mmHg diastolic (with or without medication), measured **in triplicate, taken 2-5 minutes apart and averaged** according to Appendix- **10.7**~~10.5~~**.** Patients with personal or family history of QT prolongation and/or long QT syndrome, or prolonged QTcF at baseline (> **470**~~480~~ ms).
Rationale for change		To clarify exclusion criteria related to BP and QTcF.
Section to be changed		Section 3.3.3 Exclusion criteria 6
Description of change		Patients who require full-dose anticoagulation (according to local guidelines).~~ No Vitamin K antagonist and other anticoagulation allowed;~~ **Only** LMWH **and ASA at doses for prevention/prophylaxis are** allowed~~ only for prevention not for curative treatment~~.
Rationale for change		To clarify exclusion criteria related to anticoagulant medications.
Section to be changed		Section 3.3.3 Exclusion criteria 7
Description of change		Prior anti-angiogenic therapy (with the exception of CRC Cohort **[Cohort 4]**).
Rationale for change		To clarify that the CRC cohort is Cohort 4.

Section to be changed		Section 4.2.8 Dose administration and modifications
Description of change		The **planned**~~expected~~ infusion time is 60 minutes **(+/- 10 minutes)** for BI 754091 and 60 minutes **(+/- 10 minutes)** for BI 836880; BI 754091 will be administered first, then 15 minutes (+/- 10 min) after the end of the BI 754091 infusion, BI 836880 will be administered. ~~In case no relevant infusion reactions are observed, this~~ **Infusion of BI 836880 infusion**~~can be shortened to about 30 minutes but~~ should not be prolonged to more than 6 hours~~ for BI 836880~~. Appropriate drugs and medical equipment to treat anaphylactic reactions must be immediately available and study personnel must be trained to recognize and treat anaphylaxis. In the event of an infusion-related reaction ≤ Grade 2, treat the symptoms accordingly with antihistamine or corticosteroids if needed. **Steroids, if used to manage an infusion-related reaction, are to be limited to prednisone 10 mg qd or equivalent.**
Rationale for change		To provide guidance related to treatment infusion.
Section to be changed		Section 4.2.8 Dose administration and modifications
Description of change		**Pre-treatment should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect.**
Rationale for change		To provide guidance for the administration of pre-treatment medications.
Section to be changed		Section 4.2.8 Dose administration and modifications
Description of change		**Drug re-administration criteria during Cycle 1** Before initiating a new treatment cycle the health status of the patient will be assessed according to the Module C flow chart. To continue treatment with further cycles, all of the following criteria must be met: 1. Pre-infusion SBP (measured in triplicate, taken 2-5 minutes apart, and averaged) should be < 140 mmHg and pre-infusion DBP should be < 90 mmHg; study drug administration of both study drugs should be temporarily delayed until BP < 140/90

		mmHg. Please see Table 10.7:1 in Appendix 10.7, which describes the guidelines for BP management and study drug administration. 2. QT interval corrected per Fridericia's formula (QTcF) ≤470 ms. 3. Echocardiography if clinically indicated (based on Investigator's judgment) with Left Ventricular Ejection Fraction (LVEF) ≥ 50%. Acceptable tolerability (in case of an adverse event at the planned start of a treatment cycle patients may continue therapy only after recovery to a level which would allow further therapy in the opinion of investigator).
Rationale for change		To clarify the parameters for Cycle 1.
Section to be changed		Section 4.2.8 Dose administration and modifications
Description of change		Pre-infusion SBP **(measured in triplicate, taken 2-5 minutes apart and averaged)** should be < 160 mmHg and pre-infusion DBP should be < 100 mmHg ~~(according to Exclusion Criterion #3 of Module C)~~.
Rationale for change		To highlight and clarify BP measurement methods.
Section to be changed		Section 4.2.8 Dose administration and modifications.
Description of change		QT interval corrected per Fridericia's formula (QTcF) ≤470 ms ~~(according to Exclusion Criterion #8 of Master)~~.
Rationale for change		To correct a conflict between Module C and the Master protocol.
Section to be changed		Section 4.2.8 Dose administration and modifications.
Description of change		**If the reduced dose is tolerable, and w**~~W~~here deemed in the best interest of the patient, the investigator **should re-escalate to** ~~may restart at~~ the originally assigned dose of 720 mg of BI 836880 as soon as deemed clinically appropriate.
Rationale for change		To update guidance for re-dosing after a dose reduction.
Section to be changed		Section 4.2.8 Dose administration and modifications.

