Clinical Trial Protocol

	Document Number:	**c39898864-02**
EU Trial No.	2022-502125-17-00	
BI Trial No.	1467-0001	
BI Investigational Medicinal Product	BI 1821736	
Title	An open-label, Phase I dose escalation and expansion trial to investigate safety and efficacy of BI 1821736 in patients with advanced solid tumors	
Lay Title	A study to find a suitable dose of BI 1821736 and test whether it helps people with advanced cancer	
Clinical Phase	Phase I	
Clinical Trial Leader	[redacted] Phone: Email:	
Coordinating Investigators	[redacted] Phone: Fax:	[redacted] Phone:
Current Version and Date	Version 2.0, 25 Jan 2023	
Original Protocol Date	18 Oct 2022	**Page 1 of 121**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	18 Oct 2022
Revision date	25 Jan 2023
BI trial number	1467-0001
Title of trial	An open-label, Phase I dose escalation and expansion trial to investigate safety and efficacy of BI 1821736 in patients with advanced solid tumors
Coordinating Investigators	[redacted] Phone: [redacted] Fax: [redacted] [redacted] Phone: [redacted]
Trial site(s)	Multi-centre trial conducted in approximately 3 countries
Clinical phase	Phase I
Trial rationale	BI 1821736 (VSV-GP-CD80Fc) is a [redacted] pseudotype variant of the VSV-GP encoding for an optimized human CD80-Fc fusion protein. BI 1821736 is expected to selectively replicate in and induce a potent IFN-dependent tumor cell lysis. This viral infection results in the release of tumor antigens and the generation of an adaptive anti-tumor immune response due to the T-cell priming and reactivation. This dose finding trial will evaluate the safety and recommended dose for BI 1821736. After the completion of dose escalation and the determination of the BI 1821736 intravenous (i.v.) maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D), [redacted] to further explore safety as well as initial efficacy of BI 1821736 in defined tumor types.
Trial objective	To determine the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D) for BI 1821736.
Trial endpoints	Primary endpoint: • Occurrence of dose limiting toxicities (DLTs) in the MTD evaluation period. Secondary endpoints: • Occurrence of DLTs during the on-treatment period. • Occurrence of AEs during the on-treatment period.
Trial design	First-in-human, open-label, non-randomized, dose escalation trial of BI 1821736 administered [redacted]. as a single agent.
Total number of patients treated	Approximately 27
Number of patients per treatment group	Approximately 27

Diagnosis	Patients with advanced, unresectable and/or metastatic or relapsed/refractory malignant solid tumors who have exhausted available treatment options known to prolong survival for their disease.
Main inclusion and exclusion criteria	Key Inclusion criteria: • Histologically confirmed diagnosis of malignant tumor. • Has failed conventional treatment or for whom no therapy of proven efficacy exists or who is not eligible for established treatment options. Patient must have exhausted available treatment options known to prolong survival for their disease. • Eastern Cooperative Oncology Group (ECOG) score of 0 or 1. • Life expectancy of at least ≥3 months after the start of the treatment according to the Investigator's judgement. • Adequate organ function or bone marrow reserve as demonstrated at screening by laboratory values. Key Exclusion Criteria: • Previous treatment with VSV-based agents. • Concomitant medication or condition considered a high risk for complications from biopsy as per the Investigator's judgement. • Prior (within 3 weeks of first dose) or concomitant use of interferon, immunotherapy agents, or tamoxifen.
Test product	BI 1821736
dose	BI 1821736 will be tested at [redacted] and [redacted] Median Tissue Culture Infectious Dose ([redacted]
mode of administration	[redacted]
Duration of treatment	BI 1821736 administered for a maximum of four [redacted]-day cycles (overall [redacted]. administrations including [redacted] administrations during Cycle 1)
Statistical methods	Dose escalation is guided by a Bayesian logistic regression model (BLRM) with overdose control (EWOC) that will be fitted to binary toxicity outcomes (DLTs). The estimate of parameters will be updated as data are accumulated using the BLRM. At the end of the dose escalation phase, the toxicity probability at each dose level will be calculated to determine an estimate of the MTD.

FLOW CHART

Trial Period	**Screening**		**Treatment (1 CYCLE = [redacted])**											**Post Treatment**	
Visit Day	[redacted]													**EOT**[c] 30 days after last dose EOT	**FUP**[d] Every 9 Weeks
Time window	Before [redacted]				+1 d	+1 d	-1/+2 d	-1/+2 d	-1/+2 d	-1/+2 d	-1/+2 d	-1/+2 d	-1/+2 d	+/-5 d	+/- 3 weeks
Informed Consent[1]	X														
Biobanking Informed Consent[2]	X														
Overnight Stay[3]			X		X				X						
Review in-/exclusion criteria	X	X	X												
Demographics/Med History[4]	X														
Physical exam[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG[7]		X	X						X			X		X	
12-lead ECG[8]	X		X		X				X			X		X	
Safety Laboratory Tests[9]	X	X	X[10]	X	X	X	X	X	X		X	X	X	X	
Pregnancy Test[11]		X	X						X			X		X	
SARS-CoV2 test[12]		X	X		X				X			X			
[redacted]															
IFNα [13] (blood)			X	X	X	X			X	X					
CD80-Fc [13] (blood)			X	X	X	X	X	X	X	X	X			X	
Inflammatory cytokines [13] (blood)			X	X	X	X	X		X	X				X	
Ferritin (blood)[13]			X											X	
HLA typing (blood)[13]			X												
T-cell status FACS Analysis (blood)[13]			X				X	X	X						
$CD4^+$ and $CD8^+$ T cells (blood)[13]			X						X			X		X	
Tumor Biopsy[15]			X						X					X	

FLOW CHART contd.

Trial Period	**Screening**		**Treatment (1 CYCLE = [redacted]**											**Post Treatment**	
Visit Day	[redacted]													**EOT**[c] 30 days after last dose EOT	**FUP**[d] Every 9 Weeks
Time window	Before [redacted]				+1 d	+1 d	-1/+2 d	-1/+2 d	-1/+2 d	-1/+2 d	-1/+2 d	-1/+2 d	-1/+2 d	+/-5 d	+/- 3 weeks
[redacted]															
Disease Assessment[18]	X											X		X	X
AEs/SAEs/AESIs[19]	Continuous														
Concomitant Medications[20]	Continuous														
Further anti-cancer therapies														X	X

a. To be performed within 28 days of [redacted] with exception of Hep B (HBsAg), Hep C (HCV antibody or HCV RNA), HIV and LCMV which can be obtained in routine diagnostics within 56 days of [redacted]
b. Day of first administration of study treatment. Subsequent visits should be calculated from [redacted] Treatment assignment will be done in IRT up to [redacted] working days before [redacted] See Section 6.2.2 in case of need for remote visits.
c. The End of Treatment (EOT) visit will occur 30 days (+/- 5 days) after last dose or as soon as possible if discontinuation of trial treatment is decided more than 30 days after last dose.
d. For patients without documented objective progression at EOT, imaging (same modality as screening) should be repeated every [redacted] weeks according to footnote 18. For patients with documented objective progression at EOT, a phone contact should occur to collect adverse events, or last contact date in case of lost to follow-up. A patient's End of Study (EoS) is defined as 1 year after the last dose of BI 1821736 visit as per Section 6.2.3.2.

1. Written informed consent must be obtained before any protocol-specific screening assessments are performed and must include consent to collection of demographic data. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the Sponsor's instructions.
2. Optional consent for biobanking of leftover tumor and blood (serum) samples.
3. Patients are required to stay overnight following treatment on [redacted] and [redacted] If the shedding results from C2 are above a defined threshold (≥[redacted] copies), the patient will be required to stay overnight following their [redacted] treatment for additional sampling (note: if the results are not available from C2, C1 results should be considered). The same will apply for C3 shedding results, i.e., if the results are above the threshold, the patient will be required to stay overnight

following [redacted] treatment (note: if results are not available from C3, C2 results should be considered). In both cases, shedding sampling should be extended and performed according to the same schedule as [redacted]. Note: the patient may also be required to stay overnight during C3 and C4 if Cytokine Release Syndrome (CRS) was observed during C1 or C2.

4. Must include nicotine use, smoking and alcohol status. See Section 5.6.1.
5. See Section 5.2.1 for details of assessments to be performed. Additional symptoms which have not been reported during a previous examination should be clarified. Measurement of height (in cm at screening visit only) and body weight (in kg on Day 1 of every cycle only) should be included.
6. Vital signs include body temperature, pulse oximetry, systolic and diastolic blood pressure, and pulse rate (after 5 minutes of supine or semi-recumbent rest). See Section 5.2.2. Vital signs must also be checked during and following [redacted] (see Section 4.1.4.1 and Appendix 10.2 for details).
7. See Appendix 10.5.
8. Please refer to Section 5.2.4 and Appendix 10.1. Each time point should include calculation of QTcF. (Note: all ECGs should be done in triplicate.)
9. Safety and screening labs to be done within 14 days of [redacted] with exception of Hep B (HBsAg), Hep C (HCV antibody or HCV RNA), HIV and LCMV which can be done within 56 days of [redacted] On treatment labs may be performed up to 72 hrs in advance of each study drug administration. See Section 5.2.3 for details including requirements in case of a treatment delay. See also Section 4.1.4.3.
10. Pre-treatment safety labs do not need to be repeated on [redacted] if performed within 7 days of [redacted]
11. For women of child-bearing potential only. At screening, a serum pregnancy test to be performed within 14 days of [redacted] Prior to first treatment, a urine pregnancy test to be performed within 24 hrs of [redacted] and within 72 hrs of Day 1 of subsequent cycles. At the End of Treatment visit a urine pregnancy test should be performed. In the case of a positive urine pregnancy test, this should be confirmed with a serum pregnancy test.
12. A SARS-CoV-2 test (according to local standards) should be done during screening and within 5 days of each treatment administration of BI 1821736. If the screening test is done within 5 days of [redacted] a repeat test is not required. If there is already a result within 5 days of [redacted] a repeat test is not needed. See Section 5.2.5.2.

[redacted]

15. A fresh [redacted] biopsy must only be taken for patients who have undergone screening assessments and are expected to be eligible for treatment. In case there is an archival sample taken within 6 months of trial start with no intermediate therapy, this may be provided instead (an archival block of tumor tissue or 27 freshly sectioned unstained slides of 4-5 µm thickness), but should only be provided after [redacted] once the patient has started treatment. In the absence of an archival block of tumor tissue, the fresh tumor biopsy at [redacted] is mandatory. The [redacted] tumor biopsy is also mandatory where clinically feasible. An optional tumor biopsy may be performed at the time of disease progression (EOT or FUP). The biopsy at [redacted] and [redacted] should be taken prior to respective BI 1821736 administrations.
16. See Section 4.1.4 for details on BI 1821736 administration.

17. Following each treatment of BI 1821736, patient must be observed for any complications (vital signs and assessment of CRS). See Section 4.1.4.3 and Appendix 10.2 for detail.
18. Tumor assessments must be performed according to RECIST 1.1 and should include imaging of any known or suspected sites of disease using an appropriate method (e.g. CT scan, MRI). The same radiographic procedure(s) should be used throughout the trial. [redacted] documentation of superficial lesions should be provided. Tumor assessments should be performed at the following time points: Screening (CT/MRI of known and suspected sites of disease within the 28 days prior to [redacted] at [redacted] (a time window of -7 days is allowed) and at End of Treatment visit (a time window of -7 days is allowed). If a patient continues study treatment following disease progression at [redacted] (see Section 3.3.4.1 for exceptions), the next tumor assessment will be at the EOT visit. For patients without progression at the EOT visit, every [redacted] weeks (+/- 3 weeks) thereafter until progression, or until one of the following: start of subsequent anti-cancer therapy, patient's End of Study (EoS) which is defined as 1 year after the last dose of BI 1821736 visit, until death, lost to follow up, withdrawal of consent or the end of the trial (Section 5.1).
19. From Informed consent to EOT visit (30 days from the last dose): Report any (S)AE.
    During the follow-up period up to EoS: Report any treatment related (S)AE.
    After the individual patient's end of the study: Investigators do not need to actively monitor for new AEs but should report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which they may become aware of by any means e.g. phone call. Those AEs should be reported on the BI SAE form only (Section 5.2.6.2). See Sections 4.2.3.1 and 4.2.3.2 for specific guidance on management of CRS, TLS, IRRs and events with similar symptoms.
20. Report concomitant therapy from the date of informed consent until the EOT visit.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
CA	Competent Authority
CD	Cluster of differentiation
C_{max}	Maximum Plasma Concentration
CR	Complete response
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CRO	Contract Research Organisation
CRS	Cytokine release syndrome
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CPI	Check point inhibitors
CTP	Clinical Trial Protocol
DBL	Database Lock
DC	Disease control
DEC	Dose Escalation Committee
DILI	Drug Induced Liver Injury
DL	Dose level

DLT	Dose Limiting Toxicity
DOR	Duration of response
EC	Ethics Committee
ECD	Ectodomain
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EOI	End Of Infusion
EoS	End of Study
EOT	End of Treatment
EWOC	Escalation with overdose control
FACS	Fluorescence activated cell sorting
FIH	First In Human
FUP	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	Glycoprotein
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HLA	Human Leukocyte Antigen
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
iPSC	Induced pluripotent stem cells
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRT	Interactive Response Technology
ISF	Investigator Site File

[redacted]

IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System

[redacted]

LCMV	Lymphocytic choriomeningitis virus
LDL-R	Low-density Lipoprotein Receptor
LLOQ	Lower limit of quantification
LPLT	Last patient last treatment
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Drug Regulatory Activities
MHC	Major Histocompatibility Complex
MOI	Multiplicity of infection
MRI	Magnetic Resonance Imagine
MTD	Maximum Tolerated Dose
NAb	Neutralizing Antibody
NGS	Next Generation Sequencing
OPU	Operative Unit
OR	Objective Response
ORR	Objective Response rate
OV	Oncolytic virus
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive disease
PK	Pharmacokinetics
PR	Partial Response
PRR	Pattern Recognition Receptors
RA	Regulatory Authority
RECIST	Response Evaluation Criteria In Solid Tumors
REP	Residual effect period
RP2D	Recommended Phase 2 Dose
RSD	Recommended Starting Dose
QTcF	QT Interval with Fridericia's Correction

SAE	Serious Adverse Event
[redacted]	
SD	Stable disease
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
[redacted]	
TCR	T cell receptor
TIL	Tumor infiltrating lymphocyte
TLS	Tumor Lysis Syndrome
TMF	Trial Master File
Treg	Regulatory T cells
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
VSV-GP	Pseudotype variant of the Vesicular Stomatitis Virus carrying the envelope GP of the visceral non-neurotropic WE-HPI strain of the lymphocytic choriomeningitis virus (BI 1831169)
VSV-GP-CD80Fc	Pseudotype variant of the Vesicular Stomatitis Virus carrying the envelope GP of the visceral non-neurotropic WE-HPI strain of the lymphocytic choriomeningitis virus carrying CD80Fc cargo (BI 1821736)
WE-HPE	Strain of LCMV (lymphocytic choriomeningitis virus) from which the LCMV-GP protein was obtained
WHO	World Health Organisation
WOCBP	Woman of childbearing potential
Wt	Wild-type

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Despite the continued advancements in cancer treatment, cancer remains a leading cause of death globally. In 2020, it was estimated that there were approximately 19 million new cancer cases and 10 million cancer-related deaths worldwide (R21-4456). If the disease is diagnosed in advanced or metastatic stage, the vast majority of patients eventually progress on available treatments and succumb to their disease. These statistics highlight a substantial need for novel therapeutic agents and treatment strategies to improve the treatment outcome for cancer patients.

Oncolytic viruses (OVs) have gained attention in recent years, due to their ability to selectively replicate in and lyse tumor cells as well as their potential to stimulate adaptive immune responses directed against the tumor. Vesicular stomatitis virus (VSV), a negative-strand RNA virus, is under development as an oncolytic virus due to a variety of favourable properties, including its rapid replication kinetics, interferon (IFN)-dependent tumor specificity, its pantropism and its potential to elicit a broad range of immunomodulatory responses to break immune tolerance in the tumor microenvironment (R18-2379). Low-density lipoprotein receptor (LDL-R) and its family members serve as a major entry receptor for VSV and the ubiquitous expression of the receptors enable the virus to infect virtually all animal cells (R21-1793). Although normal cells can be infected via a receptor-mediated endocytotic uptake of the viral particle, the cells recognize virus infection at an early stage and produce, secrete and respond to type I IFNs, which impede virus replication by inducing an antiviral state in the infected cell and in neighbouring cells (R18-2380, R18-2381). Thus, a VSV infection in healthy cells is efficiently controlled by the IFN-induced antiviral response. In contrast, most human tumors (in particular late stage cancers) have a defective or inhibited type I IFN signaling, most likely because many IFN responses are anti-proliferative, anti-angiogenic and proapoptotic as well as promote anti-tumor immunity (P98-8840) making a broad range of such tumors susceptible to VSV-based virotherapy (R18-2382).

Although VSV is a potent oncolytic virus which has the potential to induce significant response and improve prognosis of aggressive malignancies, one limiting factor of its use in the clinic is its potential neurotoxicity (R19-1556). VSV can infect neurons and cause lethal encephalitis when entering into the brain. Researchers have attempted to overcome this limitation by generating attenuated viruses (R19-1556, R21-1794, R21-1795). However, the reduced toxicity comes at the expense of reduced replication competence and oncolytic activity, so that it is doubtful whether the attenuated variants would be effective against the tumors (R21-1792). VSV's neurotropism is linked to the G protein and it has been shown that replacing it by the Lymphocytic choriomeningitis virus (LCMV) glycoprotein (GP) resulted in the complete abrogation of neurotoxicity, noticed even after direct injection of high doses with the respective recombinant pseudo-typed VSV (VSV-GP) into the brain (R19-0813).

[redacted] The addition of the CD80-Fc cargo leads to T-cell priming and reactivation, a feature, which is severely compromised within the immune suppressed tumor environment.

1.2 DRUG PROFILE

BI 1821736 (VSV-GP-CD80Fc) is composed of:

- The VSV-GP part that is a recombinant chimeric vesicular stomatitis virus (VSV; *Rhabdoviridae* family) of the Indiana strain carrying the envelope glycoprotein (GP) of the visceral non-neurotropic WE-HPI strain of the lymphocytic choriomeningitis virus (LCMV; *Arenaviridae* family), instead of its natural wild-type glycoprotein (G).
- The CD80-Fc cargo part - [redacted] to produce BI 1821736 (VSV-GP-CD80Fc).

1.2.1 Mode of action

BI 1821736 (VSV-GP-CD80Fc) combines two mechanisms of action:

Related to VSV-GP part: In viral infections, the host innate immune system acts as a first line of defence to prevent viral invasion or replication before more specific protection by the adaptive immune system is generated. In the innate immune response, pattern recognition receptors (PRRs) are engaged to detect specific viral components such as viral RNA or DNA or viral intermediate products and to induce type I interferons (IFNs) and other pro-inflammatory cytokines in the infected cells and other immune cells (R18-2378). However, most human tumors (in particular late stage cancers) present defective or inhibited type I IFN signaling, most likely because many IFN responses are anti-proliferative, anti-angiogenic and pro apoptotic as well as promote anti-tumor immunity (R18-2382).

Besides the use of a subset of alternative surface receptors for viral entry and the abrogation of neurotoxicity, other viral properties like the VSV-mediated interferon sensitivity are considered preserved in VSV-GP. In consequence VSV-GP, like VSV, will preferentially replicate in cancer cells leading to cell lysis while virus propagation in normal tissues will be suppressed by an antiviral interferon (IFN) response, resulting in an abortive infection in normal cells. Like most oncolytic viruses VSV-GP exerts its anti-tumor effect not only by directly lysing the infected tumor cells, but in addition by the indirect effect that (as a consequence of cell lysis) tumor specific antigens are set free, which can trigger a systemic anti-cancer immune response.

VSV-GP induces a potent tumor cell lysis resulting in the release of tumor antigens. This in combination with the signals associated with the viral infection lead to the generation of an adaptive anti-tumor immune response. The oncolytic virus (OV) may also help to breach the physical/ epithelial tumor-barrier to facilitate immune cell infiltration. Figure 1 illustrates the therapeutic principles of oncolytic virotherapy.

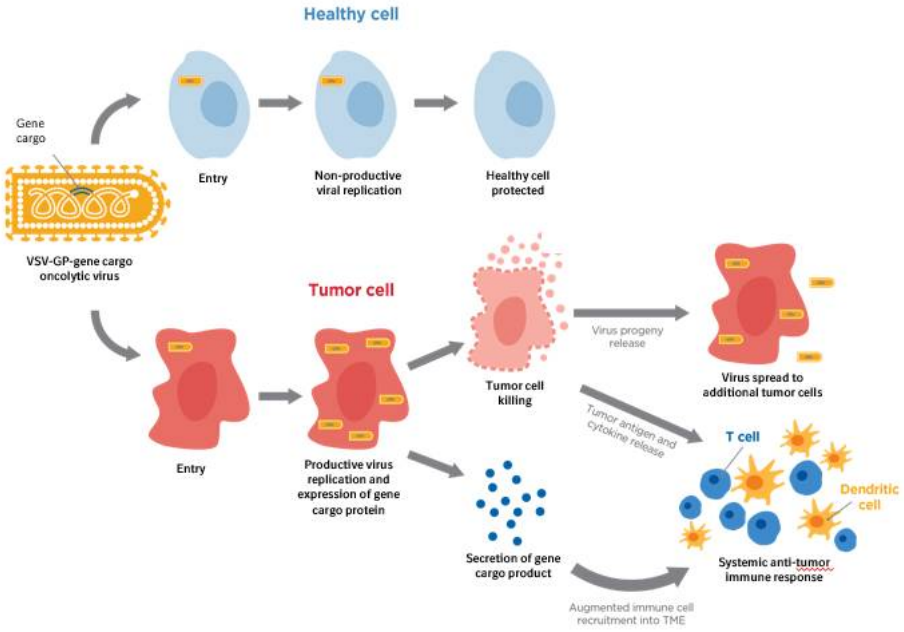


Figure 1 Therapeutic principles of oncolytic VSV-GP virotherapy

Related to CD80-Fc cargo part: The immune promoting CD80-Fc cargo was chosen to provide co-stimulation to intra-tumoral T-cells, which need further stimulation from mature dendritic cells providing an appropriate level of co-stimulation in addition to the otherwise dominating and potentially (in the absence of CD28-mediated co-stimulation) tolerizing T-cell receptor (TCR)-major histocompatibility complex (MHC)/peptide complex interaction. Secreted CD80-Fc exerts its mode of action by binding to CTLA-4 (antagonistic), thereby releasing endogenous CD80/86 or by directly engaging CD28 (agonistic) on T-cells, which they stimulate in a Fc/Fcγ receptor (FcγR)-dependent manner. It is envisaged that the use of the CD80-Fc cargo further boosts the therapeutic potential of VSV-GP-based treatments (see Figure 2).