Description of change		During combination therapy, if treatment is held or discontinued ~~due to an AE(s)~~, both BI 836880 and BI 754091 will be held or discontinued together. If treatment is to be restarted ~~after resolution (≤ Grade 1 or baseline) of the AE~~, **preferably** both BI 836880 and BI 754091 must be started together. **In some cases, in discussions with the Sponsor, treatment with one of the two investigational drugs can be allowed if there is an AE reported which can be clearly attributed to one of the two drugs and further warrants a temporary discontinuation of this drug in the interest of the patient.**
Rationale for change		To provide guidance for treatment holds, discontinuations, or re-dosing after an AE.
Section to be changed		Section 4.3.2.2 Permitted concomitant medications
Description of change		• If medically feasible, patients taking regular medication should be maintained on it throughout the trial. ~~This includes medications for the management of nausea, diarrhoea, and vomiting for which the patient must be treated according to institutional standards.~~ • **To reduce the risk of infusion related reactions, patients may be pre-treated with an antihistamine and acetaminophen or paracetamol. Pre-treatment should be administered at sufficient time prior to initiation of infusion to allow the agents to exert their effect.** • ~~Pre-medication will not be required, but may be utilised following the first dose of combination therapy, as appropriate. This includes medications for the management of nausea, diarrhoea, and vomiting for which the patient must be treated according to institutional standards.~~ • Supportive care and other medications that are considered necessary for the patient's well-being may be given at the discretion of the Investigator. **This includes medications for the management of nausea, diarrhoea, and vomiting for which the patient must be treated according to institutional standards.**

Rationale for change		To update guidance for the use of concomitant medications.
Section to be changed		Section 4.3.2.3 Restricted concomitant medications.
Description of change		Full-dose anticoagulation (according to local guidelines) ~~with Vitamin K antagonist and other anticoagulation~~ is not allowed during the trial conduct; **only** low-molecular-weight heparin (LMWH) **or ASA at prevention/prophylaxis doses are** ~~is~~ allowed ~~only for prevention not for curative treatment~~. **Any concomitant medication known to prolong the QT interval is not allowed.**
Rationale for change		To update guidance for the use of concomitant medications.
Section to be changed		Section 5.3.2 Methods of sample collection
Description of change		**If only 1 of the 2 drugs has been administered at the time of the PK sample collection, it should be noted. See the laboratory manual for further instructions.**
Rationale for change		To clarify guidelines for the collection of PK samples when only 1 of 2 treatment drugs is administered.
Section to be changed		[redacted]
[redacted]		
Section to be changed		Section 6.2.3.1 End-of-treatment visit
Description of change		**The intent is to complete the EOT as soon as the decision is to remove the patient from treatment. The decision can occur at a scheduled visit, or in between visits. If it happens on a scheduled visit, the site is to complete the EOT visit assessments for that day. If it happens in between visits, they should have patient return within 7 days of last dose (if possible) and complete EOT**

		instead of what that next scheduled visits would have been.
Rationale for change		To provided updated guidance for the EOT visit.
Section to be changed		Section 6.2.3.2 30-day post treatment safety visit
Description of change		The safety follow-up visit is performed 30 (+2) days after the **decision to** discontinue~~ation of~~ the trial medication.
Rationale for change		To clarify when the 30-day post treatment safety visit occurs.
Section to be changed		Section 10.4.1 10.4.1 Schedules for PK, [redacted] and [redacted] blood sampling
Description of change		**PKs are timed from the start of BI 754091 infusion.**
Rationale for change		To clarify the timing of PK collections.
Section to be changed		Table 10.7.1
Description of change		BP management and study drug administration guidelines following completion of **C**~~c~~ycle 1, based on pre-infusion SBP and DBP measured on study drug administration visits. **Prior to Cycle 1, BP guidelines follow inclusion/exclusion criteria.**
Rationale for change		To clarify BP measurement prior to Cycle 1 following inclusion/exclusion criteria.

11.2 GLOBAL AMENDMENT 2

Date of amendment		28 Mar 2022
EudraCT number **EU number**		2018-002344-81
BI Trial number		1381-0009
BI Investigational Medicinal Product(s)		Ezabenlimab (BI 754091 [anti-PD-1]) BI 836880 (anti-VEGF/Ang2).
Title of protocol		An open-label, Phase II trial evaluating the safety and efficacy of BI 836880 in combination with ezabenlimab in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒

To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Title Page Trial Clinical Monitor
Description of change		[redacted] Phone: [redacted] [redacted] ~~Phone:~~ [redacted] ~~Fax:~~ [redacted]
Rationale for change		The TCM changed over to [redacted]
Section to be changed		Synopsis – Duration of treatment
Description of change		From: Treatment will continue until progression of disease (PD), unacceptable toxicity, a maximum treatment duration of 1 year, or withdrawal of patient consent. Patients will be allowed to stay on treatment in case of initial radiological PD, if the Investigator feels that is in the patient's best interest. If the patient is benefiting clinically at 1 year, he/she may continue on treatment after a case-by-case review with the Medical Monitor and the Sponsor. A new informed consent will be required if the patient remains on study with radiological PD. To: Treatment may continue until progression of disease (PD), unacceptable toxicity, withdrawal of patient consent, or 53 cycles [approximately 3

		years] from the start of first treatment administration, whichever occurs first. Patients will be allowed to stay on treatment in case of initial radiological PD, until progression is confirmed or 53 cycles from the start of first treatment administration if the Investigator considers that the treatment is beneficial for the patient
Rationale for change		Treatment duration limitation added due to program discontinuation.
Section to be changed		Flow Chart (treatment duration)
Description of change		Total number of cycles limited to 53
Rationale for change		Treatment duration limitation added due to program discontinuation.
Section to be changed		Flow Chart (Survival)
Description of change		Progression-free survival follow-up visits removed including footnote h.
Rationale for change		PFS and OS will not be captured per sponsor decision.
Section to be changed		Flow Chart (biopsies and central lab samples)
Description of change		Biopsies, blood samples for PK, levels of BI 836880 and ezabenlimab, [redacted], and [redacted] removed
Rationale for change		No more biopsies and samples will be required due to program discontinuation
Section to be changed		Flow Chart (Echocardiogram)
Description of change		Echocardiogram removed from footnote d (safety laboratory) with requirement to be done ≤14 days prior to the initiation of treatment.
Rationale for change		Echocardiogram already entered under footnote p to be collected ≤28 days prior to the initiation of treatment.
Section to be changed		Flow Chart (Tumour Assessments)
Description of change		From: Tumour assessments …every 2 cycles (6 weeks ±3 days) for the first 6 months of treatment, once every 3 cycles (9 weeks ±3 days) thereafter, at the EOT visit (if not performed within the previous 4 weeks), and at the discretion of the Investigator. To:

		...afterwards can be performed according to institutional practices and SOC from the acknowledgement of the amendment.
Rationale for change		Imaging adjusted to be performed according to institution practices and SOC to reduce patient burden.
Section to be changed		Section 1.2 Drug profile
Description of change		Safety update according to last IB BI 836880 version 9 issued 03 Nov 2021 and BI ezabenlimab version 6 issued 19 Jan 2022
Rationale for change		New safety information available
Section to be changed		Section 1.3 Rationale for performing the trial
Description of change		Addition: DECISION TO TERMINATE THE TRIAL Although a preliminary assessment of the available data from the ongoing clinical program for the ezabenlimab + BI 836880 combination exhibit signs of antitumour activity and a manageable safety profile for an overall positive benefit risk ratio, careful review of the full data set performed in the context of the current standards of care for the indications under study has led to the decision taken by the sponsor in December 2021 to discontinue recruitment in study 1381-0009, and terminate further expansion of the study. An important consideration in the review process was whether the investigational combination treatment under study, namely BI 836880 plus ezabenlimab, had demonstrated benefit that delivered clear improvement over the current standards of care, some of which had evolved over the course of the study. The measure used to evaluate efficacy was the Objective Response Rate (ORR) which was the primary efficacy endpoint of the trial. It is important to note that at the time of this evaluation all cohorts had completed planned enrolment, and sufficient data had been collected to support a well-informed decision. Based on this evaluation, the efficacy observed in the different indications did not show clear improvement over the standards of care relative to published efficacy results in the