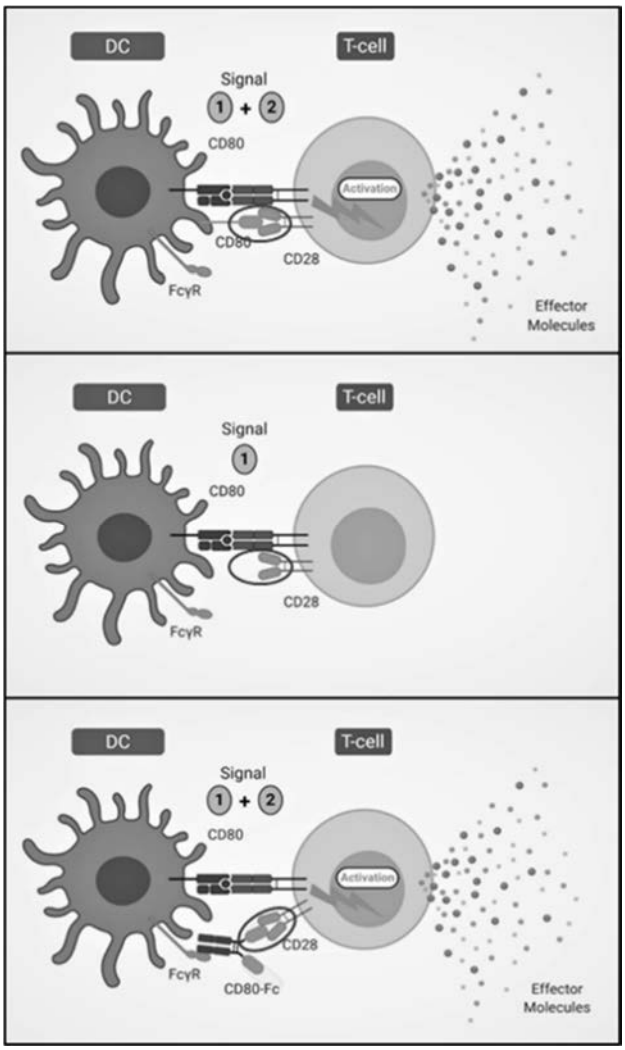


Figure 2 Schematic description of CD80-Fc function.
Dendritic cell activation of T-cells is dependent on MHC – TCR peptide recognition and co-stimulation e.g. by CD80 – CD28 interaction. Lack of endogenous CD28 stimulation of T-cell can be compensated by binding of recombinant CD80-Fc to FcγR and CD28 providing co-stimulatory activation of T-cells

1.2.2 Data from non-clinical studies

1.2.2.1 Non-clinical pharmacology

In non-clinical studies, VSV-GP-CD80Fc induced potent tumor cell lysis, and has been safely administered in animals via [redacted] or concomitant [redacted]. administration. The doses tested in tumor bearing animals ranged from [redacted] to [redacted] and [redacted] to [redacted]. or concomitant [redacted] (c38438874). [redacted] or [redacted], as well as [redacted] and [redacted] was seen in treated animals (R19-0813, R19-1584, R19-1585, R19-1587, R21-0289, n00290675).

1.2.2.2 Toxicology

Infection in healthy cells results in a transient transcription and a limited complete virus cycle with viral-induced cell death and liberation of virus progeny (c38438874).

Repeat dose toxicity studies

The toxicity profile for BI 1821736 has been assessed in the repeat dose studies in healthy and in [redacted] (n00294923, n00296875). BI 1821736 was well tolerated when administered [redacted] in healthy mice or [redacted] in tumor-bearing mice, at doses up to [redacted]

Key clinical pathology findings
BI 1821739 caused mild [redacted] Collectively, these changes were considered non-adverse, and/or were consistent with the expected inflammatory response to BI 1821736.

Organ system effects
Microscopic findings associated with administration of BI 1821736 at [redacted] were observed in [redacted] The findings did not correlate with any severe toxicity and showed reversibility or partial reversibility. There were no major differences observed between [redacted] despite a sustained replication of virus in tumor. This suggests that these findings are related to the systemic exposure and are independent of the oncolytic activity of BI 1821736.

BI 1821736-related microscopic findings at the [redacted] included minimal mononuclear cell infiltrates, which is consistent with a local application of a live virus. This finding was also dose-dependent and non-adverse.

Other toxicities

CD80Fc Superagonism
CD80 is a protein present on the surface of various immune cells, typically found on antigen presenting cells. CD28, the receptor for CD80, is expressed on T cells; the interaction between CD28 and CD80 provides a co-stimulatory signal which is required for T cell activation and survival.

The theoretical risk that expression of the transgene CD80Fc may trigger CD28 superagonism-like effects was evaluated for BI 1821736. In the *in vitro* cytokine release assay in high density PBMCs, huCD80-Fc alone did not demonstrate a TGN1412-like pro-inflammatory response while the TGN1412-like mAb demonstrated high levels of IL-2, IFNɣ, and TNFα. Further, in repeat dose toxicity studies, major expansion of regulatory T (Treg) cells, an anticipated pharmacological effect of superagonist, was not observed. Immunophenotyping of the spleen showed increases in Tregs in healthy mice only during the recovery phase, which may be a response to the increase in activated T cells during the dosing phase. Further, evaluation of cytokine levels in tumor-bearing mice revealed increases in several proinflammatory cytokines (IFNɣ, IL-6, KC-GRO, TNFα, IL-10), which is consistent with the expected mechanism of action. However, there was no increase in IL-2,

which is predominantly produced by T cells and known to be stimulated by CD28 superagonists such as TGN1412 (R08-1629). Taken together, these data suggest that the human CD80Fc transgene is not expected to have superagonist cytokine activity in vivo.

Neurotoxicity

VSV-GP was designed to specifically eliminate the neurotoxicity potential via the exchange of the wild-type (wt) VSV glycoprotein (G) with the glycoprotein (GP) of the viscerotropic LCMV WE strain (LCMV WE-HPI) (R19-0813). A neurotoxicity study in [redacted] was conducted in order to confirm the abrogation of neurovirulence for BI 1831169. In this study, [redacted] administered [redacted] developed neurological symptoms and [redacted] (n00286563). No neurotoxicity was observed in [redacted] administered VSV-GP (BI 1831169) at [redacted]. As BI 1821736 is a cargo expressing variant of VSV-GP (BI 1831169), these data suggest that neurotoxicity is not anticipated with administration of BI 1821736.

In repeat dose toxicity studies in healthy and [redacted], there were no clinical signs suggesting effects on the [redacted] and no [redacted] findings in the [redacted] at doses of BI 1821736 up to [redacted] or [redacted].

To further assess neurotoxicity of BI 1821736, [redacted] was conducted (n00297864). [redacted]. These data further support the abrogation of neurotoxicity with BI 1821736 in human cells.

1.2.2.3 Key pharmacokinetic characteristics

Classical pharmacokinetic principles following the absorption, distribution, metabolism and excretion (ADME) concept as for chemical entities, are not considered firmly applicable to replicating oncolytic viruses. Rather, pharmacokinetic studies focus on the biodistribution (viral spread) and shedding of the virus. For more detail refer to the Investigator Brochure (IB) (c38438874).

Biodistribution was determined following single-dose [redacted]. administration in [redacted] (n00290675).
At [redacted] post-administration, BI 1821736 was distributed primarily to the [redacted] followed by [redacted].
Between [redacted] and [redacted] post-administration, [redacted].
Between [redacted] and [redacted] post-administration, BI 1821736 RNA levels continued [redacted] tissues, whereas levels continued [redacted] and began [redacted]
Between [redacted] and [redacted] post-administration, BI 1821736 RNA levels began to [redacted] Thereafter, [redacted] and, excepting [redacted], were below the lower limit of quantification (LLOQ) on [redacted]

BI 1821736 [redacted] remained near or below LLOQ throughout the study except between the [redacted] and [redacted] time point where BI 1821736 [redacted] above LLOQ in the [redacted].
There was [redacted] in all the tissues and tumor samples at [redacted] post-administration.

Drug interactions
Pharmacokinetic drug-drug interactions are not expected with BI 1821736. However, it has been reported that tamoxifen, widely used in the treatment of breast cancer, was able to inhibit the replication of several viruses including VSV under in-vitro conditions. The antiviral effect against VSV was most likely related to an enhanced IFN-I response and stimulation of macrophages (R21-0236).

Residual Effect Period
The Residual Effect Period (REP) of BI 1821736 is [redacted]. Available non-clinical data for BI 1821736 show that after [redacted] (n00290675). By [redacted] was considered not infectious in all tissues. No infectious virus was detected [redacted] samples collected on [redacted] (n00290675). Moreover, after administration of BI 1821736, and similar with the course of any viral infection, the adaptive immune system (e.g. T-cells) will be fully activated within 7 to 10 days following injection and would clear remaining viruses (R21-2860). Therefore, by Day 15 after administration it is considered that no infectious virus should be present any longer.

Risk of Transmission to Third Party
Environmental safety data resulting from studies performed in [redacted] administered BI 1821736, show that the risk of viral shedding and transmission is considered minimal to negligible. The shedding level is expected to be logs below the dose of wt-VSV considered infectious for third party, i.e. [redacted], being the minimal dose required to induce clinical signs in [redacted] a natural host of VSV (R19-1390). In addition, BI 1831169 (VSV-GP) was shown to be much less pathogenic in [redacted] compared to wt-VSV and does not represent a risk in livestock. BI 1831169 was also not persistent in tap water or human urine and feces. Considering this data, BI 1821736, a cargo expressing variant of VSV GP, is not expected to represent a risk in livestock or to persist in human urine or feces.

1.2.3 Data from clinical studies

This is the first trial in humans and therefore no clinical data is available.

1.3 RATIONALE FOR PERFORMING THE TRIAL

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

Based on the non-clinical studies summarized in the previous section, the observed anti-tumor activity and safety profile warrant clinical testing of BI 1821736. This trial is the first-in-human, open-label, dose escalation trial to determine the maximum dose tolerated (MTD) and/or the recommended Phase II dose (RP2D) of BI 1821736 administered [redacted] in patients with advanced solid tumors. Results from this trial will provide the foundation for further clinical development of BI 1821736.

[redacted] sampling will contribute to the characterization of the BI 1821736 distribution properties within tissue, support the dose finding, and help to identify potential biomarkers for clinical response.

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

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

In non-clinical studies BI 1821736 induced [redacted] and [redacted] from a dose of [redacted] up to [redacted] and [redacted] and [redacted]. See the BI 1821736 IB for further information (c38438874). Based on these studies, the administration of BI 1821736 may provide benefit to patients in reduction of their tumor burden or disease stabilization. As this is the first study in humans, the extent of the potential benefit is unknown.

1.4.2 Risks

Due to the lack of clinical experience with BI 1821736, unexpected adverse events and laboratory abnormalities may occur. The safety data will be closely monitored throughout the trial, and a dose escalation committee (DEC) will be implemented for this purpose. The DEC chair will be an Investigator with oncolytic virus experience in early clinical trials. The committee will be composed of Investigators or delegates from participating investigational sites and the Sponsor. For details, refer to the DEC charter and Section 8.7.

Table 1 displays the potential risks associated with taking the investigational medicinal products based on their mechanism of action, observed non-clinical and clinical data from ongoing studies, and/or published clinical data for drugs in the same class, as well as other associated procedural risks. In addition to the mitigation strategies listed in the table, sequential enrollment of patients into a single cohort will be done in this trial (Section 3.1).

In order to minimize the risk of safety issues, this study will be conducted at sites with Investigators who are familiar with the administration of oncolytic viruses. The study sites will be selected based on their experience with oncolytic viruses, early clinical phases management, and tumor biopsies practices.

Table 1 Overview of trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product BI 1821736		
Cytokine release syndrome (CRS)	CRS could potentially occur with administration of BI 1821736 CRS is a supra-physiologic response resulting in the activation or engagement of T cells, particularly due to CD80-Fc cargo mediated mechanism of action, which can be serious or life-threatening.	This trial includes multiple measures and precautions for prevention, monitoring, early detection and treatment of CRS. - Mandatory patient surveillance following [redacted] and [redacted] (Section 4.1.4.3) - Recommendations for management of CRS (Section 4.2.3.1) - Specific lab tests (blood cytokines) - AESI reporting if ≥ Grade 2 - DEC follow-up
Infusion related reaction (IRR)	Hypersensitivity reactions are possible and can be severe if they occur.	- Close patient monitoring and early management of any symptoms. - If any signs of reaction occur, local intervention should be initiated and guidelines in Section 4.2.3.1 should be followed. - AESI reporting
Autoimmune disease	The risk of autoimmune disease could occur with the administration of BI 1821736. This potential risk is related to long-term T cells activation.	Patient monitoring up to 1 year after the last BI 1821736 dose.
Fever and flu-like symptoms	Risks associated to the administration of a live virus.	Close patient monitoring and early management of any symptoms.

Table 1 contd. Overview of trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Potential transmission of BI 1821736 (viral shedding)	Viral shedding was not observed in studies in [redacted] (equivalent to human patient) and [redacted] (natural host of VSV); and therefore, the risk of spread to others or the environment is anticipated to be extremely limited.	Mandatory overnight patient surveillance following [redacted] and [redacted] Standard isolation and sampling to assess for potential shedding will be obtained during the first and second cycle of therapy. Additional sampling during remainder of Cycle 2 and during Cycles 3 and 4. Avoiding contact with livestock and avoiding/limiting contact with people with immuno-compromised system, pregnant women, and infants for 10 days following treatment administration. Various restrictions in place for the patient during the trial to minimize risk of spreading. See administration (Section 4.2.2.2)
Drug-induced liver injury (DILI)	Rare but can be a potentially severe event, thus under constant surveillance by Sponsors and regulators for all drugs in development.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety.
Tumor lysis syndrome (TLS)	BI 1821736 may result in rapid tumor cell destruction in tumors displaying high susceptibility to treatment, causing TLS.	TLS is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia due to tumor cell destruction. These electrolyte and metabolic disturbances can progress to clinical toxic effects, including renal insufficiency, cardiac arrhythmias, seizures and death due to multi organ failure. This trial includes safety labs and AE assessment for monitoring and early detection of TLS. With prompt institution of appropriate treatment, TLS is expected to be reversible.
Unexpected adverse events	Risk due to limited clinical experience with this oncolytic virus and potential risk of direct injury of normal tissues.	Close monitoring for and early management of adverse events and regular monitoring of safety and other data by the DEC.

Table 1 contd. Overview of trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Trial procedures		
Tumor biopsies and [redacted] of investigational medicinal product [redacted]	Patients may experience pain, swelling, infection, bleeding, injury to surrounding tissue, nerves, vessels in needle track, reactions to local anesthesia if used, e.g. allergy, arrhythmia, other events (e.g. possible ulcerations, scarring after biopsy) or compression due to swelling).	The risks are clearly explained in the informed consent form. Selection of investigational sites with interventional radiology expertise and/or Investigators experienced in diagnostic biopsies, selection to avoid tumors felt to be at high risk for local complications.
Blood sampling	Blood sampling by venipuncture may be accompanied by mild bruising or pain.	The total volume of blood withdrawn per patient during the trial is expected to have no health-related risks.

1.4.2.1 Coronavirus Disease

A risk assessment in the context of the COVID-19 pandemic for patients treated with BI 1821736 has been performed.

Based on the mode of action, BI 1821736 is not expected to have a relevant impact on the susceptibility to or the course of a COVID-19 infection, however it will not be easy to differentiate between an immune reaction to BI 1821736 or an alternative infection. Potential participants with active or recent SARS-CoV-2 infection (within 2 weeks prior to the start of treatment) will not be included in the trial.

Published data provides preliminary evidence that cytokine release syndrome (CRS) may play a role in severe cases of COVID-19 (R20-2735). Since administration of BI 1821736 may also be associated with CRS, it cannot be fully excluded that patients with a COVID-19 infection may be at increased risk to develop a more severe course of illness during treatment with BI 1821736.

SARS-CoV-2 testing will be performed according to the Flow Chart and in case of suspected SARS-CoV-2 infection. In case of a confirmed infection, trial treatment will be paused immediately and appropriate measures for monitoring, treatment and quarantine will be implemented. The patient may resume trial treatment following recovery from a SARS-CoV-2 infection if the patient is expected to derive clinical benefit, as agreed between the Investigator and Sponsor. See Section 4.1.4.3 for allowed dose delays.

Patients in this trial may be immuno-compromised due to underlying malignancy and prior anti-tumor therapy, and therefore at higher risk for severe illness from COVID-19. In case of an increased risk of SARS-CoV-2 infection due to the physical visits to the sites, the visits should be avoided where the Investigator judges that this is the safest course of action. They should be replaced with remote visits (as per local standard procedures), procedures and lab testing will be done remotely as far as possible (Section 6) or omitted where a remote visit is not possible. These measures ensure the safety of the patients throughout the trial, maintain the integrity of the trial and will not affect the benefit-risk of BI 1821736.

1.4.3 Discussion

The mechanism of action of BI 1821736 is well characterized with both [redacted] and [redacted] and [redacted].

In the context of the unmet medical need and anticipated benefit of BI 1821736 in a large variety of tumors, the benefit risk evaluation, based upon the available preclinical information, is favourable. The main potential risks are the immune related risks, particularly cytokine release syndrome (see Table 1, Section 1.4.2).

Considering the medical need for the development of a better tolerated and more effective treatment for patients with advanced cancers, the anticipated benefit outweighs the potential risks and BI 1821736 may constitute a novel therapeutic option for many patients with cancer.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The trial will characterize the dose-toxicity curve of BI 1821736 given [redacted] in patients with advanced solid tumors by escalation with overdose control (BLRM-EWOC) in order to achieve the primary objective of determining the MTD and/or recommended Phase II dose (RP2D).

The primary measure is the number of patients per dose level with DLTs during the MTD evaluation period. The MTD is defined as the highest dose with less than 25% risk of the true DLT rate being equal to or above 33% during the MTD evaluation period. The MTD evaluation period is defined as the first treatment cycle (Cycle 1; [redacted]). This trial will also evaluate the safety of BI 1821736 [redacted] by monitoring the occurrence and severity of adverse events (AEs) during the study treatment period.

The primary characterisation will be based on the initial dose administered to the patient and the strategy for handling intercurrents event will be a combined composite and principal stratum approach where some intercurrent events are considered as outcome and some define the population consisting of patients who are able to adhere to the assigned treatment regimen and trial schedule over the MTD evaluation period.

Intercurrent events are events that happen after the first administration of trial medication and lead to a change in treatment or a change in the status of the patient. Examples of intercurrent events that could occur include treatment discontinuation during the MTD evaluation period for reasons other than a DLT. If such intercurrent events occur, then these patients are considered non-evaluable and will not be included in the primary endpoint analysis. For more details about patients that will be considered non-evaluable for MTD determination, please see Section 3.3.4.1.1 below.

2.1.2 Primary endpoint(s)

The primary endpoint of this trial is:

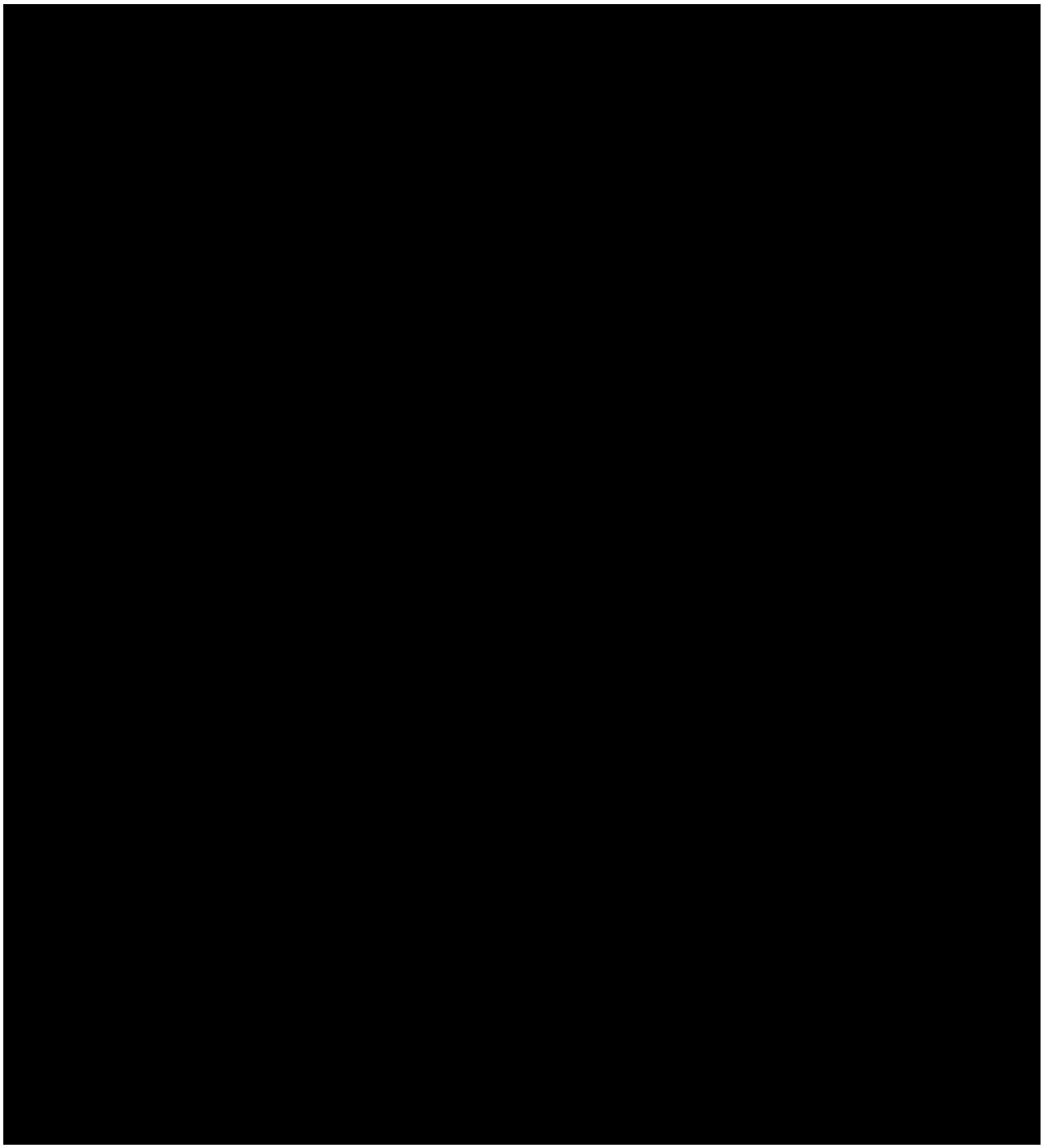
- Occurrence of DLTs in the MTD evaluation period.

2.1.3 Secondary endpoint(s)

The secondary endpoints of this trial are:

- Occurrence of DLTs during the on-treatment period.
- Occurrence of AEs during the on-treatment period.

[redacted]



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a first-in-human Phase I, open-label, non-randomized, dose escalation trial of BI 1821736 administered intravenously as a single agent. The trial design is illustrated in Figure 3. The trial design allows an escalation of dose with appropriate safety monitoring to ensure the safety of the patients.

A Bayesian logistic regression model (BLRM) with overdose control (R13-4803) will be used to determine the MTD estimate. The BLRM estimates the MTD by updating estimates of the probability of observing a DLT for each dose level. At any time in the trial, it will not be permitted to escalate to a dose which does not fulfil the escalation with overdose control (EWOC) criterion (for further details refer to Section 7).

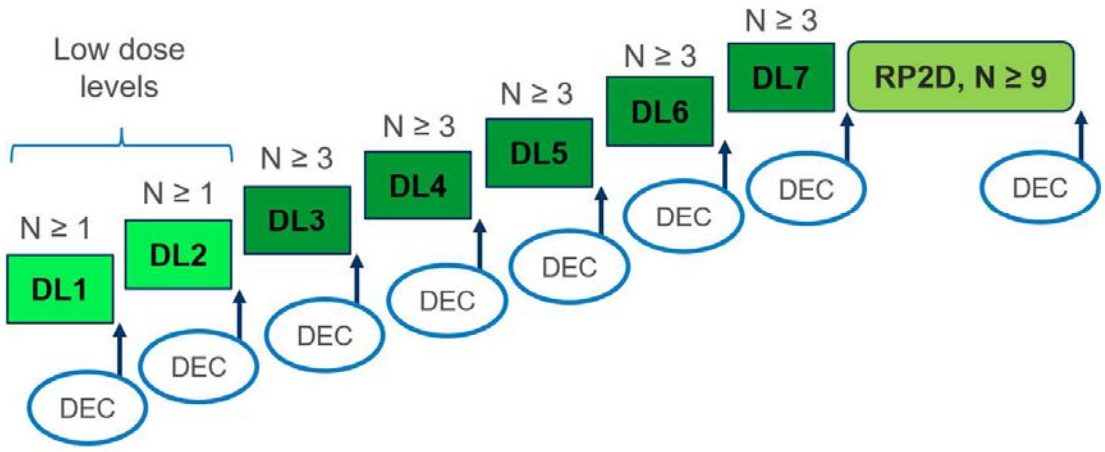


Figure 3 Trial design for 1467-0001

Abbreviations: DEC = dose escalation committee; DL = dose level; N = number of patients; RP2D = recommended Phase II dose.

Successive cohorts of patients will receive increasing doses of BI 1821736 until the MTD is reached. Incremental dose increases in successive cohorts will be approximatively [redacted] of the previous dose level but no more than [redacted] At least 1 patient will be treated at the low dose levels DL1 and DL2. From DL3 and above, all cohorts will include at least 3 patients (see also Section 4.1.2).

Dose-escalation will occur only if the minimum required number of patients per dose level are evaluable for DLT in the MTD evaluation period. The Dose Escalation Committee (DEC, see Section 8.7) may also recommend the size for the next dose escalation cohort or recommend expanding the size of the recruiting cohort.

If a DLT is observed in the first patient of a low-dose cohort (DL1, DL2), the DEC will decide on adding two additional patients to this cohort. In this case the BLRM will only be updated once the expanded cohort has been observed for DLT (at least 3 patients).

If DLTs are observed in the first two consecutive patients of a previously untested dose level (DL3 and above), subsequent enrollment to that cohort will be stopped. The BLRM will be re-run to confirm that the dose level still fulfils the EWOC criterion. Based on this information, the DEC will evaluate whether the next patients will be enrolled at the same dose level, or if they will be enrolled at a lower dose level.

After all patients in a cohort have either experienced a DLT or have been observed for at least the duration of the MTD evaluation period without experiencing a DLT, the BLRM will be updated with the newly accumulated data. The overdose risk will then be calculated for each potential dose, and dose escalation will be permitted to all doses which fulfil the EWOC criterion. At the end of each dose level, based on the model and on additional information (PK, patient profiles), the members of the DEC will reach a joint decision on the next dose level to be investigated. The DEC will also reach a decision on the size of the next cohort, which may be larger than the minimum specified above.

No further dose escalation will take place after the MTD is declared. Further patients may be included to confirm this MTD estimate, i.e. to confirm that the EWOC criterion is still fulfilled. The DEC can declare any dose fulfilling the EWOC criterion as the RP2D, independent of the MTD estimate. The RP2D will not exceed the MTD. Any DLTs occurring after the MTD evaluation period will be considered for the evaluation of the RP2D for BI 1821736. If no DLT is observed, the DEC may decide to declare the RP2D based on overall safety profile. Any available PK and biomarker data may also be considered for RP2D selection.

After definition of the MTD, at least 9 patients (including patients previously treated at this dose level) will be treated to better characterise the safety, first efficacy signals, pharmacokinetic evaluations and establish the RP2D based on all observations. If the MTD is not reached, the RP2D will be defined based on overall safety instead. This dose will be discussed and agreed by the DEC and the Sponsor.

Each patient will be followed up to 1 year after the last dose of BI 1821736, until death, lost to follow-up, withdrawal of consent or the end of the trial.

The end of the study (EoS) is defined as 1 year after the last patient has received the last dose of BI 1821736.

After the completion of dose escalation and the determination of the BI 1821736 [redacted]. MTD/RP2D, a [redacted] to further explore safety as well as initial efficacy of BI 1821736 in defined tumor types.

3.1.1 Sequential enrollment of patients

The first patient at DL1 (starting dose level) will complete the MTD observation period (Section 2.1.1). If the DEC decides that further patients are needed in that cohort (see Section 4.1.2), subsequent patients (2nd and 3rd) will start treatment at least 1 week apart. In case of DLT experienced by the first patient at DL1, and the DEC decide to expand the cohort, the 3rd patient will start treatment after the 2nd patient has completed the full MTD

evaluation period. Dose level 2 will follow the same sequential enrollment and MTD observation period as for DL1.

During recruitment of the next dose levels (DL3 and above), enrollment of the first, second, and third patient will be sequential. The first patient of each DLs will complete the MTD observation period before the next patient is dosed. The 2nd and 3rd patients will start treatment at least 1 week apart. If the decision is made that further patients are needed in a dose level, for example, due to DLTs (see Section 3.1.2 below), each subsequent patient will start treatment at least 1 week apart.

3.1.2 Enrollment stopping rules

All safety information will be carefully analyzed by the Sponsor and the DEC. Enrollment will be temporarily stopped if a clinically relevant adverse event occurs which meets both of the following criteria:

- associated with evidence suggesting a reasonable possibility that the investigational product caused the adverse event.
- occurs at a frequency or with severity that suggest that the benefit-risk profile of the investigational product should be reassessed.

Enrollment will also be temporarily stopped if either of the following criteria are met:

- A death occurring within 30 days from administration of the study drug unless clearly due to disease progression.
- A death at any time during the study period considered by the investigator or Sponsor as at least possibly related to the study drug.
- Occurrence of two Grade ≥4 DLTs occurring in two patients.

If the DEC determine that any of the above criteria are met, the enrollment to the trial will be temporarily stopped to allow for in-depth analysis of the safety profile of BI 1821736. The benefit-risk profile of BI 1821736 will be re-assessed by the DEC. This assessment will be used to determine if the trial should continue as planned, be permanently discontinued or whether the trial should continue with a modification to the protocol. The purpose of any modifications to the protocol will be to mitigate patient risk and ensure that the benefit-risk assessment for continued investigation of BI 1821736 remains positive. The DEC will also consider and provide guidance for the management of patients who are already receiving treatment. The outcome of the analysis and the recommendations will be shared with all involved regulatory health authorities prior to a planned re-start of enrollment. In case the benefit-risk assessment is no longer considered to be positive, the trial will be discontinued.

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

Dose escalation and cohort size will be determined by the DEC, guided by a BLRM with overdose control. An EWOC design will increase the chance of treating patients at efficacious doses while reducing the risk of overdosing. This design is based on practical experience and is an efficient method due to its ability to identify the dose with a desired toxicity rate and its allocation of a greater proportion of patients to doses at, or close to, that desired dose (R13-4802, R13-4804, R13-4805). The use of Bayesian models has also been

advocated by the EMA guideline on small populations (R07-4856) and for Phase I trials by the FDA (R13-4881).

This trial is a first-in-human trial in patients with advanced solid tumors. The open-label design of dose escalation will evaluate [redacted]. administration in advanced solid tumors in order to determine MTD and/or RP2D.

BI 1821736 is considered suitable for [redacted]. administration based of nonclinical investigations (c38438874). Tolerability is expected to be limited by increasing doses of BI 1821736, thus this trial aims to characterize the safety of dose range of VSV-GP CD80-Fc.

Up to [redacted] of BI 1821736 will be administered:

- The results of the [redacted] support the choice of a repeated treatment regimen instead of [redacted] approaches (c38438874).
- To assess the full therapeutic potential of BI 1821736 for patients suffering from cancer the repetitive treatments will stop after [redacted], which is [redacted] cycle after the latest anticipated occurrence of neutralizing antibodies based on data originating from the [redacted] with BI 1831169 (VSV-GP) in [redacted] dogs (n00279792). In addition, anti-drug antibodies (ADAs) have been described for several oncolytic viruses without any negative impact on safety and in some cases even improved efficacy (R20-0268).

The additional treatment ([redacted]) is based on the hypothesis that for [redacted], the addition of a second infusion prior to the immune system reaction will enhance the oncolytic effect. This hypothesis is backed by [redacted] treated with BI 1821736 on [redacted] and [redacted] compared to [redacted] on [redacted] only (c38438874).

3.3 SELECTION OF TRIAL POPULATION

Patients with advanced, unresectable and/or metastatic solid tumors who are refractory after standard therapy for the disease or for whom standard therapy is not appropriate will be eligible. It is anticipated that approximately 27 patients may be treated in this trial. The total number of patients will depend on the number of patients needed in each dose escalation. The trial will be conducted at sites in Europe and North America at approximately six sites.

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. During the dose escalation phase, Investigators will be regularly updated on available treatment slots and will be asked to provide details of any potentially eligible patients for the trial in order that allocation of patients to available lots can be done fairly (see also Section 4.1.3). Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial. Patients already in screening at this time will be allowed to continue to randomisation if eligible.

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 retrospectively it is found that a patient has been enrolled in error (did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment a decision will be made whether continued trial participation is possible or not.

Assessments may be repeated within the screening period if patients do not initially meet the inclusion/exclusion criteria. Eligibility must always be assessed using the latest results available. In addition, re-screening of patients who have previously failed screening will be permitted. In this situation patients will be handled as a new patient i.e. sign a new informed consent, allocated a new patient number, and undergo full screening assessments.

3.3.1 Main diagnosis for trial entry

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

The patient population for this trial includes patients with histologically confirmed advanced solid tumors. Patients must also have exhausted treatment options known to prolong survival for their disease.

3.3.2 Inclusion criteria

Patients will only be included in the trial if they meet all the following criteria:

1. Histologically confirmed diagnosis of malignant tumor.
2. Advanced, unresectable and/or metastatic or relapsed/refractory solid tumors.
3. Has failed conventional treatment or for whom no therapy of proven efficacy exists or who is not eligible for established treatment options. Patient must have exhausted available treatment options known to prolong survival for their disease.
4. Has at least one tumoral lesion which is amenable to biopsy.
5. Signed and dated, written informed consent form (ICF) in accordance with ICH-GCP and local legislation obtained prior to any trial-specific procedures, sampling, or analyses that are not part of normal standard of practice care.
6. Eastern Cooperative Oncology Group score of 0 or 1 (R01-0787).
7. Adequate organ function or bone marrow reserve defined as demonstrated at screening by the following laboratory values:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1.5 x 10^3/µL)(≥ 1500/mm^3); haemoglobin ≥ 90 g/L (≥ 9.0 g/dL)(≥ 5.6 mmol/L); platelets ≥ 100 x 10^9/L (≥ 100 x 10^3/µL)(≥ 100 x 10^3/mm^3) without the use of haematopoietic growth factors within 4 weeks of start of trial medication.
    b. Creatinine ≤ 1.5 times the upper limit of normal (ULN).
    c. Total bilirubin ≤ 1.5 times the ULN, except for patients with Gilbert's syndrome: total bilirubin ≤ 3 times ULN or direct bilirubin ≤ 1.5 times ULN.
    d. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3 times ULN if no demonstrable liver metastases, or otherwise ≤ 5 x ULN if transaminase elevation is attributable to liver metastases.

e. PT / aPTT <1.5 times ULN unless on a stable dose of an anticoagulant.

8. All toxicities related to previous anti-cancer therapies have resolved to ≤ CTCAE Grade 1 prior to trial treatment administration (except for alopecia and peripheral neuropathy which must be ≤ CTCAE Grade 2 and amenorrhea/menstrual disorders which can be any grade).
9. Patients ≥18 years of age or over the legal age of consent in countries where that is greater than 18 years at the time of signature of the ICF.
10. Life expectancy of ≥3 months after the start of patients' treatment according to the Investigator's judgement.Male or female patients. Women of childbearing potential (WOCBP)[1] and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria and instructions on the duration of their use is provided in the patient information and in Section 4.2.2.3.

3.3.3 Exclusion criteria

1. Major surgery (major according to the investigator's assessment) performed within 4 weeks prior to start of study treatment.
2. Previous treatment with VSV-based agents.
3. Patients with brain metastases unless they have completed brain radiotherapy and are asymptomatic.
4. Radiotherapy within 4 weeks prior to the start of study treatment, except in case of a brief course of palliative radiotherapy (e.g. for analgesic purpose or for lytic lesions at risk of fracture) which can then be completed within two weeks prior to start of study treatment. Note: No radiation must have been given to any lesions planned to be biopsied within 6 months of start of treatment.
5. Prior (within 3 weeks of first dose) or concomitant use of systemic corticosteroids (>10 mg daily prednisone or equivalent).
6. Prior (within 3 weeks of first dose or less than 5 half-lives) or concomitant use of a medication or a condition considered a high risk for complications from biopsy as per the Investigator's judgement.
7. Prior (within 3 weeks of first dose or less than 5 half-lives) or concomitant use of interferon, immunotherapy agents, or tamoxifen.
8. Active infection requiring systemic therapy (antibacterial, antiviral, antiparasitic or antifungal therapy) at the start of treatment in the trial.
9. Active hepatitis B or C infection e.g. hepatitis B surface antigen (HBsAg) positive, or hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative), which in the opinion of the Investigator may interfere with participation in the trial.
10. Patients with history of human immunodeficiency virus (HIV) infection who meet one or more of the following criteria:
    a. CD4+ count <350 cells/µL.

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

b. Viral load >400 copies/µL (local laboratory assessment).
c. Not receiving antiretroviral therapy.
d. Receiving established antiretroviral therapy for less than four weeks prior to the start of study treatment.
e. History of AIDS-defining opportunistic infections within 12 months prior to start of study treatment.

Patients with a history of HIV who do not meet any of the criteria above are eligible to participate but the patient must be under the care of a HIV/Infectious Disease specialist, or an HIV/Infectious Disease specialist must be consulted prior to inclusion.

11. Any severe or serious, acute or chronic medical or psychiatric condition or laboratory abnormality as per Investigator's judgement that may increase the risk associated with study participation or study drug administration, including ongoing or active infection requiring systemic antibiotics.
12. History of allergy or hypersensitivity to study agent components.
13. History of primary immunodeficiencies, history of allogenic organ transplant, history of interstitial lung disease.
14. Patients with an active known or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
15. Any documented history of prior malignancy within 5 years prior to screening, with the exception of appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix, or other local tumors considered cured by local treatment.
16. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
17. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable trial participant).
18. Currently enrolled in another investigational device or drug trial, or less than 28 days since ending another investigational device or drug trial(s) or receiving other investigational treatment(s).
19. Women who are pregnant, nursing, or who plan to become pregnant while in the trial or within 6 months after the last dose of study treatment.
20. Patients with a confirmed active infection/positive test with SARS-CoV-2 (as confirmed by PCR or antigen test, see Section 5.2.5.2) and still positive by PCR or antigen test 2 weeks before the first dose.
21. Live vaccines within 4 weeks of first dose.
22. Patients with cardiac risks including congestive heart failure (as defined by New York Heart Association Functional Classification III or IV), unstable angina, serious uncontrolled cardiac arrhythmia, a myocardial infarction within 6 months of first dose of study treatment or a history of myocarditis.

3.3.4 Discontinuation of patients from treatment or assessments

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

However, if the patient agrees, they should stay in the trial. Even if continued trial treatment is not possible, they should attend further trial visits to ensure their safety and to collect important trial data. Should the patient not agree, at least phone contacts should occur at the scheduled visit time points, should that not be acceptable, a phone contact every 9 weeks (+/- 3 weeks) should occur to collect the most relevant information: adverse events, or last contact date in case of lost to follow-up.

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

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and eCRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Section 5.2.6.2).
Ideally, the patient should attend all remaining visits.

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient experiences DLT(s).
- The patient experiences an unacceptable adverse event. Refer to Section 4.2.3 for treatment related AEs that require discontinuation.
- The patient experiences disease progression. If tumor assessment done at [redacted] documents a disease progression according to RECIST version 1.1, the patient may be allowed to continue the study treatment only in the case where of all the following criteria are met:
    - Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease,
    - Absence of decline in ECOG performance status that is judged to be attributed to disease progression,
    - Absence of tumor progression at critical anatomical sites (e.g. leptomeningeal disease) requiring urgent alternative medical intervention, and
    - Absence of significant, unacceptable or irreversible toxicities related to study treatment.
- The patient wants to discontinue trial treatment. The patient will be asked to explain the reasons but has the right to refuse to answer.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, the safety of the patient cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.

- The patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.
- The patient needs to take concomitant medication that interferes with the safety of the investigational medicinal product or other trial treatment. Refer to Section 4.2.2.1 for prohibited concomitant medications.
- The patient experiences an infection with SARS-CoV-2. The patient may resume trial treatment following recovery from SARS-CoV-2 infection if the patient is expected to derive clinical benefit, as agreed between the Investigator and Sponsor in line with Section 4.1.4.3.
- The patient becomes pregnant. The study treatment must be immediately stopped, and the patient will be followed up until delivery or termination of pregnancy (Section 5.2.6.2.3 for information on pregnancy forms). The data of the patient will be collected and reported in the electronic case report form (eCRF) until the last patient's last visit and any events occurring thereafter will be reported in the BI drug safety database.

In case of a temporary reason for trial treatment interruption, trial treatment may be restarted if medically justified, please see Section 4.1.4.3.

If new efficacy / safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

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

3.3.4.1.1 Replacement of patients during dose escalation

Patients will be considered non-evaluable for MTD determination in the following circumstances:

- Patient withdrawal for a reason other than DLT before completing the MTD evaluation period
- Patient who does not receive the full planned dose (i.e. <90%) in the MTD evaluation period and does not experience a DLT
- Patient who misses more than one visit during the MTD evaluation period
- Patients who miss one visit during the MTD evaluation period may be considered non-evaluable after discussion between the Sponsor and the Investigator if the information that needs to be collected during this visit is not available and makes the patient non-evaluable for determining DLT.

Non-evaluable patients will be replaced and not included in the primary analysis model whenever additional patients are required in order to ensure there are a sufficient number of evaluable patients in a cohort. All safety data, including adverse events reported in patients who are replaced, will be taken into account when determining dose escalation steps.
All other patients who withdraw, including all patients who are withdrawn from the trial due to a DLT, and all patients who withdraw after the MTD evaluation period will not be replaced.

3.3.4.2 Withdrawal of consent to trial participation

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

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrollment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see Section 3.3.4.1.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.
4. The Sponsor reserves the right to discontinue trial for strategic reasons (e.g. stop of development).

Further treatment and follow up of patients affected will occur as described in Section 3.3.4.1.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are given below in Table 2.

Table 2 Test product

Substance:	BI 1821736
Pharmaceutical formulation:	Solution for [redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	[redacted]
Posology:	Day 1 of a [redacted] plus [redacted] of cycle 1
Mode of administration:	[redacted]

Refer to instructions for the preparation and administration of BI 1821736 in the ISF.

4.1.2 Selection of doses in the trial and dose modifications

The recommended starting dose (RSD) of BI 1821736 for the first-in-human (FIH) clinical trial was selected based on [redacted] originating from [redacted] conducted in the highly susceptible [redacted] c39811008). The regression analyses revealed a [redacted] at a dose of [redacted] (c39811008). Based on the Guidance for Industry "Estimating the Maximum Safe Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" of July 2005, dose/kg was considered for scaling between species (https://www.fda.gov/media/106900/download). Considering an average body weight of 20 g for [redacted] and 60 kg for humans, a dose of [redacted] in the [redacted] corresponds to a human dose of [redacted].

The anticipated starting dose was lowered to [redacted]. Clinical safety data from [redacted] administration of BI 1831169 (VSV-GP) at [redacted] and clinical safety data from [redacted]. administration of VSV-GP128 at [redacted] are available supporting the lowered starting dose of [redacted] This starting dose is supported by the toxicology data as the NOAEL following a concomitant [redacted]. administration was [redacted], which is [redacted] higher than the starting dose of [redacted]) for the [redacted]. route in the FIH trial adjusted on a body weight basis. For further details refer to the BI 1821736 Investigator's Brochure (c38438874). Once the starting dose level has been determined safe, the dose of BI 1821736 is planned to be escalated as shown in Table 3.

Table 3 Dose escalation of BI 1821736

Planned Dose level (DL)	**BI 1821736 Total dose** [redacted]
1 (starting DL)	[redacted]
2	
3	
4	
5	
[redacted]	
7	

The chosen starting dose is [redacted] (DL1).

At least 1 patient will be treated at the low dose levels (DL1, DL2). At the end of the MTD evaluation period, the DEC will decide if two additional patients need to be treated at the same dose level if the first patient experiences a BI 1821736 related AE Grade ≥2 (including DLT) during the MTD evaluation period. In the event that no BI 1821736 related AE Grade ≥2 is observed during the MTD evaluation period, the DEC may decide to escalate to the next dose level. In case DL1 has to be expanded, at least 3 patients will be treated at DL2.

From DL3 onwards, cohorts of at least 3 patients will be enrolled at escalating dose levels.

At the end of the MTD evaluation period in each treatment cohort, BI will convene a meeting with the DEC members. At this meeting, the clinical course (safety information including both DLTs and all AEs during the MTD evaluation period, all available PK and pharmacodynamic biomarker data (if needed), for each patient in the current dose cohort will be reviewed. Updated safety data on other ongoing patients, including data beyond the MTD evaluation period, will be reviewed as well. Based on that, a decision on the next dose level to be explored is made. Incremental dose increases in successive cohorts will be no more than [redacted]-fold of the previous dose level. Dose escalation will continue until identification of the MTD or RP2D in case no MTD is established, safety concerns arise, or the trial is terminated for other reasons.

Additional/intermediate dose levels can be explored at the decision of the DEC as long as they fulfil the EWOC criterion.

4.1.3 Method of assigning patients to treatment groups

There will be no randomisation in this trial, as it is a single-arm open-label trial. At any time during the trial, a single dose cohort will be open for recruitment and each patient will be allocated to the next available dose cohort.
The appropriate medication number will be assigned and documented in the eCRF.

4.1.4 Drug assignment and administration of doses for each patient

Each patient will receive the appropriate dose for their assigned dose cohort. Medication will be assigned via Interactive Response Technology (IRT) for each treatment cycle. Each medication vial will have a unique medication number.
BI 1821736 will be prepared, handled and administered according to the "Instructions for preparation and administration of BI 1821736", which will be filed in the ISF. BI 1821736 and the [redacted] of BI 1821736 will be provided by BI.

Upon notification that a patient will be treated in the trial, the trial drug will be prepared at the assigned dosage for administration to the patient, as provided by the IRT system.
BI 1821736 will be [redacted] so that each patient will receive the appropriate dose for their assigned dose level.

BI 1821736 will be given as an [redacted]. Administration of [redacted]. doses will be given by authorized staff in a specialized unit where emergency care can be provided (e.g. intensive care unit available, medical personnel trained in advanced life support). Supportive anaesthesia should be given as per local institution standards. No routine premedication will be required for BI 1821736.

BI 1821736 is administered in [redacted]-day treatment cycles. [redacted] cycles of therapy are planned as noted in Figure 4 below. In the first cycle BI 1821736 will be administered on Day 1 and Day [redacted] In each of the following cycles BI 1821736 will be administered on Day [redacted] with a total of [redacted] administrations.

[redacted]

The [redacted]. infusion should be administered using a [redacted] over a period of approximately [redacted]. The maximum [redacted] duration including the interruption time, the [redacted] rate and storage conditions are indicated in the ISF.

4.1.4.1 Observation period for CRS/IRR

Close monitoring of the patient during and after treatment with BI 1821736 is required for early detection/management of CRS and IRRs. Monitoring will include measurement of body temperature, pulse oximetry, pulse rate, and blood pressure as well as assessment of pain and

observation [redacted] (where applicable). Observations following the treatment should be performed according to Table 11 for at least the minimum times suggested or until vital signs are stable, whichever is longer. The following measures are mandatory:

- [redacted] to the individual patient: Hospitalization with access to intensive care unit for at least 24 hrs after end of administration. A longer hospitalization period may be decided by the Investigator based on the patient's condition.
- At subsequent administrations to the individual patient: If no IRR or CRS occurred following the initial 3 administrations, an observation period and vital sign monitoring of 6 hrs in the hospital will suffice after the completion of BI 1821736 treatment.

In case of CRS/IRR, refer to CRS/IRR management guidance in Section 4.2.3.1 (Table 4 and Table 5). The monitoring period for subsequent infusions should be extended following the guidance above, re-starting as if for the first administration.

Any additional diagnostic measures need to be implemented as medically appropriate.

4.1.4.2 Criteria for receiving further treatment

Before administering treatment at the next dosing visit the Investigator must review the assessments performed according to the Flow Chart and check that the following criteria are met:

- Treatment related adverse events have resolved to CTCAE Grade 1 (or baseline if higher than Grade 1)
- Recovery from CRS or other IRR at least 24 h prior to next administration of trial medication (in accordance with the recommendations in Section 4.2.3)
- Decreased neutrophils and platelets have resolved to CTCAE Grade ≤1
- Increased AST, ALT and bilirubin have resolved to CTCAE Grade ≤1 (or baseline if higher than Grade 1 at baseline)

If the above criteria are not met but the patient is recovering, the patient should continue to be assessed regularly and the next dose of treatment may be delayed up to 2 weeks (see Section 4.1.4.3) until the criteria are met.

Treatment interruption due to unrelated adverse events is allowed if agreed between Sponsor and Investigator (see Section 4.1.4.3).

4.1.4.3 Guidance for temporary treatment interruptions and dose reductions for BI 1821736

Dose reductions of BI 1821736 in any patient are not allowed.

In the case that the patient does not meet the re-treatment criteria in Section 4.1.4.2 above, and to permit recovery from adverse events (both related and unrelated), treatment will be paused according to the rules below:

BI 1821736 must be given on Day [redacted] of the given cycle (with additional dose on Day [redacted] of Cycle [redacted]). It may be paused and interrupted according to the following rules:

- For all doses other than Cycle [redacted] Day [redacted] dose: BI 1821736 may be paused for up to 2 weeks to permit recovery to the requirements as per Section 4.1.4.2. If a patient has not recovered to CTCAE Grade ≤ 1 or baseline within 14 days, continuation of treatment should be discussed with the Sponsor. If the patient is deriving obvious clinical benefit according to the Investigator's judgement, continuation of treatment will be decided by the Sponsor and the Investigator.
- Cycle [redacted] Day [redacted] dose: If the patient is not able to receive the Day [redacted] dose by Day [redacted] they must be withdrawn from the treatment.

Note: In case cycles are delayed due to adverse events or scheduling, the imaging schedule should remain per the original plan and not be delayed.

4.1.5 Blinding and procedures for unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated Contract Research Organisation (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply of BI 1821736, [redacted] BI 1821736 to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites. For BI 1821736 the expiry date will be omitted on primary packaging due to small unit size. The investigator name and patient information will be omitted from the label as they are recorded in the IRT System. The "Keep out of reach of children" statement is omitted from the label due to the fact that the medication stays on site. For details of packaging and the description of the label(s), refer to the ISF.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site,

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

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

All concomitant therapy, including pre-medication, anaesthetic agents, vitamins, and nutritional supplements, must be recorded in the eCRF along with the reason for the treatment, starting from the date of signature of informed consent until the EOT visit. Between the EOT visit and the individual's patients EoS, only concomitant therapy indicated for treatment of a related AE has to be reported.

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. Rescue medications to reverse the effects of BI 1821736 are not available. Adverse events should be treated symptomatically and must be recorded. Concomitant medications or therapy to provide adequate supportive care may be given as clinically necessary.

Use of inhaled, topical, intraocular, intranasal corticosteroids or local steroid injections (e.g. intra-articular injection) are permitted. Brief/temporary (up to 48 h) use of corticosteroids for concurrent illnesses (e.g. food allergies, computed tomography (CT) scan contrast hypersensitivity) are acceptable.

Palliative radiotherapy is allowed after the start of Cycle [redacted] provided that the reason for radiotherapy does not reflect radiologic disease progression requiring discontinuation and does not interfere with response assessment. Lesions that have been exposed to radiotherapy

are no longer evaluable as target lesions and may not be included in the imaging-based response assessment of target lesions.

Supportive care for disease-related symptoms may be offered to all patients on the trial.

4.2.1.1 Premedication

No pre-medication is required to start BI 1821736 treatment. In case patient experiences IRRs or CRS Grade 2, premedication is recommended for further BI 1821736 treatments (see Table 4 and Table 5).
If applicable, the DEC can recommend appropriate mandatory premedication to all subsequent patients at any dose level in the respective regimen. This DEC decision will be communicated to all participating investigators via an Investigators' letter.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Unless otherwise stated the following medications are prohibited from 3 weeks of first dose, during all the study treatment period (up to EOT visit):

- Tamoxifen
- Immunosuppressive agents, (e.g. methotrexate, azathioprine, and tumor necrosis factor-alpha blockers)
- Immunosuppressive doses of systemic corticosteroids (doses exceeding 10 mg/day of prednisone or equivalent) are prohibited (except as stated in Section 4.2.1).
- Any other investigational therapy or anti-cancer agent. If such agents are required for a patient, then the patient must first be withdrawn from the trial. Patients will be allowed to continue prior luteinizing hormone-releasing hormone (LHRH) agonist/antagonist therapy. Patients on bisphosphonates (e.g. zoledronic acid) or denosumab will also be permitted to continue treatment.
- Concomitant use of interferon or other immunotherapy regimens
- Concomitant use of oral anticoagulants or platelet aggregation inhibitors are only permitted if biopsies are performed in the skin or subcutaneous tissue. In the case that biopsies of any other superficial location are planned, the oral anticoagulation treatment will be changed to heparin and paused as medically appropriate to minimize the bleeding risk. Post-interventional re-start of anticoagulants or platelet aggregation inhibitors should be based on institutional standards. Patients with a high risk for thromboembolic events related to interruption of anticoagulant or antiplatelet therapy should not be treated in this trial.
- Live vaccines (within 4 weeks of first dose).
- Herbal preparations/medications are not allowed throughout the trial. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using herbal medications at least 14 days prior to first dose.
- Palliative radiotherapy is not permitted during the first cycle of treatment as it could interfere with the DLT evaluation (see Section 4.2.1 for allowable radiotherapy.)

Palliative radiotherapy is allowed after the start of Cycle 2 provided that the reason for radiotherapy does not reflect radiologic disease progression.

4.2.2.2 Restrictions on diet and lifestyle

Any restrictions on diet that were already applicable for a given patient before entry into the trial should be continued, if feasible. In order to avoid potential transmission of the virus to other people or the environment, patients should adhere to the following guidance (R21-2043):

From [redacted] to End of Treatment Visit:

- Wash hands frequently with soap and water or alcohol-based products.
- Patients with respiratory syndrome (e.g. runny nose, cough) should avoid crowded or poorly ventilated public places and, where applicable avoid contact with susceptible animals (e.g. farm animals) or pets.
- Ensure that all surface infusion sites or any open wounds are covered with an airtight and watertight dressing until the wound site has healed and avoid scratching infusion sites.
- Ensure that gloves are worn when changing dressing(s) to ensure that the patient and close contacts do not come in direct contact with any of the dressings or infusion sites.
- Collect any potentially soiled waste (e.g. bandages, plasters/Band-Aids, sanitary pads, tampons), store separately in a sealed plastic bag, and bring back to the hospital to be destroyed, following the hospital's infectious waste management protocol.
- Do not donate organs, tissues, cells, blood or blood plasma for the duration of study participation and for 6 weeks after last treatment of BI 1821736.

For 10 days following each treatment of BI 1821736:

- Cover mouth and nose while coughing or sneezing with a single-use tissue and dispose the tissues after use.
- Avoid close contact with young children, pregnant women, immuno-compromised people and livestock (e.g. pigs, cows, horses, rodents, etc.). When unavoidable, a surgical grade mask (FFP1) should be worn when within touching distance.
- Ensure infusion site or any bodily fluids (including transmission via kissing) do not come into direct contact with any close contacts.
- Store any soiled clothing separately from any other people living in the same accommodation. Wash any clothes, household linens, cleaning cloths etc. at either 60ºC (140ºF) or using a washing detergent on a regular basis.
- Clean home on a regular basis with standard household cleaners, particularly areas where shedding from bodily fluids occurs.
- Where possible use a separate toilet, adding bleach or equivalent products to the toilet after each use, with no sharing of utensils such as towels.
- Avoid sharing of any items such as cutlery, crockery, drinking vessels, razorblades or toothbrushes which may allow transmission of body fluids to close contacts. (Note: once washed with soap or detergent, such objects can be used by other people).
- Shower or bathe daily.

- As no study has been performed to assess shedding in genital fluids, sexual intercourse should be avoided for the 10 days following each treatment with BI 1821736.

See also Appendix 10.3 for details on patient restrictions while at the trial site.

4.2.2.3 Contraception requirements

WOCBP (for the definition please refer to Section 3.3.2) and men able to father a child must use two medically approved methods of birth control throughout the trial, and for a period of at least 6 months after last trial drug intake, one barrier method (i.e. condom), and one highly effective non-barrier method.

Male trial participants or male partner of trial participants that are vasectomized should be surgically sterile with a documented absence of sperm at least 6 months prior to the first study drug administration. They must still use a condom, even if vasectomized, provided it has been 10 days since last BI 1821736 administration, irrespective of their partner's possibility of conception.

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

These methods include:
- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable).
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.

Or

Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

Females *not of childbearing potential* must have evidence of such by fulfilling one of the following criteria at screening:
- Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy
- Post-menopausal: defined as more than 50 years-of-age and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
- Women under 50 years-of-age would be considered postmenopausal if they have been amenorrhoeic for at least 12 months following the cessation of exogenous hormonal treatments and have serum follicle-stimulating hormone and luteinizing hormone levels in the postmenopausal range for the institution.

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

4.2.3 Management of adverse events

4.2.3.1 Management of CRS, other IRRs and events with similar signs/symptoms

Cytokine release syndrome (CRS) could potentially occur with BI 1821736. CRS is a supra-physiologic response following any therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, include fever at the onset, and may include hypotension, hypoxia, capillary leak syndrome and end organ dysfunction. Other signs/symptoms of CRS can be for example tachypnea, headache, tachycardia, rash, nausea, vomiting, increased transaminases, and increased bilirubin. CRS can be serious or life threatening.

CRS signs/symptoms may occur quickly during or after administration, or after several hours or few days. Occurrence of such signs/symptoms temporally related to administration of trial medication, requires immediate management and rapid diagnosis to avoid severe complications. The manifestations of CRS overlap with those of other types of IRRs, infection, capillary leak syndrome and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). IRRs can be allergic or non-allergic (due to release of histamine or cytokines, respectively). Mixed type reactions may occur. CRS, other IRRs and events with similar signs/symptoms are difficult to distinguish.

In case of CRS, other IRRs, or events with similar signs/symptoms, appropriate measures depending on the type and severity of the reaction should be taken by the Investigator according to international recommendations (R19-0311, R20-2020), best medical judgement, and local guidelines. Supportive therapy including administration of Interleukin 6 receptor (IL6R) antagonists and steroids should be used as clinically indicated.

Appropriate drugs and medical equipment to treat CRS, other IRRs and events with similar signs/symptoms, must be immediately available, and trial personnel must be trained to recognize and treat such events. The trial site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit, if necessary. The recommendations for the treatment of CRS and other IRRs are provided in Table 4 (CRS) and Table 5 (Other IRRs) below.

Safety laboratory testing for CRS may be done as detailed in Section 5.2.5.1.

Table 4 Recommendations for the management of CRS

CTC AE Grade	Description of severity	Management of current admin. of BI 1821736	Minimum treatment intervention	Management of BI 1821736 at next administration
1	CRS: Fever with or without constitutional symptoms	• Consider temporary interruption or reduced [redacted] if not fully administered.	• Acetaminophen / paracetamol as needed • IV fluids as needed • Assess for infection with blood and urine cultures, further diagnostic methods as needed • Consider IL-6 antagonist or corticosteroid for persistent or refractory fever	• Continue treatment with the subsequent administration of BI 1821736 provided that all symptoms have completely resolved for at least 24 hrs • Delay/skip the subsequent administration if needed to ensure that all symptoms have completely resolved for at least 24 hrs
2	CRS: Hypotension responding to fluids; hypoxia responding to <40% O_2	• Interrupt treatment if not fully administered. • Restart using premedication once recovery to baseline so long as within maximum stability time of BI 1821736 • Use reduced [redacted].	• IV fluid bolus to maintain systolic blood pressure greater than 90 mmHg (up to 2 boluses) • If hypotension persists after two fluid boluses, administer IL-6 antagonist, start vasopressor and transfer patient to ICU • Use supplemental oxygen as needed to maintain oxygen saturation above 90% • If hypoxia persist below 90% saturation, administer IL-6 antagonist and transfer patient to ICU • Consider early administration of IL-6 antagonist together with i.v. fluids for high risk patient (e.g. co-morbidities or older age) • Manage fever and assess for infections as in Grade 1	• Continue treatment with the subsequent administration of BI 1821736 provided that all symptoms have completely resolved for at least 24 hrs • Delay/skip the subsequent administration if needed to ensure that all symptoms have completely resolved for at least 24 hrs • At subsequent administration of the respective drug, patients should be under close surveillance of appropriate duration • Use premedication

Table. 4 contd. Recommendations for the management of CRS

CTC AE Grade	Description of severity	Management of current admin. of BI 1821736	Minimum treatment intervention	Management of BI 1821736 at next administration
3	CRS: Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2	• Stop administration • Do not re-start	• Transfer patient to ICU • Initiate hemodynamic monitoring • Use fluid boluses and vasopressors as needed • Use supplemental oxygen with appropriate breathing device as needed to maintain oxygen saturation above 90% • Use IL-6 antagonist or steroids • Manage fever and assess for infections as in Grade 1	• Permanently discontinue BI 1821736
4	CRS: Life-threatening consequences; urgent intervention indicated	• Stop administration • Do not re-start	• ICU transfer, hemodynamic monitoring, IV fluids, vasopressors, IL-6 antagonist or steroid as indicated for Grade 3 • Start high dose methylprednisolone or equivalent • Use mechanical ventilation as needed • Manage fever and assess for infections as in Grade 1 CRS • Symptomatic management of organ toxicity as per local guidelines	• Permanently discontinue BI 1821736

Table 5 Recommendations for the management of other IRRs

CTC AE Grade	Description of severity	Management of current admin. of BI 1821736	Minimum treatment intervention	Management of BI 1821736 at next admin
1	IRR: Mild transient reaction; [redacted] interruption not indicated; intervention not indicated	• Consider temporary interruption or reduced [redacted].	• None	• Continue at the same dose level
2	IRR: Therapy or [redacted] interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	• If ≥ 50% of planned dose of BI 1821736 was administered, no further treatment will be administered until next scheduled dose. • If < 50% of planned dose of BI 1821736 was administered due to IRR, a further dose of 50% of the intended total dose may be administered on the following day and after recovery to baseline for at least 24 hrs. • During the first re-exposure patients should be hospitalized for at least 24 hrs and closely monitored.	• Symptomatic treatment with e.g. anti-histamines (H1 and H2 antagonists), acetaminophen / paracetamol, corticosteroids	• Continue at the same dose level at reduced [redacted] • During the first re-exposure patients should be hospitalized for at least 24 hrs and closely monitored. • For subsequent treatment cycles consider premedication including a steroid according to Section 4.2.1.1

Table. 5 contd. Recommendations for the management of IRRs

CTC AE Grade	Description of severity	Management of current admin. of BI 1821736	Minimum treatment intervention	Management of BI 1821736 at next admin
3	IRR: Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption [redacted]); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	• Stop [redacted] Do not re-start [redacted]	• Treatment with antihistamines (H1 and H2 antagonists) and high dose glucocorticoid • Monitoring over 24 hrs after recovery because of the risk for a biphasic reaction • In addition, if anaphylaxis is suspected: • Treat patient immediately with epinephrine • Volume resuscitation • Supplemental oxygen and /or bronchodilator , if needed	• Permanently discontinue BI 1821736
4	IRR: Life-threatening consequences; urgent intervention indicated	• Stop [redacted] Do not re-start [redacted]	• Treatment with antihistamines, glucocorticoid, and / or treatment of anaphylaxis as indicated for Grade 3 • Use other vasopressors, glucagon and / or atropine as clinically indicated	• Permanently discontinue BI 1821736

4.2.3.2 Management of Tumor Lysis Syndrome (TLS)

Appropriate monitoring should be performed to proactively manage the onset of TLS. In case of clinical or biological signs of TLS treatment must be initiated immediately according to local standards.

4.3 TREATMENT COMPLIANCE

BI 1821736 will be administered as [redacted] at the clinical site under the supervision of trained site personnel. Therefore, actual dosing is expected to follow the protocol. The dose administered will be recorded in the eCRF and any irregularities in dosing will also be documented in the eCRF by the Investigator or designee.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Tumor response will be evaluated at the site according to Response Evaluation Criteria in solid tumors (RECIST version 1.1). The assessment by the Investigator and/or the local radiologist will be the one basis for continuation or discontinuation of the trial in an individual patient (in addition to safety).

Tumor assessments should include computed tomography (CT) scans or magnetic resonance imaging (MRI) of suspected sites.

Baseline imaging should include imaging of all known or suspected sites of disease using an appropriate method. The baseline imaging must have been performed within 4 weeks prior to treatment with the trial medication and the Investigator will record the target and non-target lesions in the eCRF. The same method of assessment and the same imaging technique must be used at each subsequent time point to characterize each reported lesion throughout treatment and during follow-up. A lesion in a previously irradiated area cannot be selected as a target lesion at baseline unless there is a documented progression and more than 6 months has passed since the completion of the radiotherapy. A lesion that is biopsied cannot be selected as a target lesion.

Tumor assessment will be performed at the time points indicated in the Flow Chart. In the case that there is an interruption or delay to treatment, the tumor assessment schedule should remain as originally planned (prior to/at [redacted] at EOT visit and then every 9 weeks ± 3 weeks from EOT for patients without progression at the EOT visit, thereafter until progression) Note: In case visit windows are used, visits should always be recalculated back to original to schedule based on [redacted] Additional unscheduled tumor assessments may be performed at the discretion of the Investigator. [redacted]-documentation of any applicable lesions will be taken at the same time points as imaging.

If the patient stops trial medication for a reason other than progression, tumor assessment according to RECIST version 1.1 will continue until progression (or until one of the following occurs: death, lost to follow-up, end of study).

Treatment will be discontinued when a patient is considered to have progressive disease according to RECIST version 1.1 (PD) (see Section 3.3.4.1 for exceptions). In case a patient continues study treatment after disease progression at [redacted] the next tumor assessment will be at the EOT visit.

Copies of images, as well as [redacted]-documentation of lesions collected during this study may be sent to a central imaging facility of an independent CRO where they will be stored for up to 30 years. During this time, if needed, an independent assessment of tumor response may be performed but individual results will not routinely be reported to Investigators and will not influence treatment or medical decisions while the patient is participating in this trial. Clinical imaging data acquired in this trial might also be analyzed further to build diagnostic, prognostic and predictive models using radiomics. This exploratory analysis might be performed in collaboration with an independent third party nominated by the Sponsor.

5.2 ASSESSMENT OF SAFETY

All patients will be required to stay overnight following their first treatments on Cycle 1 [redacted], Cycle 1 [redacted], and Cycle 2 [redacted] for observation and collection of PK and shedding samples. Standard isolation safety precautions, including those for handling and disposal of patient waste materials, will be implemented during the admission (see Appendix 10.3 for details). In the case that any viral shedding is seen above a certain threshold during these first [redacted], patients may be requested to stay overnight for subsequent cycles (see Footnote 3 of Flow Chart).

5.2.1 Physical examination

A physical examination as well as an evaluation of the ECOG performance score (see Appendix 10.5) will be performed at time points as indicated in the Flow Chart.

A physical examination serves as a clinical tumor assessment and should include at minimum a cardiovascular examination, neurological examination (when indicated), examination of regional lymph nodes, general appearance, head/neck, lungs, abdomen, extremities, and skin. Additional symptoms which have not been reported during a previous examination should be clarified. Whenever possible the same Investigator should perform this examination. Measurement of height (in cm at screening visit only) and body weight (in kg on day 1 of each cycle only) should be included. The results of all procedures must be included in the source notes available at the site.

5.2.2 Vital signs

Vital signs (body temperature, pulse oximetry, systolic and diastolic blood pressure and pulse rate after 5 minutes of supine or semi-recumbent rest) will be recorded at the time points specified in the Flow Chart. They should be taken prior to blood sampling with the exception of the routine safety labs (haematology and biochemistry), which may be obtained prior to the vital signs if obtained on the same day as study drug administration, provided at least 10 minutes has passed before the vital signs are taken. The results must be included in the source documents available at the site.

In addition to the vital signs taken pre-treatment, additional vital signs must be taken during or following study drug administration (see Section 4.1.4.1 and Appendix 10.2 for details). In case of CRS/IRR the recommendations in Section 4.2.3.1 should be followed.

5.2.3 Safety laboratory parameters

Safety laboratory parameters will be analyzed at a local laboratory. Safety laboratory parameters to be assessed are listed in Table 6 and should be obtained at the time points specified in the Flow Chart. Patients are not required to be fasting. Screening laboratory assessments performed within 7 days of the first trial treatment administration are not required to be repeated on Cycle 1 [redacted] At subsequent visits, safety laboratory should be performed within 72 hrs of the visit.

Table 6 Safety laboratory tests

Functional lab group	Test name
Haematology	Haemoglobin White blood cells (WBC) Platelet count
Automatic WBC differential (absolute)	Neutrophils Lymphocytes Eosinophils Basophils Monocytes
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin Time (PT)
Enzymes	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase (AP) Gammaglutamyl transferase (GGT) Creatine kinase (CK) Amylase Lipase
Substrates	Glucose Creatinine Uric Acid Total bilirubin Direct bilirubin Total protein Albumin Ferritin
Electrolytes	Calcium Sodium Potassium Chloride Phosphate
Serum Pregnancy test (only for female subjects of childbearing potential) at screening within 14 days of [redacted] within 24 hrs of [redacted] and within 72 hrs of Day 1 of subsequent cycles and if urine pregnancy test is positive	Human Serum Chorionic Gonadotropin
Urine Pregnancy test (only for female subjects of childbearing potential) at EOT	Human Chorionic Gonadotropin in the urine
Urinalysis (qualitative determination). In case of pathological urinalysis findings, further evaluation should be performed, and results documented.	Urine protein Urine glucose Urine haemoglobin (detects erythrocytes) Urine leukocyte esterase (detects leucocytes) Urine pH

Table 6 contd. Safety laboratory tests

Functional lab group	Test name
Infectious Disease (Screening only)	Hepatitis B surface antigen (HBsAg), Hepatitis C (HCV antibody or HCV RNA), HIV and LCMV. Results obtained in routine diagnostics are acceptable if done within 56 days before the first treatment.

It is the responsibility of the Investigator to evaluate laboratory values prior to treating patients as well as evaluating all laboratory reports performed at other time points. In case a treatment cycle is delayed due to a laboratory abnormality or urgency, the patient should repeat laboratory testing weekly or more frequently per the Investigator's judgement. More frequent visits may be appropriate as assessed by the Investigator. Any abnormal and clinically relevant findings from these investigations will be reported as an adverse event.

Additional parameters may be measured if they are part of the standard panel of the institution laboratory, or the Sponsor and Investigator may discuss and agree that individual parameters will not be measured if they are not part of the standard panel of the institution laboratory. The Investigator should complete additional evaluations of laboratory tests as clinically indicated. Any abnormal and clinically relevant finding from these investigations will be reported as an Adverse Event.

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

5.2.4 Electrocardiogram

Triplicate 12-lead resting ECGs will be administered by a qualified technologist and be digitally recorded at various time points throughout the trial as per the Flow Chart. ECGs will be obtained after the patient has been resting supine or semi-recumbent for at least 5 minutes by a qualified technologist prior to the indicated times. The Investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. Details of timings of ECGs are provided in Appendix 10.1.

Electrocardiogram machines will be provided for the trial to facilitate central readings. Before study start, the study sites will be trained for the proper use of the equipment and transfer of the electronic data to the vendor. All ECGs will be transmitted to the central vendor (where they will be stored for up to 30 years) for central evaluation and the results will be reported to the site. Clinical decisions will be made based on Investigator review of the ECG recordings, but the results of central evaluation must be taken into consideration if available.

The ECG recordings must also be analyzed and checked for abnormality by the Investigator (or designated physician) who will also calculate the QTcF value (using Fridericia's formula $QTcF = QT/RR^{-1/3}$). Particular attention must be paid to new T wave inversions.

ECGs may be repeated for quality reasons and a repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECGs with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and / or treated as medically appropriate.

5.2.5 Other safety parameters

5.2.5.1 Testing for Cytokine Release Syndrome and infusion-related reaction

Patients must remain under observation for potential signs and symptoms of CRS as described in Section 4.1.4.1 and Appendix 10.2.

Ferritin and inflammatory cytokines including but not limited to IL-2, IL-6, IL-10, IFN-γ, TNF-α will be measured in [redacted] in order to monitor release of cytokines as a part of the exploratory safety assessment (Section 5.4). Blood for the inflammatory cytokine measurements will be taken from all patients according to the Flow Chart and Appendix 10.1 to be sent to the central laboratory. In cases when CRS occurs outside of the timepoints indicated in the Flow Chart and Appendix 10.1, additional blood samples for the inflammatory cytokine measurements are requested at onset of CRS (before start of corticosteroid treatment) and then approximately 48 hrs and 72 hrs after the development of symptoms. Additional blood sample for the inflammatory cytokine measurements should also be taken at the time of an infusion-related reaction. Ferritin levels will be measured to monitor for hemophagocytic lymphohistiocytosis (HLH). Blood for the ferritin measurement will be taken at baseline, at the time of CRS onset (taken simultaneously with the blood sample for the inflammatory cytokine measurements, as described above) and at EOT to be sent to the central laboratories. Details are specified in the Laboratory Manual.

In addition to the assessments in the central laboratory, levels of inflammatory cytokines and ferritin could be measured locally according to local institution standards at time of manifested CRS, if considered necessary by the investigators.

5.2.5.2 Testing for SARS-CoV-2

A SARS-CoV-2 test will be performed, using a site kit according to local guidance, during screening and within 5 days of administration of BI 1821736 according to the Flow Chart. Note, in the case of [redacted] if the result from [redacted] is within the 5 days from [redacted] treatment, a repeat test is not needed. Results of the SARS-CoV-2 should be obtained before BI 1821736 administration. In case of a positive result treatment should be delayed and should only resume following recovery from the SARS-CoV-2 infection (i.e., negative test), so long as the patient is expected to derive clinical benefit, as agreed between the Investigator and Sponsor and in line with Section 4.1.4.3.

5.2.5.3 Testing for $CD4^+$ and $CD8^+$ T cells

CD4+ and CD8+ cells will be collected according to the Flow Chart and Appendix 10.1 in order to evaluate a change in CD4+/CD8+ counts and will be quantitatively analyzed by a

standard flow cytometry in a central laboratory. Detailed instructions for the blood sampling, handling, and shipment of samples are provided in the lab manual. The blood samples that are analyzed are expected to be exhausted during the course of investigative analysis.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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

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

The following should also be recorded as an (S)AE on the appropriate eCRF(s) (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions if certain criteria are met – see Section 5.2.6.2.4 Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

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

5.2.6.1.2 Serious adverse event

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

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

NOTE: The following hospitalizations are not considered SAEs.

- Patient admissions as per protocol for a planned medical/surgical procedure
- Patients hospitalized for administrative reasons during the trial, including respite care.

- Hospitalizations/surgical procedures which were planned before the patient signed informed consent if they have been documented at or before signing of the informed consent and have been performed as planned (the condition requiring hospitalization /surgical procedure has not changed/worsened after signing informed consent).
- A visit to the emergency room or other hospital department which lasted less than 24 hrs and did not result in admission (unless considered "important medical event" or event was life threatening).

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined in Section 5.2.6.1.2.

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

5.2.6.1.4 Adverse events of special interest

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

The following Adverse events are considered as AESIs:

Potential Severe DILI
A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

For patients with normal liver function at baseline (ALT, AST, and bilirubin within normal limits at baseline):

- An elevation of AST (Aspartate Aminotransferase) and / or ALT (Alanine Aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or ALT and / or AST elevations ≥10-fold ULN.

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

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

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

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

These laboratory findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF. For further details, see Figure 5 below.

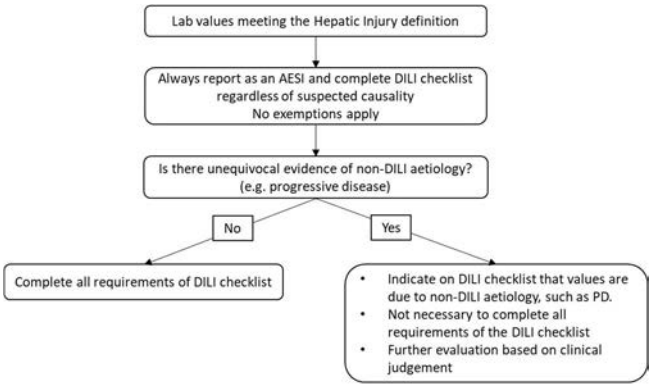


Figure 5 Hepatic injury reporting

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

Dose Limiting Toxicity

Any medical event fulfilling the criteria of DLT (see Section 5.2.7) should be reported as an AESI.

Cytokine Release Syndrome

Recommendations for the management of cytokine release syndrome are presented in Section 4.2.3.1. Cytokine release syndrome ≥ Grade 2 should be reported as an AESI.

Tumor Lysis Syndrome

Tumor lysis syndrome ≥ Grade 3 should be reported as an AESI.

Infusion-related Reactions

The following AEs, when occurring with a temporal relationship to the infusion, are considered as potential infusion-related reactions and should be reported as AESIs, regardless of their CTCAE grade:

- Infusion-related reaction (synonyms: infusion reactions, infusion-like reactions)

- Allergic reaction
- Anaphylaxis
- Any other event which the Investigator considers as a potential infusion-related reaction.

Recommendations for the management of infusion related reactions are presented in Section 4.2.3.1.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of adverse events should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (R18-1357), with the exception of Cytokine release syndrome which will be based on ASBMT consensus grading (R19-0309).

5.2.6.1.6 Causal relationship of AEs

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

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

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

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

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

- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

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

Per default SAEs/AESIs should be reported via the eCRF in the eDC system. If the eDC system is not or no longer available (e.g. after database lock [DBL]), the BI paper SAE form should be used; please see Section 5.2.6.2.2. The following must be collected and documented:

- From signing the informed consent onwards until the EOT visit (30 days from the last dose): all AEs (non-serious and serious) and all AESIs.
- After EOT visit until the individual patient's EoS (EoS is considered as 1 year after last BI 1821736 dose): cancers of new histology and exacerbations of existing cancer, all trial treatment related AEs (non-serious and serious) and all trial treatment related AESIs.
- After the individual patient's end of the trial: the Investigator does not need to actively monitor the patient for new AEs but should report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the Investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the eCRF.

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

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the AE or SAE eCRF pages to the sponsor's unique entry point immediately (within 24 h of becoming aware of the event), the country specific process will be specified in the ISF. The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone.

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

Should the eDC system not be available for more than 24 h, reporting must occur via the BI SAE forms.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure

during pregnancy in a trial patient immediately (within 24 h) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

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

The ISF will contain the Pregnancy Monitoring Form for Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and / or AESI, only the Pregnancy Monitoring Form for Studies is to be completed. However, an SAE and / or AESI associated with the pregnancy must be reported as described in Section 5.2.6.2.2.

5.2.6.2.4 Exemptions to SAE reporting

Protocol specified exempted events should be collected on the appropriate CRF page only.

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

If the disease progression does not meet standard seriousness criteria (see Section 5.2.6.1.2), then it is exempt from AE reporting, and will only be recorded on the appropriate page of the eCRF. For example, asymptomatic disease progression detected on a routine scan would be exempt from AE reporting, even if disease progression is on the "always serious" list. However, if there is evidence suggesting a causal relationship between the trial drug and the progression of the underlying malignancy, the event must be recorded on the SAE page in the eCRF.

If disease progression meets the standard seriousness criteria (see Section 5.2.6.1.2) it will be recorded on the SAE page in the eCRF and the SAE reporting process will be followed.

Lab values meeting the potential severe DILI definition must always be reported as AESI, even if the most likely cause is disease progression. No exemption to AE reporting applies. Clinical symptoms and/or signs of PD will be recorded on the AE page in the eCRF. If signs and symptoms of disease progression of the patient's underlying malignancy meet standard seriousness criteria, they will additionally be reported as SAEs on the SAE page in the eCRF and SAE reporting procedures will be followed. If signs and symptoms are attributable to a diagnosis, reporting the diagnostic term is preferable e.g. pulmonary embolism rather than dyspnoea, intestinal obstruction rather than abdominal pain.

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

5.2.7 Dose Limiting Toxicities (DLT)

All DLTs occurring during the MTD evaluation period (see Section 2.1.1) or subsequent treatment cycles should be reported as AESIs according to the same timelines as serious AEs.

DLTs will be recorded throughout the trial. Only DLTs occurring during the MTD evaluation period are required for dose-escalation decisions made by the DEC. Late DLTs are AEs that meet the DLT criteria but occur on treatment after the completion of the initial DLT evaluation period. If any late DLT is reported during dose escalation, updated results will be reviewed in the DEC meeting during evaluation of proceeding to the next dose level.

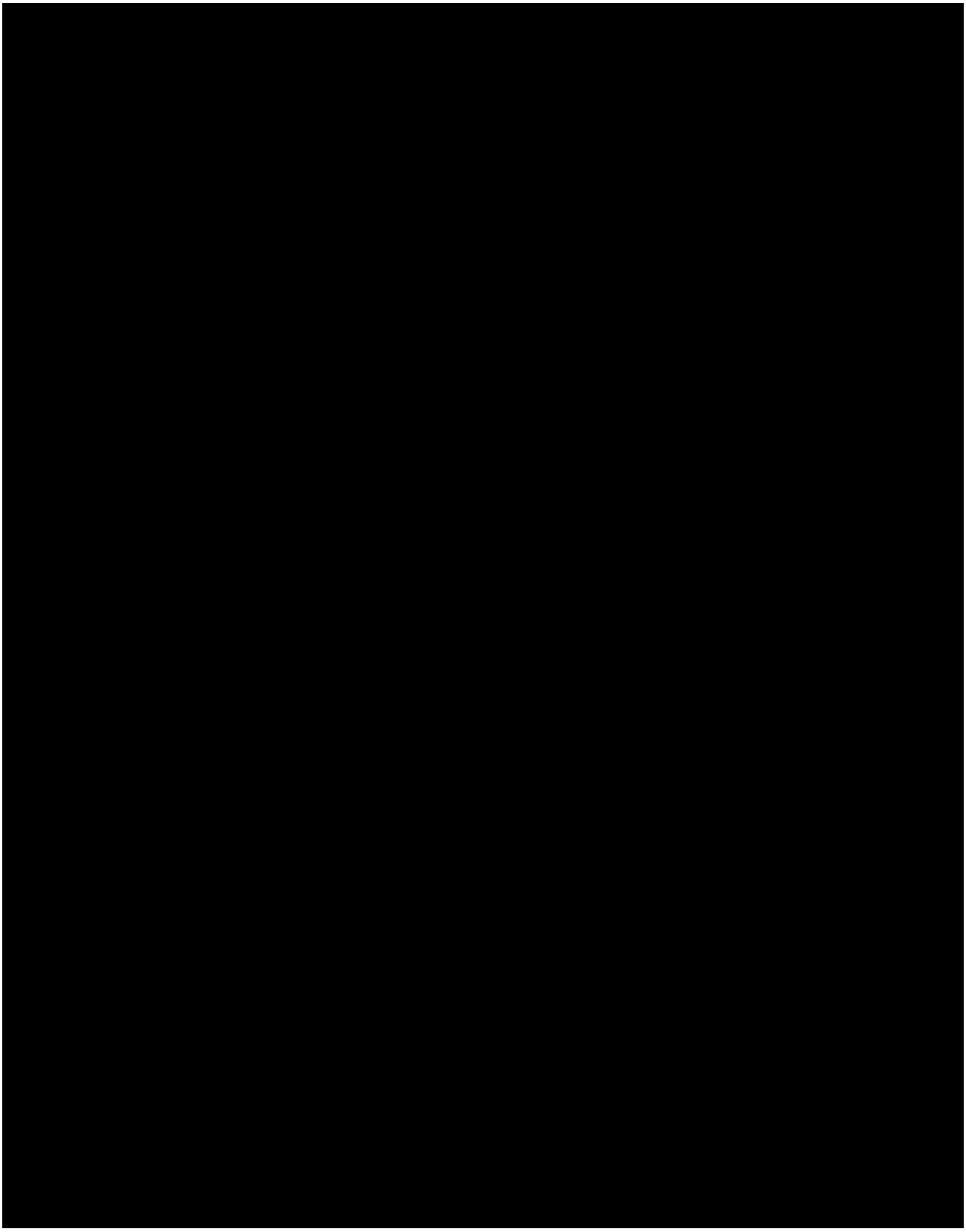
The following AEs, if not clearly due to underlying malignancy or an extraneous cause, will be classified as DLTs, following review by the investigator, the Sponsor and the DEC;

- Cytokine release syndrome ≥ Grade 3
- Any other ≥ Grade 3 event with the <u>following exceptions (which will not be considered a DLT)</u>:

  a) Hematologic toxicity
  - Grade 3 leukopenia
  - Grade 3/4 lymphopenia
  - Grade 3 neutropenia
  - Grade 4 neutropenia lasting for ≤ 5 days
  - Grade 3 thrombocytopenia lasting ≤ 5 days without bleeding

  b) Non-haematological toxicity
  - AST or ALT elevation < 10 x ULN if liver metastases present
  - Grade 3 electrolyte abnormality that lasts < 72 h, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention.
  - Grade 3 nausea or vomiting that lasts < 48 h and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention.

- Any other AE that the DEC identifies during their review that should be considered a DLT due to frequency, severity, and time to onset.



5.4 ASSESSMENT OF BIOMARKER(S)

This section refers to exploratory biomarkers. Established biomarkers of efficacy and safety are described and discussed in Sections 5.1 and 5.2.

Exploratory biomarkers will be analyzed to provide clinical evidence of the biological mode of action of BI 1821736 (i.e. pharmacodynamic biomarkers), to support dose selection, and to molecularly characterize individual patient's cancer. Biomarkers will be used to retrospectively identify patient subgroups with differential responses to treatment and/or prognoses. These analyses are hypothesis generating and will be used to expand the current understanding of the trial treatment and the disease. Participation in the biomarker testing is mandatory and is a prerequisite for participation in the study.

Peripheral blood collected before and after BI 1821736 administration will be used for exploratory biomarkers assessments that may include, but are not limited to:

- Measurement of levels of inflammatory cytokines, such as IL-6, IL-10, IFN-γ and TNF-α, levels of IFNα and CD80-Fc fusion protein.
- In cases of infusion-related reactions or in cases when clinically manifested CRS occur outside of the indicated timepoints, additional blood samples will be taken for inflammatory cytokine measurements at the time of infusion-related reaction or clinically manifested CRS (at CRS onset and then approximately 48 hrs and 72 hrs after the development of symptoms), respectively.
- Analysis of T cell activation status and presence of T cell subsets.

A fresh tumor biopsy is requested before BI 1821736 administration at [redacted] (mandatory in the absence of an archival block of tumor tissue), and at [redacted] (mandatory), and at EOT or FUP (optional). Tumor tissue will be used for exploratory biomarkers assessments that may include, but are not limited to:

- Expression of immunomodulatory markers such as T cell markers and PD-L1.
- Transcriptomic and genomic analyses of tumor cells and cells of tumor microenvironment.
- [redacted] before and after BI 1821736 administration and presence of virus specific [redacted] after BI 1821736 administration.
- Detection of tumor cell apoptosis triggered by BI 1821736 using [redacted]

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

Exploratory biomarker analyses will be performed by Boehringer Ingelheim or by a laboratory authorized by Boehringer Ingelheim. Any remaining samples or derived material from pre-specified analyses (RNA, DNA) will be destroyed no later than 5 years after the final trial report is signed, except leftover tumor and blood (serum) samples for which a patient has voluntarily accepted a biobanking option and have provided a signed ICF.

Detailed instructions on sampling, preparation, processing, and shipment of the samples are provided in the Lab Manual. For sampling timepoints see Flow Chart and Appendix 10.1.

Sampling timepoints and periods may be adapted during the trial based on information obtained during trial conduct, including addition or reduction of samples and visits. Such changes would be implemented via non-substantial CTP Amendments.

5.4.1 Pharmacodynamics biomarkers, safety biomarkers and biomarkers predictive of outcome

5.4.1.1 Pharmacodynamics biomarkers

Pharmacodynamics biomarkers related to the mode of action of BI 1821736 will be measured [redacted] and in [redacted] before BI 1821736 administration and on-treatment. [redacted] and [redacted] have to be collected at the timepoints indicated in the Flow Chart and in Appendix 10.1.

Pharmacodynamics evaluation in [redacted] may include, but is not limited to, analysis of changes in [redacted] changes. Individual analyses from [redacted] will be prioritized based on availability of sufficient tissue material.

Pharmacodynamic evaluation in [redacted] may include, but is not limited to, assessment of changes in levels of [redacted] and [redacted] subsets.

Specific assays and readouts may change as data becomes available.

5.4.1.2 Biomarkers for safety

A panel of inflammatory cytokines that may include, but not limited to IL-6, IL-10, IFN-γ and TNF-α will be measured in peripheral blood in order to monitor release of cytokines after BI 1821736 administration as a part of the safety assessment. In cases of infusion-related reaction and in cases when CRS occur outside of the timepoints indicated in the Flow Chart and in Appendix 10.1 additional blood samples for the inflammatory cytokine measurements will be requested as described in Section 5.4.

Specific assays and readouts of biomarkers for safety may change as data becomes available.

5.4.1.3 Biomarkers predictive of outcome

[redacted] and [redacted] samples collected before BI 1821736 administration will be used for assessments of biomarkers that may be predictive of outcome. These assessments may include, but not limited to:

- Analysis of pre-treatment [redacted] that may correlate with patient outcomes.
- Analysis of pre-treatment [redacted] to BI 1821736.

Specific assays and readouts of biomarkers predictive of outcome may change as data becomes available.

5.4.2 Methods of sample collection

5.4.2.1 Tumor biopsies

Fresh biopsies will be requested for biomarker analysis as described in the Flow Chart. The biopsies requested at [redacted] and [redacted] are mandatory and the biopsy requested at EOT or FUP is optional. If, in the judgment of the investigator, the on-treatment biopsy collection is not clinically feasible due to patient safety or tumor accessibility for a particular patient, it may be acceptable to skip provision of the fresh on-treatment biopsy. In cases when on-treatment biopsies cannot be collected, patients will not be discontinued from the trial and will be able to continue the treatment.

[redacted] and [redacted] biopsies should be taken before respective BI 1821736 administrations. [redacted] biopsy must only be taken for patients who have undergone screening assessments and are expected to be eligible for treatment. In case there is an archival sample taken within 6 months of trial start with no intermediate therapy this may be provided instead (FFPE tumor tissue block or 27 freshly sectioned unstained slides of 4-5 µm thickness) but should only be provided after [redacted] once patient has started treatment. C2D1 biopsies may be taken up to 3 days before the study visit. EOT/ FUP biopsy should be taken at the time of disease progression or any time after disease progression, but before administration of subsequent anti-cancer therapy.

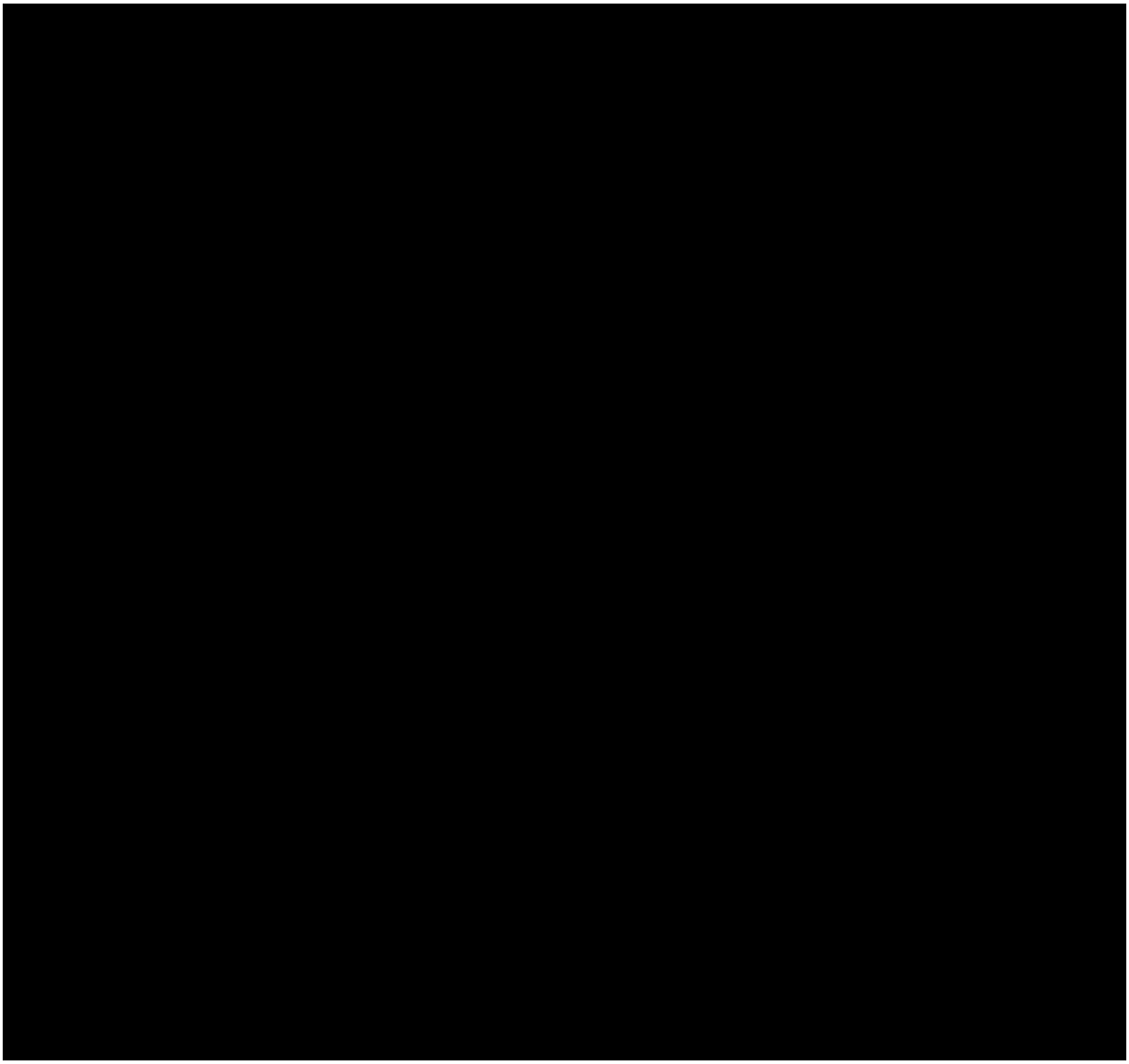
If feasible, [redacted] and [redacted] biopsies should be collected from the same non-target lesion. An optional biopsy at EOT or FUP should be collected from lesions that have progressed. Ideally the optional biopsy should be collected from the same lesion as at [redacted] and [redacted] if this lesion has progressed. Should a given tumor lesion not be suitable for re-biopsy due to, for example, the size or degree of necrosis, then an alternative non-target tumor lesion should, where clinically feasible, be biopsied.

Left over tumor samples may be biobanked (Section 5.5). For patients who do not consent to biobanking, remaining samples will be disposed of at the latest 5 years after the final trial report has been signed. Until then, samples will be stored at Boehringer Ingelheim or a designated CRO.

5.4.2.2 Blood sampling

Blood samples required for the analyses of immunomonitoring parameters and exploratory biomarkers are outlined in the Flow Chart.

All blood samples are expected to be exhausted during the course of investigative analysis. Should this not be the case, remaining samples will be disposed of at the latest 5 years after the final trial report has been signed or may be biobanked (Section 5.5). Samples will be stored at Boehringer Ingelheim or a designated CRO.



5.5 BIOBANKING

In order to be able to address future scientific questions, patients will be asked to voluntarily donate leftover tumor or blood samples (serum samples collected for IFNα measurement) for banking. If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event, or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

Participation in biobanking is not a prerequisite for participation in the trial. If the patient agrees, they will be asked to provide a separate optional informed consent in accordance with local ethical and regulatory requirements.

5.5.1 Methods and timing of sample collection

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. For sampling timepoints see Flow Chart.

Leftover tumor and blood samples (serum samples collected for IFNα measurements) may be banked as described in Section 5.5. All samples will be stored either at the sponsor's site or at an external biobanking facility contracted by the sponsor.

5.6 OTHER ASSESSMENTS

5.6.1 Demographics and Medical History

Demographic information including sex, age on the day of informed consent (in years), race/ethnicity (where allowed according to local law), information on nicotine use, smoking and alcohol use, as well as general medical history and detailed oncological disease history will be collected. This will include date of first diagnosis of malignancy, staging and grading information, and details of previous treatment for malignancy. Where available, results of pre-existing tumor molecular marker information (i.e., Next Generation Sequence (NGS) testing) will be provided to either Sponsor or an independent CRO nominated by the Sponsor where it will be stored for up to 30 years.

5.6.2 Immunogenicity testing

For assessment of anti-drug antibodies and neutralizing anti-drug antibodies (ADA/NAb), blood samples will be drawn at the time points listed in the Flow Chart. Details on sample collection, characteristics, processing, handling, and shipment are provided in the Laboratory Manual.

The samples may be used for further methodological investigations, (e.g. for further investigations to characterize ADA response or to address Health Authority questions regarding the results/methodology), however, only data related to the anti-drug antibodies will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the final trial report has been signed.

The presence of ADAs to BI 1821736 or to CD80-Fc will be assessed using validated immunohistochemistry assays (titration analysis, as appropriate).

[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

All methods used are standard. Determination of MTD is based on toxicities graded according to CTCAE version 5.0 (R18-1357) and/or ASBMT consensus grading (R19-0309) (for CRS). The CTCAE criteria are commonly used in the assessment of AEs in cancer patients. RECIST 1.1 (R09-0262) is used for evaluation of response. These criteria are well-established and scientifically accepted.

Information about race and ethnicity should be obtained from all study participants as allowed by local regulations. This is because the prevalence and characteristics of cancer may differ widely between patients of different racial origin. It will thus be worthwhile to assess if patients of different race or ethnicity will respond differently to the study treatment.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients should adhere to the visit schedule as specified in the Flow Chart. If treatment administration is delayed at any time, the schedule of all subsequent visits/cycles will be recalculated based on the actual date of treatment (with the exception of imaging – see Section 5.1). Visits may take place over more than one day for logistical reasons, as long as all assessments fall within the window defined in the Flow Chart.

If a patient misses a visit during which there is no treatment administration planned, the visit should be rescheduled as soon as possible, and the delayed visit documented with the actual date and reason for the delay. The scheduling of subsequent visits must not be altered, so if it is not possible to reschedule prior to the next planned visit, the missed visit should be skipped.

Each cycle has a duration of [redacted] days. Cycles [redacted] and [redacted] require multiple visits and other cycles require [redacted] visits on Day [redacted] and Day [redacted] (-1/+2 days window). Additional flexibility (e.g. to allow for public holidays and patient unavailability) may be allowed if agreed between the Investigator and the Sponsor.

If a patient is hospitalized for administrative reasons to allow treatment and sampling (e.g. overnight stay following Days [redacted] and [redacted] of Cycle [redacted] and Day [redacted] of Cycle [redacted]) this will not be considered an SAE, unless any other criteria for an SAE are fulfilled (see Section 5.2.6.1.2).

In addition to the scheduled assessments, unscheduled assessments for safety reasons may be performed at any time according to clinical need. In situations where an individual patient is unable or unwilling to attend a clinic visit (because of force majeure or other disrupting circumstances such as pandemic, war), the Investigator must assess the risk-benefit for the individual patient and may decide to perform a visit remotely if this is in the best interests of the patient and if agreed with the Sponsor. Patient safety must be ensured when determining if a visit may be remote. All deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Screening Period
Following informed consent, the patient will undergo screening assessments as indicated in the Flow Chart. Demographic information will be collected, including age on the day of informed consent (in years), sex (male, female in order to describe the patient's sex at birth), for women: of childbearing potential yes / no in order to characterize the patient population and as a basis for contraception requirements, ethnicity and race (where allowed according to local law) in order to sufficiently characterize the patient population, to support possible subgroup analyses if needed unless not acceptable according to local regulations.

The assessments must fall within the acceptable screening visit window but do not need to be performed on the same day. Screening assessments may be repeated as long as they fall

within the windows indicated. If more than one screening assessment is available, the latest assessment prior to the start of treatment must be used to assess eligibility.

Tumor assessments performed prior to informed consent as part of routine clinical practice will be accepted if they meet the time frame requirements of the protocol and are performed within the screening visit window.

If the patient meets the eligibility criteria during screening, the first treatment visit should be scheduled. Any baseline conditions which are present at the screening visit should be reported in the eCRF. Re-screening of patients who have previously failed screening will be permitted. In this situation patients will be handled as a new patient i.e., sign a new informed consent form, allocated a new patient number, and undergo full screening assessments.

6.2.2 Treatment period(s)

The Investigator must perform a final assessment of eligibility when the results of all screening assessments are available. If the patient does not meet the eligibility criteria, the patient must be recorded as a screen failure.

Once eligibility is confirmed, treatment is allocated using IRT and the patient will be considered enrolled. Treatment allocation is allowed up to 3 working days prior to first treatment to allow time prior to [redacted] for scheduling of procedures. Eligible patients will be administered BI 1821736 for [redacted] cycles (in [redacted] cycles) according to the Flow Chart.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war), the trial conduct may need to be adjusted and remote visits performed. If a patient is not able to come to the site for a trial visit, a remote visit (by phone) should be performed instead. The following assessments can be done remotely: adverse event and concomitant therapy assessment. If blood sampling at the trial site is not possible, safety lab analyses can be performed at a local lab to the patient. The results of the lab tests must be transferred to the Investigator who ensures medical review and proper documentation in the eCRF. Minimum required safety lab parameters are haematology, biochemistry, coagulation and pregnancy tests. The implementation of these measures will depend on participant's consent, operational feasibility, local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

In the case that prior information regarding results of pre-existing tumor molecular marker information (i.e., Next Generation Sequence (NGS) testing) is available, a copy of the report will be provided to the Sponsor. See also Section 5.6.1.

6.2.3 Follow-up period and trial completion

If needed in the opinion of the investigator, after the final FUP (Follow-up visit) visit additional visits may be scheduled for continued safety monitoring.

Abnormal assessments or lab values judged clinically relevant by the investigator will be monitored until they have returned to a medically acceptable level.

6.2.3.1 End of Treatment visit

After the decision to permanently discontinue treatment within the trial is taken, no further administration of study medication should take place. The EOT visit should be performed 30 ± 5 days from the last dose of BI 1821736 or, if more than 30 days since last dose, as soon as possible, but within 7 days of the decision.

The assessments to be performed at the EOT visit are described in the Flow Chart. Tumor assessment/imaging will be performed at the time of EOT, unless it has been done within the past 4 weeks.

6.2.3.2 Follow-up visits

For those patients who did not progress by the EOT visit, follow-up scans for progressive disease (PD) will be performed once every 9 (±3) weeks with follow-up results reported in person or by telemedicine until progression, introduction of a new anti-cancer treatment, death, loss to follow-up, withdrawal of consent, end of trial/trial completion for the patient (EoS), or end of the whole trial. An exploratory biomarker sample will also be taken at progression. See Flow Chart.

For all patients, regardless of whether they have progressed by the EOT visit or not, follow-up visits will be performed to assess for new treatment related AEs and the status of ongoing drug-related AEs. AEs should be followed until resolved, returned to baseline or deemed chronic, patient is lost to follow-up, withdraws consent to be followed, or starts a new therapy. Start date and type of new anti-cancer therapy should be documented, if applicable.

Wherever possible the follow-up visit must be performed in person, but if the Investigator judges appropriate (e.g. in the event the patient is undergoing end-of-life care), follow-up information may be collected by telephone.

Trial completion (EoS) for a patient is up to 1 year after the last dose of BI 1821736 visit, death, lost to follow-up, withdrawal of consent or until the end of the trial. Following trial completion, the patient will return to standard of care.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

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

7.2 PLANNED ANALYSES

7.2.1 General considerations

The primary analysis will be conducted once the MTD has been agreed on by the DEC. The BLRM will be re-run after the RP2D was confirmed at the end of the dose escalation. For the determination of the MTD, only MTD evaluable patients will be considered.

For the analysis of secondary and further endpoints (efficacy and safety), all patients in the treated set (TS) (i.e. patients treated with at least one dose of trial medication) will be included.

The PK set includes all subjects in the TS who provide at least one valid observation for at least one PK endpoint without important protocol deviations relevant to the evaluation of PK. It will be used for the descriptive analysis of blood exposure.

Any other analysis sets will be defined in the TSAP.

No per protocol set will be used in the analyses. However, important protocol deviations will be identified and listed. Any exclusion from the analysis sets is to be decided in the Report Planning Meeting (RPM) at the latest and will be documented in the decision log.

7.2.2 Handling of Intercurrent Events

The expected intercurrent events of interest of this trial are:
- Permanent treatment discontinuation
- Disease progression
- Death
- Breaks from treatment
- Missed visits

A combined composite and principal stratum strategy will be applied for the primary analysis of the primary endpoint. This is the effect of the treatment in the principal stratum of patients who do not discontinue treatment, miss visits, progress, reduce dose (not allowed) or die during the MTD evaluation period for any reason other than DLT. That means patients experiencing one of these intercurrent events are excluded from the analysis. The intercurrent event treatment discontinuation due to DLT will be handled using a composite strategy, that

is, patients experiencing this intercurrent event are included in the analysis. Refer to ICH E9 R1 for definitions of the principal stratum strategy and the composite strategy. Table 7 provides an overview of the intercurrent events and the respective handling strategies. Handling of intercurrent events not listed below will be determined before database lock and will be documented in the TSAP.

The strategy for handling intercurrent events in this trial is as follows:

Table 7 Overview of intercurrent event handling strategies for the primary analysis (Phase I dose-escalation)

Intercurrent event	**Combined composite and principal stratum**
Treatment discontinuation during the MTD evaluation period due to DLT	Composite
Treatment discontinuation during the MTD evaluation period due to other reason than DLT	Principal stratum
Progressive disease during the MTD evaluation period	Principal stratum
Death during the MTD evaluation period where the death event is not a DLT	Principal stratum
Any events other than DLT that cause missed visits during the MTD evaluation period	Principal stratum

Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand for each main analysis in this protocol is the combination of the relevant detailed clinical objective from Section 2.1 and this strategy.

7.2.3 Primary objective analyses

The trial will be performed as an open-label trial. The objective of the design is to determine the MTD of BI 1821736. The Phase I dose-finding will be guided by a Bayesian 2-parameter logistic regression model with overdose control (R13-4806; R13-4803). The MTD is the primary objective of this trial and will be assessed from the occurrences of DLTs during the MTD evaluation period on an individual patient level, guided by the BLRM and the EWOC criterion. The MTD will be determined as described below.

The model is given as follows:

[redacted]

π_d represents the probability of having a DLT in the MTD evaluation period at dose [redacted] is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose [redacted] is the parameter vector of the model.

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

- Under toxicity: [redacted])
- Targeted toxicity: [redacted]
- Over toxicity: [redacted]]

In this context, the intervals are referred to as underdosing, target dosing, and overdosing intervals.

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

Whenever a dose-escalation decision is required during the trial conduct, the BLRM will be fitted with all available data, i.e. data from all patients from dose escalation cohorts, MTD/RP2D confirmation cohorts that are evaluable for MTD. Based on this, the EWOC criterion given the observed data is evaluated for each dose level of interest. This analysis will use the combined [redacted] defined in Section 7.2.2 for intercurrent event handling. This information will guide the decision on the next dose level as outlined in Section 4.1.2. The next dose of a schedule must always satisfy the EWOC criterion as well as the increments stated in Section 4.1.2. Patients are considered evaluable for MTD determination if they completed the MTD evaluation period and were not considered non-evaluable for DLT as per the rules specified in Section 3.3.4.1.1.

The MTD may be considered reached if all of the following criteria are fulfilled:

- Next recommended dose by the BLRM = current dose (stabilisation condition)
- Number of DLTs in trial is at least 0.
- At least [redacted] patients have been treated in the trial.

And at least one of the following criteria is fulfilled:

- The posterior probability of the true DLT rate in the target interval [redacted]) of the MTD is above [redacted], OR
- At least [redacted] patients have been treated at the MTD.

No further dose escalation will take place after the criterion for MTD is fulfilled. Further patients may be included to confirm this MTD estimate. If no DLT is observed at a dose at which the efficacy is considered sufficient, the DEC may decide to include an additional number of patients at this dose level and to declare this dose as the dose recommended for further testing (RP2D). Any DLTs occurring after the MTD evaluation period will be considered by the DEC for the evaluation of the recommended dose for further testing (RP2D).

Prior derivation:

[redacted]

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

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

1. A **weakly informative prior** was derived reflecting the a priori assumption that the median DLT rate at the starting dose of [redacted] would equal [redacted], and the median DLT rate at the anticipated MTD of [redacted] would equal [redacted]. This yields [redacted]). The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding [redacted] respectively. The prior weight a_1 for the first component was chosen as [redacted].
2. A **high-toxicity weakly informative prior** was derived reflecting the case that the compound would be much more toxic than expected. For this prior component, it was assumed that the median DLT rate at the starting dose of [redacted] would equal [redacted] and the median DLT at the anticipated MTD of [redacted] would equal [redacted] These assumptions yield [redacted]). The standard deviations and correlations were set identical to the weakly informative prior, i.e. [redacted] and [redacted], respectively. The prior weight a_2 for the second component was chosen as [redacted].
3. A **low-toxicity weakly informative prior** was derived reflecting the case that the compound would be much less toxic than expected. For this prior component, it was assumed that the median DLT rate at the starting dose of [redacted] would equal 0.01, and the median DLT at the anticipated MTD of [redacted] would equal 0.05. These assumptions yield [redacted]), i.e. basically a flat curve. The standard deviations and correlations were set to [redacted], therefore almost fixing the slope parameter to its mean. The [redacted]s set to [redacted]. The prior weight a_3 for the third component was chosen as [redacted].

A summary of the prior distribution is provided in Table 8. Additionally, the prior probabilities of DLTs at different doses, as well as the corresponding probability of under-,

targeted and overtoxicity, are shown in Table 9. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 6. As can be seen from both, the table and the figure, the prior medians of the DLT probabilities are in-line with the prior medians derived from the weakly informative prior, and the uncertainty around the medians is large, showing the low amount of information this prior provides. This is also supported by the prior sample size, i.e. the information contained in the prior. This is approximately equal to 1.53 patients. A detailed evaluation of the model using hypothetical data scenarios and operating characteristics is provided in the statistical appendix (see Appendix 10.4) .

Table 8 Summary of prior distribution

Prior Component	Mixture Weight	Means Vector (log(α), log(β))	SD# Vector (log(α), log(β))	Correlation
1: Realistic Tox.	[redacted]			0
2: High Tox.				0
3: Low Tox.				0

SD, standard deviation

Table 9 Prior probabilities of DLTs at selected doses

Dose ([redacted])	Probability of true DLT rate in					Quantiles		
	[0-0.16)	[0.16-0.33)	[0.33-1)	Mean	SD#	2.5%	50%	97.5%
[redacted]								

SD, standard deviation
$, dose meets the overdose criterion at the start of study (P(overdose) < 0.25)

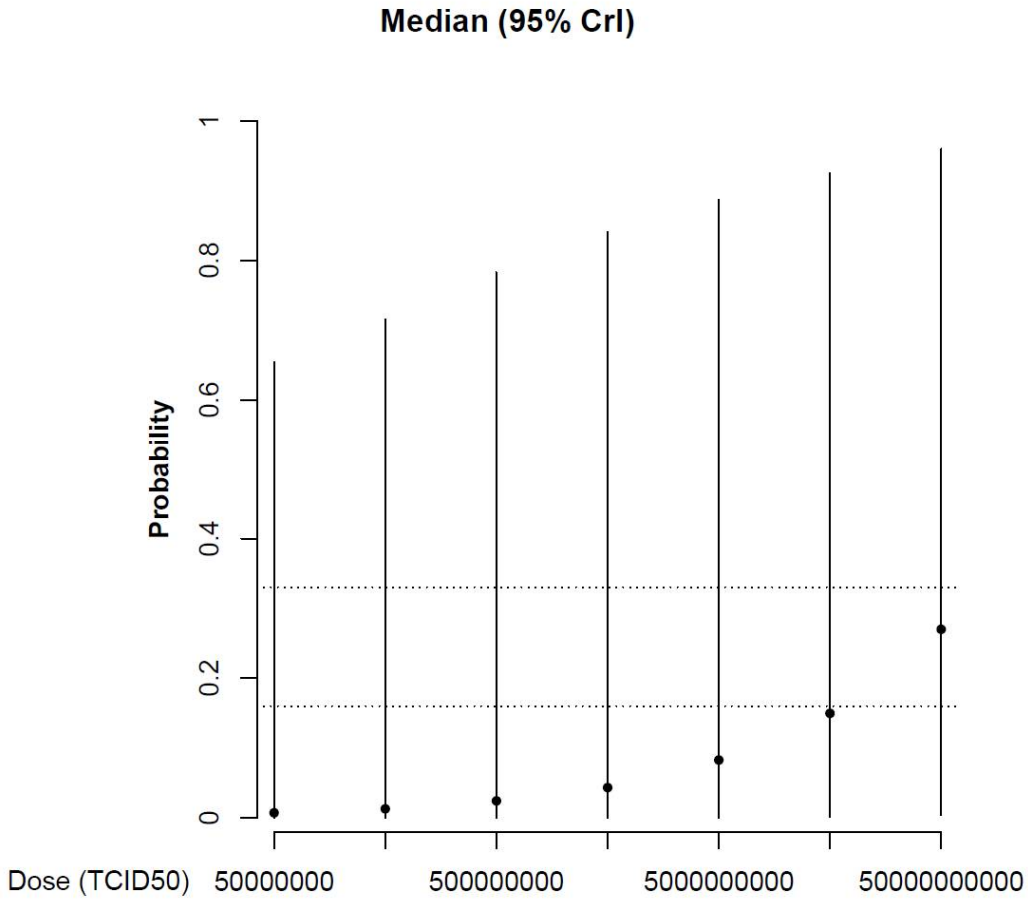


Figure 6 Prior medians and 95% credible intervals

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

Statistical model assessment:
The initial model was assessed using two different metrics:

1. Hypothetical data scenarios: for various potential data constellations as they could occur in the actual trial, the maximal next doses as allowed by the model and by certain escalation limits are investigated. Data scenarios, thus, provide a way to assess the "on-study" behavior of the model.
2. Simulated operating characteristics: these illustrate, for different assumed true dose toxicity relationships, how often a correct dose would be declared as MTD by the model. They are a way to assess the "long-run" behavior of the model.

In summary, the model showed very good behavior, as assessed by these metrics. More details of these assessments can be found in Appendix 10.4.

7.2.3.1 Sensitivity Analyses

No sensitivity analyses are planned.

7.2.3.2 Subgroup Analyses

No subgroup analyses are planned.

7.2.3.3 Supplementary Analyses

As a supplementary analysis, the BLRM may be analysed using the treated set (all patients receiving at least one dose of trial medication) and the number of patients with a DLT during the whole treatment period as recorded in the eCRF, instead of DLTs during the MTD evaluation period. If applicable, intercurrent events will be handled using the Treatment Policy strategy as defined in ICH E9 R1 (R21-0743) for this supplementary analysis. That is, all treated patients and the outcome (patient experienced DLT or not) are included in the analysis regardless of the occurrence of intercurrent events.

7.2.4 Secondary objective analyses

All secondary endpoints will be analysed descriptively. Details of the secondary endpoint analyses will be specified in the trial statistical analysis plan (TSAP). The secondary endpoints are defined in Section 2.1.3.

7.2.5 Further objective analyses

Analyses of further endpoints will be detailed in the TSAP, if applicable.

7.2.6 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 15 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

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

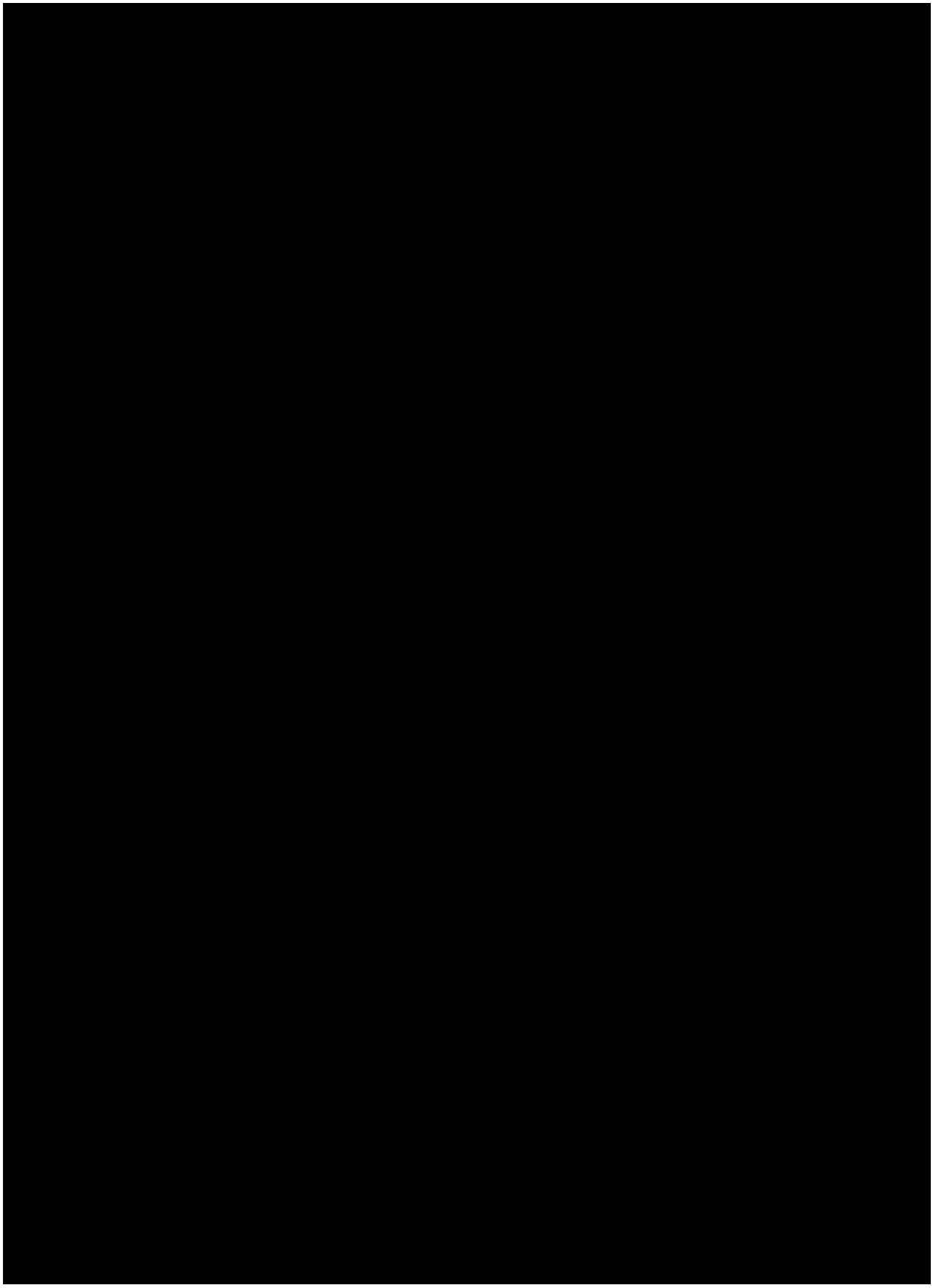
Statistical analysis and reporting of AEs will concentrate on treatment-emergent adverse events, i.e. all AEs occurring between start of treatment and end of the residual effect period. AEs that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

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

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

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

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



7.2.8 Other analyses

Other analyses will be specified in the TSAP if applicable.

7.2.9 Interim analyses

No formal interim analysis is planned.

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

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

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

7.3 HANDLING OF MISSING DATA

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

Handling of missing PK data will be performed according to the current relevant BI SOPs. PK parameters that cannot be reasonably calculated based on the available drug concentration time data will not be imputed.

In general, missing efficacy data will not be imputed and all reasonable efforts will be taken during the trial to obtain such data. Every effort will be made to obtain complete information on all AEs with particular emphasis on potential DLTs.

7.4 RANDOMISATION

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

7.5 DETERMINATION OF SAMPLE SIZE

No formal statistical power calculations to determine sample size were performed for this trial. A sample size of approximately 27 patients is estimated for this trial based on the number of dose levels/cohorts that are tested (assuming ~[redacted] patients per dose level, and [redacted] patients at the MTD/RP2D). A different number of patients might be needed based on the recommendation of the DEC and the criteria specified (see Section 7). However, the actual number of patients will depend on the number of dose cohorts tested and the underlying dose-toxicity profile. Based on the simulation study to evaluate operating characteristics of the BLRM (see Appendix 10.4), approximately [redacted] evaluable patients are expected to be treated in the dose escalation part ([redacted] including RP2D confirmation) for the model to have reasonable operating characteristics relating to its MTD recommendation.
The replacement of patients is described in Section 3.3.4.1.1.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014, the US Code of Federal Regulations and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as a "protocol deviation".

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

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

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

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

investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

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

Copies of source documents necessary for tumor assessment scans, any available results of pre-existing tumor molecular marker information (i.e., Next Generation Sequence (NGS) testing) and any photo documentation will be collected by the Sponsor for later assessment. This could include imaging of any known or suspected sites of disease using an appropriate method. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

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

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

- Patient identification: sex, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion / exclusion criteria does not make the patient eligible for the clinical trial.
- Technical information collected on PK and shedding sampling days (e.g. sampling times, repeated vital signs linked with PK) may be collected on specific paper logs, which will be considered as source data for related entries in eCRF and are considered part of the ISF.
- Data on subsequent anti-cancer treatments, administration dates and response.

8.3.2 Direct access to source data and documents

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

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

Exemptions from expedited reporting are described in Section 5.2.6.2.4.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

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

To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a patient identification number instead of the patient's name. The code is only available at the site and must not be forwarded to the sponsor. In case patient's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the patient will be redacted by the site prior to forwarding. Access to the patient files and clinical data is strictly limited: personalised treatment data may

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

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs / IECs and patients will be informed as appropriate.

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

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

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

8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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

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

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

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. In addition, interim reports may be written after the last treated patient discontinues trial medication

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).
A Coordinating Investigator is responsible to coordinate Investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A Dose Escalation Committee (DEC) composed of participating Investigators or delegates and members of the BI trial team will be established to review individual and aggregated safety data at regular intervals to determine the safety profile and risk/benefit ratio and make decisions on next dose level, dose escalation, dose de-escalation, dose modification and next cohort size. Further details are contained in the DEC charter. Details of the DEC responsibilities and procedures are described in the DEC charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

The Investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

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

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

In the participating countries the trial will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a CRO based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.

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

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

A central laboratory service, an ECG provider, a digital camera provider, an imaging and tumor-related service provider, an IRT vendor and an ancillary supplies vendor will be used in this trial. Details will be provided in the IRT Manual, ECG Manual, Imaging Manual and Central Laboratory Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P98-8840 Grander D, Einhorn S. Interferon and malignant disease - how does it work and why doesn't it always? Acta Oncol. 1998;37(4):331-8. doi: 10.1080/028418698430548

R01-0787 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol; 1982; 5; 649-655.

R07-4856 European Medicines Agency (EMEA). Committee for Medicinal Products for Human Use (CHMP): guideline on clinical trials in small populations (London, 27 July 2006, doc. ref. CHMP/EWP/83561/2005); London: EMEA; 2006.

R08-1629 Stebbings R, Findlay L, Edwards C, Eastwood D, et al. 'Cytokine storm' in the phase I trial of monoclonal antibody TGN1412: better understanding the causes to improve preclinical testing of immunotherapeutics. J Immunol; 2007; 179; 3325-3331.

R09-0262 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009 Jan; 45(2):228-47.

R13-4802 Jaki T, Clive S, Weir CJ. Principles of dose finding studies in cancer: a comparison of trial designs. Cancer Chemother Pharmacol; 2013; 71; 1107-1114.

R13-4803 Neuenschwander B, Branson M, and Gsponer T. Critical aspects of the Baysian approach to phase I cancer trials Jun 15;27(13):2420-39.

R13-4804 Rogatko A, Schoeneck D, Jonas W, Tighiouart M, Khuri FR, Porter A. Translation of innovative designs into phase I trials. J Clin Oncol; 2007; 25(31); 4982-4986.

R13-4805 Tourneau C le, Gan HK, Razak ARA, Paoletti X. Efficiency of new dose escalation designs in dose-finding phase I trials of molecularly targeted agents. Plos One; 2012; 7(12); e51039.

R13-4806 Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med; 1998; 17; 1103-1120.

R13-4881 FDA's critical path initiative (page last updated: 12/28/2012). http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm07668 9.htm (access date: 8 November 2013); Silver Spring: U.S.Food and Drug Administration; 2012.

R18-1357 U.S. Department of Health and Human Services Common terminology criteria for adverse events (CTCAE) version 5.0 (published: November 27, 2017).

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf#search=%22CTCAE%22 (access date: 9 April 2017); U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute (2017)

R18-2378 Koyama S, Ishii KJ, Coban C, Akira S. Innate immune response to viral infection. Cytokine; 2008; 43; 336-341

R18-2379 Melzer MK, Lopez-Martinez A, Altomonte J. Oncolytic vesicular stomatitis virus as a viro-immunotherapy: defeating cancer with a 'hammer' and 'anvil'- Biomedicines 5 (1), 8 (2017)

R18-2380 Hastie E, Grdzelishvili VZ, Vesicular stomatitis virus as a flexible platform for oncolytic virotherapy against cancer. J Gen Virol 2012; 93; 2529-2545

R18-2381 Hastie E, Cataldi M, Marriott I, Grdzelishvili VZ, Understanding and altering cell tropism of vesicular stomatitis virus. Virus Res 2013; 176 (1/2); 16-32

R18-2382 Felt SA, Grdzelishvili VZ, Recent advances in vesicular stomatitis virus-based oncolytic virotherapy: a 5-year update. J Gen Virol 2017; 98; 2895-2911.

R19-0309 Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASBMT consensus grading for cytokine release syndrome and neurological toxicity associated with immune effector cells. Biology of Blood and Marrow Transplantation, Accepted Manuscript, Published online: December 25, 2018, doi: 10.1016/j.bbmt.2018.12.758; 2018.

R19-0311 Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol. 2018. 15: 47-62.

R19-0313 Eggermont AMM, Kroemer G, Zitvogel L. Immunotherapy and the concept of a clinical cure. Eur J Cancer; 2013; 49; 2965-2967.

R19-0318 Andrews MC, Wargo JA, Immunotherapy resistance: the answers lie ahead – not in front – of us. J Immunother Cancer 2017; 5; 10

R19-0813 Muik A, Stubbert L, Jahedi R, et al. Re-engineering Vesicular Stomatitis Virus to Abrogate Neurotoxicity, Circumvent Humoral Immunity, and Enhance Oncolytic Potency - Cancer Res 2014;74:3567-3578

R19-1390 Howerth EW, Stallknecht DE, Dorminy M, Pisell T, Clarke GR. Experimental vesicular stomatitis in swine: effects of route of inoculation and steroid treatment. J Vet Diagn Invest 1997; 9; 136-142

R19-1556 Muik, Kneiske et al. Pseudotyping Vesicular Stomatitis Virus with Lymphocytic Choriomeningitis Virus Glycoproteins enhances infectivity for glioma cells and minimizes neurotropism – Journal of Virology (2011) 85: 5679-5684

R19-1566 Clarke, D. K., et al. Synergistic attenuation of vesicular stomatitis virus by combination of specific G gene truncations and N gene translocations. J. Virol. 81:2056–2064 (2007).

R19-1584 Dold C, Urbiola CR, Wollmann G, Egerer L, Muik A, Bellmann L, et al. Application of interferon modulators to overcome partial resistance of human ovarian cancers to VSV-GP oncolytic viral therapy. Mol. Therapeutics Oncolytics (2016)

R19-1585 Kimpel J, Urbiola C, Koske I, Tober R, Banki Z, Wollmann G, et al. The oncolytic virus VSV-GP is effective against malignant melanoma. Viruses (2018)

R19-1587 Urbiola, Santer, Petersson et al. Oncolytic activity of the rhabdovirus VSV-GP against prostate cancer – International Journal of Cancer (2018).

R20-2020 Restellini S, Chazouilleres O, Frossard JL (2017). Hepatic manifestations of inflammatory bowel disease.

R20-0268 Berkeley RA, Steele LP, Mulder AA, Wollenberg DJM van den, Kotte TJ, Thompson J, et al, Antibody-neutralized reovirus is effective in oncolytic virotherapy. Cancer Immunol Res 2018; 6(10); 1161-1173

R20-2735 Moore JB, June CH. (2020). Cytokine release syndrome in severe COVID-19: Lessons from arthritis and cell therapy in cancer patients point to therapy for severe disease.

R21-0236 Lamin et al. Tamoxifen protects from vesicular stomatitis virus infection. Pharmaceuticals (2019) 12; 142

R21-0289 Schreiber et al. The lytic activity of VSV-GP treatment dominates the therapeutic effects in a synergistic model of lung cancer. British Journal of Cancer (2019) 121:647-658

R21-0743 Committee for Medicinal Products for Human Use: ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials: step 5 (17 February 2020, EMA/CHMP/ICH/436221/2017). Source: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-e stimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_e n.pdf (access date: 26 February 2021) ; European Medicines Agency (EMA); 2020.

R21-1792 Wollmann G et al. Some attenuated variants of vesicular stomatitis virus show enhanced oncolytic activity against human glioblastoma cells relative to normal brain cells. J. Virol. 84:1563–1573 (2010)

R21-1793 Finkelshtein, D. et al. LDL receptor and its family members serve as the cellular receptors for vesicular stomatitis virus. Proc. Natl Acad. Sci. USA 110, 7306–7311 (2013)

R21-1794 Kelly, E. J., R. Nace, G. N. Barber, and S. J. Russell. Attenuation of vesicular stomatitis virus encephalitis through microRNA targeting. J. Virol. 84:1550–1562 (2010)

R21-1795 Stojdl, D. F., et al. VSV strains with defects in their ability to shutdown innate immunity are potent systemic anti-cancer agents. Cancer Cell 4:263– 275 (2003)

R21-2043 Oncolytic Virus: Considerations for the evaluation of shedding (version 1, December 2020); European Commission; 2020

R21-2860 Murphy K, Weaver C. Janeway's Immunobiology 9th Edition, 2017.

R21-4456 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.

9.2 UNPUBLISHED REFERENCES

c38438874 BI 1821736 Investigator's Brochure, current version

c39811008 Efficacy analysis of BI 1821736 [redacted]

n00279792 Tolerance evaluation of the oncolytic virus VSV-GP in healthy [redacted]

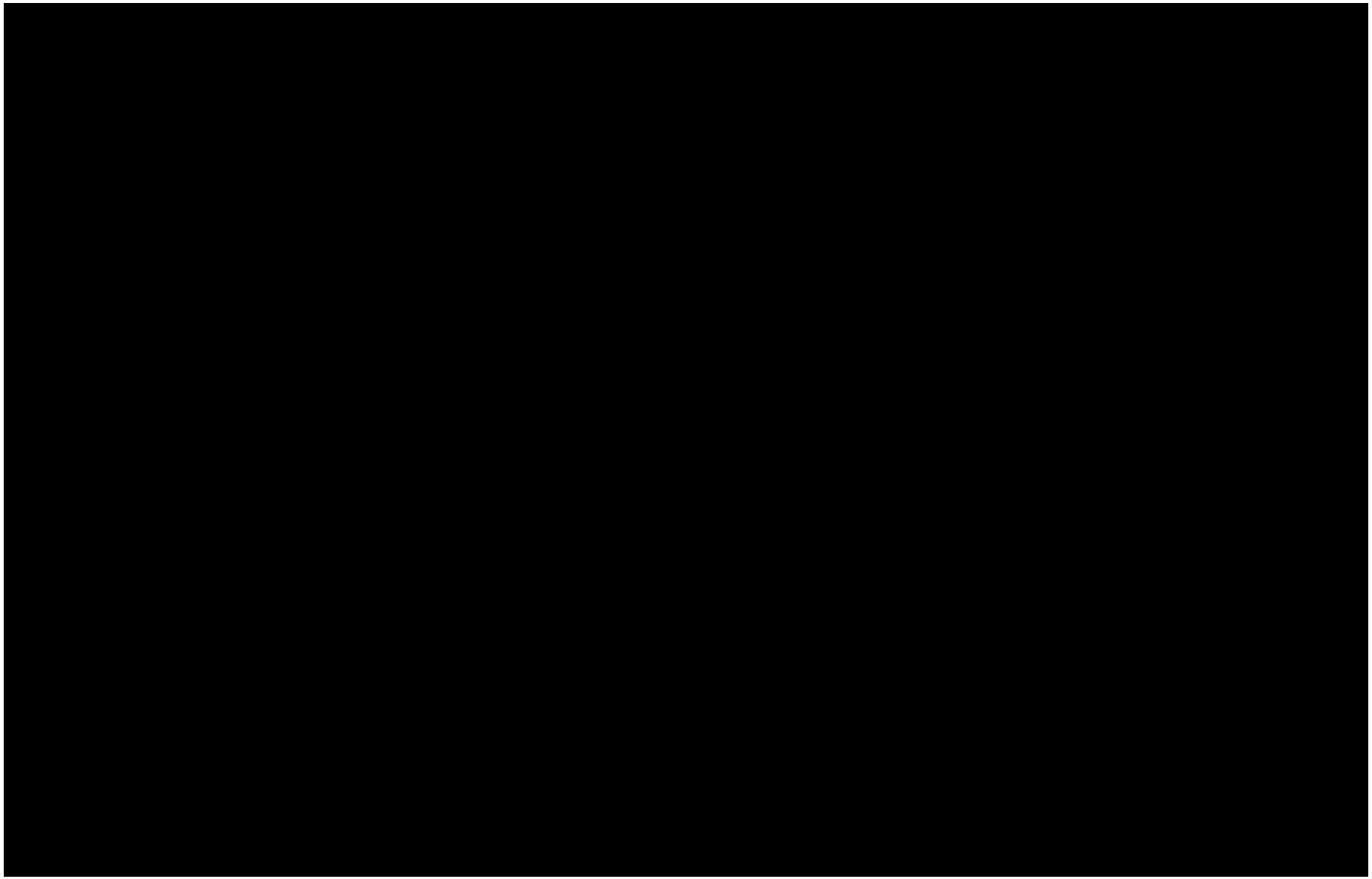
n00286563 Neurotoxicity Study of BI 1831169/VSV-GP and WT-VSV [redacted] 14 Dec 2021.

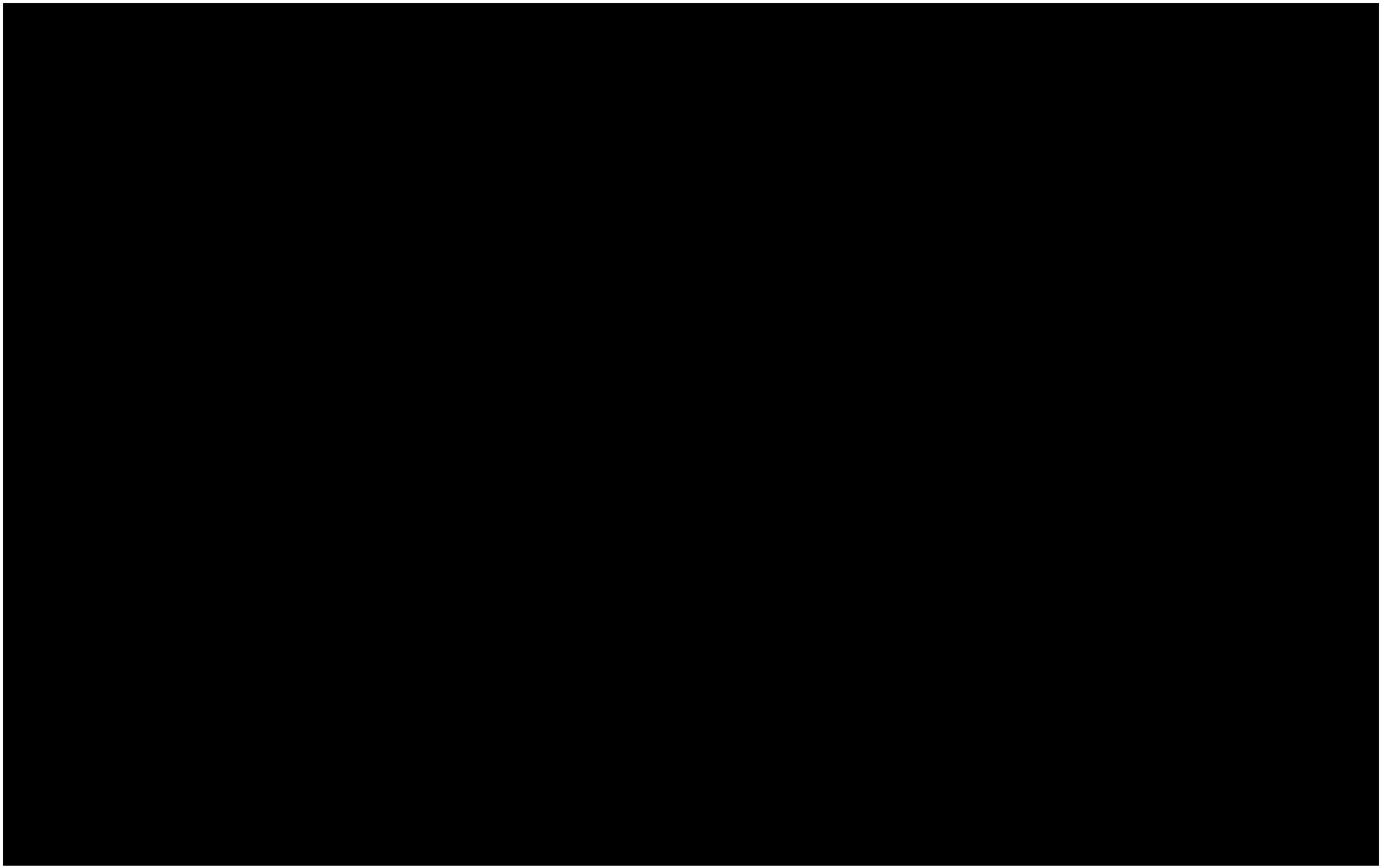
n00290675 BI 1821736: Biodistribution Study in [redacted]. 21R119. 18 Jul 2022.

n00294923 Toxicokinetics for BI 1821736: Repeat Dose [redacted] Study of BI 1821736 in Healthy [redacted] Followed by a Recovery Period. 21R116. 23 Sep 2022.

n00296875 Toxicokinetics for BI 1821736: Repeat [redacted] Study in [redacted] 21R117. 15 Sep 2022.

n00297864 [redacted] safety profiling of BI 1821736. 22R093. Report in progress





10.2 PATIENT OBSERVATION REQUIREMENTS

Table 11 Minimum assessments and duration of surveillance in patients receiving [redacted] of BI 1821736

Time Point (calculated from the [redacted])	**Vital signs** (pulse rate, blood pressure, pulse oximetry, and body temperature)	**Assessment of CRS symptoms** e.g. fever, hypotension, tachycardia, hypoxia, nausea, fatigue, headache, myalgias, and malaise
30 (+/-10) min	X	X
60 (+/-10) min	X	X
90 (+/-10) min	X	X
2 hrs (+/-15 min)	X	X
3 hrs (+/-15 min)	X	X
4 hrs (+/-15 min)	X	X
6 hrs (+/-15 min)	X	X
Every 4 hrs (+/- 30 min) from 10 hrs with a final assessment at 26 hrs after [redacted]	X[a]	X[a]

a From [redacted] onwards, the recommended surveillance period is 6 hrs from completion of all treatment, but this may be shortened as medically appropriate, provided there were no CRS symptoms observed in the previous administration. In case patient suffered from CRS symptoms at previous [redacted] surveillance at subsequent administration must be prolonged according to Section 4.1.4.3.

10.3 PRECAUTIONS FOR STAFF AND PATIENT MANAGEMENT FOR BI 1821736 TREATMENT

10.3.1 Preparation and Administration of BI 1821736

Pharmacy staff must have a good handwashing technique and must use protective equipment; minimum of single use gloves, gown, masks (recommended N95/FFP2) and eye protection where there is a risk of splashes. They must use a class II Biosafety Cabinet using sterile technique. Syringes prepared should be transported in a disposable impermeable plastic container with an absorbent material (e.g. paper towel) at the bottom.

Precautions, including those listed below, must always be taken with sharp items. These include:

- Careful management of needles and other sharps are of primary importance. Needles must not be bent, sheared, broken, recapped, removed from disposable syringes, or otherwise manipulated by hand before disposal.
- Used disposable needles and syringes must be carefully placed in conveniently located puncture-resistant containers used for sharps disposal.
- Non-disposable sharps must be placed in a hard-walled container for transport to a processing area for decontamination, preferably by autoclaving.
- Broken glassware must not be handled directly. Instead, it must be removed using a brush and dustpan, tongs, or forceps. Plastic ware should be substituted for glassware whenever possible.

On departure from the room, staff must remove all protective equipment and dispose of appropriately within the patient's private room or within pharmacy accordingly.

10.3.2 Patient Management whilst at the trial site

Following their treatment with BI 1821736, the patient must be admitted to a private room and remain in a private room until discharge; patient's movements within the hospital should be limited to the minimum necessary (for example a patient may move from a phase I unit-private room to another private room for overnight stay).

When outside the room, the patient must wear a surgical grade mask and ensure that all injected and biopsied sites are covered with airtight and watertight dressings.

Patients should be provided a sealed bin for storing any soiled plasters/Band-Aids/dressings as well as a supply of surgical grade masks for their use in between visits.

10.3.3 Disposal of materials, handling of spillages, and cleaning of potentially affected areas including patient room

After patient's discharge, potentially contaminated surfaces (e.g. bathroom equipment [faucet, toilet, sink, etc.], room furniture [nightstand, table, chair etc.], floor, hand rails etc.) should be disinfected following applicable local cleaning procedures.
All patient materials should be handled as infected articles. For disposal, all materials should be decontaminated by steam sterilization, chemical disinfection, and/or incineration; needles

and sharp instruments should be stored in dedicated containers. Note: Recommendations should also be adapted following local protocols and regulations.

Any spills or soiled material handled per standard procedures for infectious/contaminated material.

- **Inactivation**: BI 1821736 is susceptible to all disinfectants for enveloped viruses and is inactivated by 1% cresylic acid, phenolics, chlorinated phenol, 2.5% phenol, 0.4% HCl, 2% sodium orthophenylphenate, and 1% sodium hypochlorite. Physical inactivation: BI 1821736 is inactivated by heating (60ºC, 30 min). BI 1821736 survives temporarily on contaminated surfaces.
- **Handling of spills**: Inform and warn colleagues in direct proximity. Allow aerosols to settle and, wearing protective clothing, gently cover spill with paper towels and apply appropriate disinfectant, starting at the perimeter and working towards the centre. Allow sufficient contact time before cleaning up (30 min).

10.4 STATISTICAL APPENDIX

10.4.1 BLRM for dose escalation

10.4.1.1 Model description of BLRM

This is an open-label trial. To determine the MTD and RP2D, patients are entered sequentially into escalating dose cohorts (see Section 3.1). The dose escalation will be guided by a Bayesian 2-parameter logistic regression model with overdose control (BLRM-EWOC). The model is defined as follows: Let π_d be the probability of experiencing a DLT during the MTD evaluation period (Cycle 1) under dose d of BI 1821736. A logistic regression is performed to model the dose-toxicity relationship:

[redacted]

π_d represents the probability of having a DLT during the MTD evaluation period at dose d, d* is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose [redacted] is the parameter vector of the model. Here, the dose [redacted] was chosen to represent the reference dose for BI 1821736.

Since a Bayesian approach is applied, a prior distribution for the unknown parameter vector θ needs to be specified. A weakly informative 3-component mixture prior distribution was chosen (Table 12).

Table 12 Summary of 3-component mixture prior distribution

Parameter	Tox scenario	Means vector (log(α), log(β))	SD vector (log(α), log(β))	Correlation	Mixture weight
[redacted]					

The prior may be updated once the trial has started in case new data that can be used will be available. If different to the prior described here, the prior that is used for each BLRM analysis for the DEC meetings will be documented in the DEC minutes, and the prior used for the final analysis will be documented in the TSAP.

The following intervals will be used to summarize the estimated probabilities π_d of a DLT at each dose level:

- Under toxicity: [redacted])
- Target toxicity: [redacted])
- Over toxicity: [redacted]]

Prior probabilities of a DLT at different doses and the corresponding probability of under-dosing, targeted dosing and overdosing are summarized in Table 13. The prior probability of over toxicity at the starting dose of [redacted] formally fulfills the EWOC criterion and is, therefore, a suitable starting dose.

Table 13 Prior probabilities of DLT

Dose ([redacted])	Probability of true DLT rate in					Quantiles		
	[0-0.16)	[0.16-0.33)	[0.33-1)	Mean	SD[#]	2.5%	50%	97.5%
[redacted]								

*, probability for over toxicity at the starting dose; #, dose meets the overdose criterion at the start of trial (P(overdose) < 0.25); number of simulations = 20,000

The primary analysis of the primary objective, determination of the MTD, is based on the above-specified BLRM, which is built on the escalation with overdose control (EWOC) principle. As per EWOC criterion, at any given dose escalation decision, the probability of over-dosing (i.e. of the DLT rate lying in [redacted]]) must be below 0.25 for the dose assigned to the next cohort of patients. These probabilities will be determined using the above-specified BLRM including all available data on DLTs within the MTD evaluation periods from all patients evaluable for MTD. Patients are considered evaluable for MTD if they either experienced DLT or if they completed the MTD evaluation period without experiencing DLT and were not replaced.

At any point in time, the BLRM-recommended dose is the dose level with the largest posterior probability of targeted dosing (i.e. of the DLT rate lying in [0.16-0.33)) that satisfies the EWOC principle given the current data. The dose level assigned to a cohort of patients must never exceed the highest dose satisfying the EWOC principle.

The DEC may decide to stop dose escalation once the criteria for MTD selection are reached. However, the DEC may recommend enrolling additional patients at the MTD or a lower dose level to confirm the initial estimate.

A detailed evaluation of the model using hypothetical data scenarios and operating characteristics is provided below.

10.4.1.2 Model evaluation of BLRM

A monotherapy BLRM with overdose control will be used to guide all dose-escalation decisions during the trial. After patients in each cohort have completed the MTD evaluation period, the prior distribution will be updated through MCMC (Markow-Chain-Monte-Carlo) sampling procedures with the accumulated DLT data (from the MTD evaluation period). Posterior probabilities for the rate of DLTs will be summarized. Selection of the next dose will then be based on these probabilities (recommendation) as well as on other safety and laboratory data (DEC decision). None of the dose levels are allowed to be skipped.

Below, performance metrics (operating characteristics) are presented (Table 16 and Table 17) that illustrate the precision of the design in estimating the MTD under various dose-toxicity relationships through computer simulation. In addition, recommendations of the next dose level in each schedule by the joint BLRM with overdose control principle are also provided under various hypothetical outcome scenarios to show how the model facilitates on-trial dose-escalation decisions (see Table 14). The recommended next dose is computed as defined above, i.e. as the dose with the highest probability of having a DLT rate in the target interval [0.16-0.33) among all doses that satisfy the EWOC criterion, i.e. the probability of the DLT rate of a dose exceeding 0.33 must be below 0.25.

10.4.1.3 Hypothetical data scenarios of BLRM

Hypothetical data scenarios are shown in Table 14. These scenarios reflect potential on-trial data constellations and related escalation as allowed by the model. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target dose and over-dosing are shown.

- Scenario 1: If no DLTs is observed in the first patient, escalation to dose level 2 is allowed by the model.
- Scenario 2: In case the first patient experiences DLT, 2 more patients will be recruited at the discretion of the DEC. If no more DLTs are observed, the model will recommend to stay at DL2.
- Scenario 3: With 2 DLTs in first 3 patients at dose level 1, the model recommends to de-escalate (stop the trial).
- Scenario 4: With 1 DLT in 6 patients at the first dose level the model allows to escalate to DL2.
- Scenario 5: With 2 DLTs in 6 patients at the first dose level the model recommends to de-escalate (stop the trial).
- Scenario 6: With no DLTs in the single patient cohorts at dose levels 1 and 2, the model allows to escalate to DL3.

- Scenario 7: With no DLT at the starting dose level and a single DLT in 3 patients at dose level 2, the model recommends to stay at DL2. This scenario may happen when the first patient at DL2 experiences DLT and the DEC decides to expand the cohort to 3 patients.
- Scenario 8: Building on scenario 7 (add 3 patients at DL2): If no further DLTs happen at DL2 the model recommends to escalate to DL3.
- Scenario 9: With no DLTs recorded at the first 3 dose levels the model recommends to escalate to DL4.
- Scenario 10: With 1/3 DLTs at dose level 3 (and no DLTs below) the model recommends to stay at dose level 3.
- Scenario 11: Building on scenario 11: With 3 more patients at dose level 3 and no more DLTs (1/6) the model recommends to escalate to DL4.
- Scenario 12 describes the odd/unlikely case where both sentinel patients at dose levels 1 and 2 experience DLTs and the DEC decides to expand cohorts to 6 patients (no further DLTs). With no DLT observed in 3 patients at dose level 3, the model recommends to escalate to DL4.
- Scenario 13: Same as scenario 13, but now 1/3 patients at dose level 3 has DLT. The model recommends to stay at DL3. No escalation allowed.
- Scenario 14: Building on scenario 14: After adding 3 more patients to DL3 (no further DLT) the model does not allow to escalate (conservative behavior). See next scenario 16.
- Scenario 15: Building on scenario 14/15: After adding a seventh patient to dose level 3 (nore more DLT) the model allows to escalate to DL4.
- Scenario 16: With no DLT at dose levels 1-4 the model allows to escalate to DL5.
- Scenario 17: With 1/3 DLTs at dose level 4 (and no DLT below) the model recommends to stay at DL4.
- Scenario 18: Building on scenario 18: After adding 3 more patients to DL4 and no further DLT the model recommends to escalate to DL5.
- Scenario 19: Like scenario 18 but 2/3 DLT at dose level 4: Model recommends to de-escalate to DL3.
- Scenario 20: With no DLT recorded up to dose level 5, the model recommends to escalate to DL6.
- Scenario 21: With 1/3 DLT at dose level 5 and no DLT below, the model recommends to stay at DL5.
- Scenario 22: After adding 3 more patients at DL5 and no further DLT (1/6) , the model allows to escalate to DL6.
- Scenario 23: Same as scenario 22 but 2/3 DLT at dose level 5: Model recommends to de-escalate to DL4.
- Scenario 24: With no DLT recorded up to dose level 6, the model recommends to escalate to DL7.
- Scenario 25: With 1/3 DLT at dose level 6 and no DLT below, the model recommends to stay at DL6.
- Scenario 26: After adding 3 more patients to DL6 (no further DLT; 1/6) the model does not allow to escalate (conservative behavior). See next scenario 28.
- Scenario 27: Building on scenario 26/27: After adding a seventh patient to dose level 6 (no further DLT; 1/7) the model allows to escalate to DL7.

- Scenario 28: With 2/3 DLTs at dose level 6 and no DLTs below, the model recommends to de-escalate to DL5.
- Scenario 29: With no DLT recorded up to dose level 7 and no higher dose level to explore, the model recommends to stay at to DL7.
- Scenario 30: With 1/3 DLT at dose level 7 and no DLT below, the model recommends to stay at DL7.
- Scenario 31: After adding 3 more patients to DL7 (no further DLT; 1/6) and no higher dose levels to explore, the model recommends to stay at DL7 and pursue MTD/RP2D.
- Scenario 32: With 2/3 DLTs at dose level 7 and no DLTs below, the model recommends to de-escalate to DL6.
- Scenario 33: Building on scenario 32: After adding 3 more patients to dose level 7 and no further DLTs (1/9), the escalation may be stopped with MTD not reached at DL7.
- Scenario 34: Building on scenario 33: With excessive toxicity at dose level 7 (2/3 DLT) and 1/9 DLT at dose level 6 the MTD may be declared.

Table 14 Hypothetical data scenarios

Scenario	Observed Data			P(OD) at max. tested dose[#]	Next recommended dose level*§	At next allowed dose:		
	Dose level	# Patients	# DLTs			P(UD)	P(TD)	P(OD)
1	1	1	0	0.035	2	0.882	0.066	0.052
2	1	3	1	0.234	1	0.502	0.264	0.234
3	1	3	2	0.691	NA	NA	NA	NA
4	1	6	1	0.067	2	0.579	0.295	0.126
5	1	6	2	0.289	NA	NA	NA	NA
6	1 2	1 1	0 0	0.026	3	0.865	0.083	0.051
7	1 2	1 3	0 1	0.174	2	0.551	0.275	0.174
8	1 2	1 6	0 1	0.048	3	0.573	0.299	0.127
9	1 2 3	1 1 3	0 0 0	0.009	4	0.900	0.077	0.023
10	1 2 3	1 1 3	0 0 1	0.152	3	0.562	0.286	0.152
11	1 2 3	1 1 6	0 0 1	0.043	4	0.557	0.316	0.127
12	1 2 3	6 6 3	1 1 0	0.081	4	0.351	0.424	0.225
13	1 2 3	6 6 3	1 1 1	0.243	3	0.245	0.512	0.243
14	1 2 3	6 6 6	1 1 1	0.114	3	0.379	0.507	0.114
15	1 2 3	6 6 7	1 1 1	0.078	4	0.249	0.523	0.227
16	1 2 3 4	1 1 3 3	0 0 0 0	0.005	5	0.880	0.089	0.031
17	1 2 3 4	1 1 3 3	0 0 0 1	0.092	4	0.626	0.282	0.092
18	1 2 3 4	1 1 3 6	0 0 0 1	0.027	5	0.556	0.311	0.133
19	1 2 3 4	1 1 3 3	0 0 0 2	0.343	3	0.470	0.386	0.144

Table 14. contd. Hypothetical data scenarios

Scenario	Observed Data			P(OD) at max. tested dose[#]	Next recommended dose level*§	At next allowed dose:		
	Dose level	# Patients	# DLTs			P(UD)	P(TD)	P(OD)
20	1	1	0	0.007	6	0.828	0.126	0.047
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	0					
21	1	1	0	0.089	5	0.623	0.289	0.089
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	1					
22	1	1	0	0.028	6	0.509	0.316	0.176
	2	1	0					
	3	3	0					
	4	3	0					
	5	6	1					
23	1	1	0	0.343	4	0.556	0.358	0.086
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	2					
24	1	1	0	0.011	7	0.731	0.165	0.105
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	0					
	6	3	0					
25	1	1	0	0.096	6	0.602	0.302	0.096
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	0					
	6	3	1					
26	1	1	0	0.035	6	0.729	0.237	0.035
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	0					
	6	6	1					
27	1	1	0	0.025	7	0.435	0.321	0.244
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	0					
	6	7	1					
28	1	1	0	0.373	5	0.613	0.313	0.074
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	0					
	6	3	2					

Table 14. contd. Hypothetical data scenarios

Scenario	Observed Data			P(OD) at max. tested dose[#]	Next recommended dose level*§	At next allowed dose:		
	Dose level	# Patients	# DLTs			P(UD)	P(TD)	P(OD)
29	1	1	0	0.022	(7) *	0.867	0.111	0.022
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	0					
	6	3	0					
	7	3	0					
30	1	1	0	0.178	7	0.470	0.352	0.178
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	0					
	6	3	0					
	7	3	1					
31	1	1	0	0.062	(7) *	0.660	0.278	0.062
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	0					
	6	3	0					
	7	6	1					
32	1	1	0	0.535	6	0.611	0.332	0.058
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	0					
	6	3	0					
	7	3	2					
33	1	1	0	0.017	(7)*	0.786	0.197	0.017
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	0					
	6	3	0					
	7	9	1					
34	1	1	0	0.545	6	0.574	0.382	0.044
	2	1	0					
	3	3	0					
	4	3	0					
	5	3	0					
	6	9	1					
	7	3	2					

*If the maximum allowed dose based on the EWOC criterion exceeds the dosing scheme, the maximum allowed next dose is displayed in brackets. Probabilities of overdosing, underdosing, and target dosing are displayed for the maximum allowed dose in this case.
§Entry NA indicates that none of the pre-specified doses is allowed by the EWOC criterion. In practice, dose escalation may continue on doses below the pre-specified ones if agreed between the sponsor and the DEC.
$OD/UD/TD: overdosing (DLT rate ≥0.33), underdosing (DLT rate <0.16), target dosing (0.16 ≤ DLT rate <0.33).

10.4.1.4 Operating characteristics of the BLRM

Operating characteristics are a way to assess the long-run behaviour of a model by illustrating the precision of the design in estimating the MTD. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation. Table 15 summarizes the assumed 5 dose-toxicity scenarios which were used to assess the operating characteristics of the model. The toxicity scenarios reflect a wide range of possible cases as follows:

- Scenario 1: realistic toxicity (aligned with prior medians)
- Scenario 2: medium-high toxicity scenario
- Scenario 3: low-toxicity scenario
- Scenario 4: non-logistic scenario
- Scenario 5: high tox scenario

Table 15 Assumed true dose-toxicity scenarios

Tox. Scenario	Dose ([redacted]						
1: realistic	0.008	0.013	0.025	0.04	0.08	0.15	0.27
2: medium-high	0.19	0.23	0.27	0.39	0.45	0.54	0.60
3: low	0.001	0.005	0.01	0.02	0.04	0.08	0.17
4: non-logistic	0.01	0.07	0.13	0.19	0.25	0.31	0.37
5: high	0.32	0.46	0.59	0.69	0.77	0.83	0.89

For each of these scenarios, 1000 trials were simulated. For simplicity reasons, a uniform cohort size of 3 patients (all assumed evaluable) was employed for the determination of the operating characteristics. The number of patients with DLTs were simulated sequentially for cohorts of patients according to the DLT rates specified in the dose-toxicity scenarios. Using this, the posterior of the BLRM was computed and used to decide on the dose level for the next cohort to be recruited.

Dose escalation decision were simulated using the following rules:

- Escalate to the dose among the considered dose levels which maximizes the probability of the targeted toxicity region among the doses satisfying the overdose criterion, provided that this dose is at most double the previous dose
- The MTD was considered reached if (1) at least 9 patients had been evaluated overall, (2) a dose level is the model's recommendation for the next dose cohort 2 times in a row, and (3) for this dose the posterior probability of targeted toxicity was at least 50% or (4) at least 6 patients have been treated at this dose. In this case, the dose satisfying these conditions is declared the MTD.

The trial was considered stopped without declaring an MTD when the number of patients exceeded a pre-specified maximum sample size (n=50; e.g. considering 6 per dose level, 8 for MTD confirmation) before the conditions for MTD selection were satisfied. It was then assessed how often a dose was declared as MTD with true DLT rate in the under-, target or

overdose interval. Furthermore, the average, minimum and maximum number of patients per simulated trial and the average number of DLTs per simulated trial are reported.

Results are summarized in Table 16. Additional metrics are presented in Table 17.

Scenario 1 (moderate/realistic toxicity): most simulated trials (86%) declared a MTD with true DLT rate in the target toxicity interval.

Scenario 2: (medium-high tox) assumed a medium to high dose-toxicity relationship. Ca. 47% of the simulated trials declare MTDs with true DLT rate in the target interval and around 0% of the trials declare MTDs with true DLT rate in the underdose interval. About 16% of the simulated trials chose an overdose MTD. 37% of the trials stopped before finding an MTD.

Scenario 3 (low-toxicity scenario): Ca. 75% of the simulated trials have declared MTDs with true DLT rate in the target interval and the remaining 25% of the trials have declared MTDs with true DLT rate in the underdose interval. This is expected based on the assumed true DLT rates, which are all very low, with just the highest dose level reaching into the low end of the target interval.

Scenario 4 (non-logistic): around 78% of the simulated trials have declared MTDs with true DLT rate in the target interval and ca. 16% of the trials have declared MTDs with true DLT rate in the underdose interval, while 6% of trials declared an MTD in the overdose range. 0.4% of simulated trials stopped before declaring an MTD.

Scenario 5 (high tox): around 87% of simulated trials were stopped without identifying a MTD since no dose level was considered safe anymore. This behaviour is considered acceptable since the starting dose is associated with a DLT rate 32% in this scenario, which is very close to the overdose range. The number of patients at the higher dose levels was low on average which demonstrates that the overdose control principle implemented in the model is effectively protecting patients from being treated at toxic doses. Of those trials that found a MTD, approximately 6% of the trials declared dose level 1 as MTD, which has a true DLT rate right at the upper end of the target interval.

In summary, the 2-parameter monotherapy BLRM as specified above exhibits acceptable operating characteristics under various dose-toxicity scenarios. Escalation decisions are considered conservative in nature due to the overdosing criterion.

Table 16 Simulated operating characteristics – results summary

Scenario	% of trials declaring MTD with true rate in interval:				# Patients Mean (Min,Max)	# DLTs Mean (Min,Max)
	underdose	target	overdose	(trial stopped*)		
1	13.7	86.3	0	0	22.3 (15,36)	2.5 (0,6)
2	0	47.1	16.0	36.9	13.3 (3,33)	3.5 (2,9)
3	24.9	75.1	0	0	24.7 (12,39)	1.4 (0,6)
4	15.8	77.5	6.3	0.4	20.4 (3,42)	3.2 (0,10)
5	0	6.1	7.3	86.6	6.0 (3,33)	2.4 (1,10)

*Stopped without reaching the MTD; trials are stopped when none of the pre-specified doses satisfies the EWOC criterion or when they reach the maximum sample size before selecting an MTD

Table 17 Simulated operating characteristics – additional metrics

Scenario	% of trials declaring MTD at dose ([redacted]						
	[redacted]						
1	0 (UD)	0 (UD)	0.8 (UD)	12.9 (UD)	35.5 (TD)	31.9 (TD)	18.9 (TD)
2	3.3 (TD)	20.5 (TD)	23.3 (TD)	14.0 (OD)	2.0 (OD)	0 (OD)	0 (OD)
3	0 (UD)	0 (UD)	0.1 (UD)	0.1 (UD)	5.4 (UD)	19.3 (UD)	75.1 (TD)
4	0.1 (UD)	4.5 (UD)	11.2 (UD)	35.2 (TD)	31.5 (TD)	10.8 (TD)	6.3 (OD)
5	6.1 (TD)	6.9 (OD)	0.4 (OD)	0 (OD)	0 (OD)	0 (OD)	0 (OD)

UD, underdose; TD, target dose; OD, overdose

10.5 ECOG PERFORMANCE STATUS CRITERIA

ECOG Status	MEANING
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hrs
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hrs
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.*Am J Clin Oncol.* 1982; 5:649-655.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of Amendment		25 Jan 2023
EU Trial No.		2022-502125-17-00
BI Trial No.		1467-0001
BI Investigational Medicinal Product		BI 1821736
Title of protocol		An open-label, Phase I dose escalation and expansion trial to investigate safety and efficacy of BI 1821736 in patients with advanced solid tumors
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Synopsis
Description of change		The approximate total number of patients treated has been updated to 27.
Rationale for change		The approximate total number of patients treated has been updated due to the addition of 3 DLs.
Section to be changed		Synopsis
Description of change		BI 1821736 will be tested at [redacted] and [redacted].
Rationale for change		FDA request to limit the dose escalation interval to approximately 3-fold.
Section to be changed		Flowchart
Description of change		Footnote d: Addition of sentence that for patients with documented objective progression a phone contact should occur to collect the most relevant information: adverse events, or last contact date in case of lost to follow-up. Footnote 2: Updated to confirm that optional consent for biobanking also includes leftover blood (serum/ plasma) samples. Footnote 6: Addition of pulse oximetry to vital signs. Footnote 14: Updated to include potential VSV-related skin lesion (i.e. mouth vesicles) swabs. Footnote 15: Update to confirm that [redacted] biopsy is mandatory only where clinically feasible. Footnote 18: Clarification that tumor assessment/imaging will be performed at the time of EOT, regardless of progression at [redacted]
Rationale for change		Footnote d: Clarification that all patients should be followed up after EOT regardless of their progression status.

		Footnote 2: Administrative update to provide clarity. Footnote 6: French Health Authority request to add to 1456-0001 (VSV-GP) CTP. Footnote 14: FDA request. Footnote 15: Update to provide clarity around the collection of the [redacted] biopsy. Footnote 18: Administrative update to provide clarity.
Section to be changed		Section 1.4.2 and Appendix 10.6
Description of change		The risk-benefit assessment in the context of the COVID-19 pandemic has been moved to Section 1.4.2.1 and Appendix 10.6 has been removed.
Rationale for change		The COVID-19 pandemic is now active in less countries. All risks in the context of the COVID-19 pandemic contained in one section.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 3.1
Description of change		Figure 3 has been updated due to the addition of the 3 DLs. Incremental dose increases in successive cohorts will be approximatively 3-fold of the previous dose level but no more than [redacted]-fold. At least 1 patient will be treated at DL1 and DL2. From DL3 and above, all cohorts will include at least 3 patients. Dose escalation will occur only if the minimum required number of patients per dose level are evaluated for DLT in the MTD evaluation period.
Rationale for change		FDA requests.
Section to be changed		Section 3.1.1
Description of change		The first patient at each DL will complete the MTD observation period before the next patient is dosed. The subsequent patients will start treatment at least 1 week apart.
Rationale for change		FDA requests.
Section to be changed		Section 3.1.2
Description of change		The two following reasons of enrollment stop have been added:

		• A death occurring within 30 days from administration of the study drug unless clearly due to disease progression. • A death at any time during the treatment period considered by the investigator or Sponsor as at least possibly related to the study drug.
Rationale for change		FDA requests
Section to be changed		Section 3.3.3
Description of change		The following exclusion criterion has been added: Patients with cardiac risks including congestive heart failure (as defined by New York Heart Association Functional Classification III or IV), unstable angina, serious uncontrolled cardiac arrhythmia, a myocardial infarction within 6 months of first dose of study treatment or a history of myocarditis. Administrative update to exclusion criterion 6 to ensure correct implementation.
Rationale for change		FDA request. Administrative change.
Section to be changed		Section 3.3.4
Description of change		Updated to confirm that patients with documented objective progression should have a phone contact every 9 weeks (+/- 3 weeks).
Rationale for change		Consistency with FUP visits for patients without documented objective progression at EOT.
Section to be changed		Section 4.1.2
Description of change		Table 3 has been updated due to the addition of the 3 DLs. At least 1 patient will be treated at the low dose levels (DL1, DL2). In case DL1 had to be expanded, at least 3 patients will be treated at DL2. From DL3 onwards, cohorts of at least 3 patients will be enrolled at escalating dose levels.
Rationale for change		FDA requests.
Section to be changed		Section 4.1.4.2
Description of change		The following criteria have been added • Decreased neutrophils and/or platelets have resolved to CTCAE Grade ≤1 • Increased AST, ALT and/or bilirubin have resolved to CTCAE Grade ≤1 (or baseline if higher than Grade 1 at baseline).
Rationale for change		FDA requests.
Section to be changed		Section 4.1.7

Description of change		Addition of text that the procedure described in the ISF has to be followed if the storage conditions are found to be outside the specified range.
Rationale for change		Administrative updates to provide clarity.
Section to be changed		Section 4.2.2.2
Description of change		Removal of the word 'protected' to confirm that all sexual intercourse should be avoided for the 10 days following each