		different indications, with the one possible promising result in the 2L Endometrial carcinoma cohort. Given the evolution of the standard of care for 2L Endometrial carcinoma to combination treatment with immune checkpoint inhibitor plus an tyrosine kinase inhibitor (KEYNOTE-775), it was determined that this setting does no more present an opportunity for further development moving forward. Based on this evaluation, the decision was taken to terminate the trial. As a part of this decision, for patients still under active treatment, treatment with BI 836880 plus ezabenlimab may continue until disease progression, undue toxicity, withdrawal of patient consent, or 53 cycles [approximately 3 years] from the start of first treatment administration, whichever occurs first (see Section 4.2.8, "Treatment duration" for full details).
Rationale for change		To include information regarding the program discontinuation decision.
Section to be changed		Section 1.4 Benefit – risk assessment.
Description of change		Updated information on BI 836880 monotherapy and combination trials with ezabenlimab.
Rationale for change		Update with new available information.
Section to be changed		Section 3.1 Overall trial design and plan
Description of change		Updated wording on tumour assessments and duration of treatment in this section to be aligned.
Rationale for change		To align information in this section.
Section to be changed		Section 4.1 Investigational treatments (tables 4.1.1.1: 1 and 4.1.1.2: 1).
Description of change		Duration of use added as: until progression, unacceptable toxicity, or up to a maximum of 53 cycles.
Rationale for change		Treatment duration limitation added due to the program discontinuation.
Section to be changed		Section 4.2.8 Dose administration and modifications.
Description of change		Addition: <u>Treatment duration:</u>

		Treatment with BI 836880 plus ezabenlimab may continue until disease progression, undue toxicity, withdrawal of patient consent, or 53 cycles [approximately 3 years] from the start of first treatment administration, whichever occurs first. Patients will be allowed to stay on treatment also in the case of initial radiological PD, until progression is confirmed or up to 53 cycles from the start of first treatment administration if the investigator considers that the treatment is beneficial for the patient. Investigators may consider discontinuing BI 836880 and continue therapy with ezabenlimab for up to 53 cycles from the start of the first treatment administration if the patient has been on therapy ≥ 6 months, has achieved at least SD by RECIST 1.1 and can tolerate the therapy, and if the investigator considers this to be in the best interest of the patient. For any patient still on treatment with the investigational combination of BI 836880 plus ezabenlimab 53 cycles from the start of the first treatment administration, treatment extension will be considered on a case-by-case basis upon request by the investigator for a maximum additional 6 cycles, to complete no later than 30 April 2025, if the investigator considers this to be in the best interest of the patient. After this date treatment with the investigational combination BI 836880 plus ezabenlimab will no longer be available. Investigators are requested to prepare for discontinuation of patients from the current investigational treatment of BI 836880 plus ezabenlimab and to switch them to alternative available treatment options outside of the current protocol no later than by the final availability date of 30 April 2025.
Rationale for change		Treatment duration limitation details added due to the program discontinuation.
Section to be changed		Section 5.1 Assessment of efficacy
Description of change		Added:

		As of the decision of Boehringer Ingelheim in December 2021 no additional patients will be further included to this trial. From the acknowledgement of this amendment forward tumour assessment can be performed according to institutional practices and SOC; and not required to follow master protocol specified schedule.
Rationale for change		To reduce patient burden after program discontinuation decision on December 2021.
Section to be changed		Section 5.3.1 assessment of pharmacokinetics
Description of change		Added: As of the decision of Boehringer Ingelheim in December 2021 no additional blood samples for pharmacokinetics will be collected.
Rationale for change		To reduce patient burden after program discontinuation decision on December 2021.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section [redacted]
[redacted]		
Rationale for change		Clarification.
Section to be changed		[redacted]
Description of change		Added:

		[redacted]
Rationale for change		To reduce patient burden after program discontinuation decision on December 2021.
Section to be changed		[redacted]
[redacted]		
Section to be changed		Section 6.1 Visit schedule
Description of change		Removed: PFS follow-up wording.
Rationale for change		PFS and Overall Survival will not be captured per sponsor decision.
Section to be changed		Section 6.2 Details of trial procedures at selected visits
Description of change		Tumour assessment wording aligned for change.
Rationale for change		To clarify text
Section to be changed		Sections 6.2.3.3 (PFS) and 6.2.3.4 (Overall Survival status)
Description of change		Wording removed
Rationale for change		To clarify text
Section to be changed		Section 7.4 Interim analyses
Description of change		Added: Subsequent upon the decision of Boehringer Ingelheim in December 2021 that no additional patients will be included in this trial, no interim analyses will be performed.
Rationale for change		To include information regarding the enrolment stop and decision about interim analyses.
Section to be changed		Section 9.2 Unpublished references
Description of change		References for last versions of IBs for BI 836880 and ezabenlimab added.
Rationale for change		Added references.
Section to be changed		Section 10.4.1 Tables 10.4.1: 1 and 10.4.1: 2

Description of change		Added "From December 2021 on, no further blood samples should be obtained for central lab shipments."
Rationale for change		To include information regarding the decision to stop collection of central lab samples.

11.3 GLOBAL AMENDMENT 3

Date of amendment		13 JUN 2023
EudraCT number **EU number**		2018-002344-81
BI Trial number		1381-0009
BI Investigational Medicinal Product(s)		Ezabenlimab (BI 754091 [anti-PD-1]) BI 836880 (anti-VEGF/Ang2)
Title of protocol		An open-label, Phase II trial evaluating the safety and efficacy of BI 836880 in combination with ezabenlimab in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		Title Page/Clinical Trial Leader
Description of change		~~Trial Clinical Monitor~~**Clinical Trial Leader** [redacted] ~~Phone: +~~[redacted]

		[redacted] **Phone:** [redacted]
Rationale for change		Role of 'Trial Clinical Monitor' changed to 'Clinical Trial Leader' due to update in role title within BI; role changed over to [redacted].
Section to be changed		Title Page/Coordinating Investigator and Synopsis
Description of change		[redacted] Phone: [redacted]
Rationale for change		Updated company name.
Section to be changed		Throughout the document
Description of change		BI 754091 was changed to its INN, 'ezabenlimab'.
Rationale for change		Change was communicated with Global Amendment 1 (14 Jul 2021) but was not replaced throughout the document.
Section to be changed		Section 4.1.1 Identity of the Investigational Medicinal Products: Table 4.1.1.2: 1 Ezabenlimab – CMC 1
Description of change		Updated CMC 1 information for ezabenlimab: 20 mg/mL **(vial with 15 mL filling volume)**; name of the table changed to 'Ezabenlimab ~~(BI 754091)~~ **– CMC 1**'.
Rationale for change		To provide more details on CMC 1 material packaging and to distinguish from CMC 2 material.
Section to be changed		Section 4.1.1 Identity of the Investigational Medicinal Products
Description of change		**Table 4.1.1.2: 2 Ezabenlimab – CMC 2** added.
Rationale for change		To provide details on CMC 2 material of ezabenlimab and show the difference with CMC 1 material.

APPROVAL / SIGNATURE PAGE

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Title: An open-label, Phase II trial evaluating the safety and efficacy of BI 836880 in combination with ezabenlimab in PD-(L)1 naïve and PD-(L)1 pretreated patient populations with advanced and/or metastatic solid tumours who have had at least one line of systemic therapy

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	13 Jun 2023 14:42 CEST
Author-Trial Statistician		13 Jun 2023 14:43 CEST
Approval-Team Member Medicine		13 Jun 2023 18:37 CEST
Verification-Paper Signature Completion		27 Jun 2023 09:46 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed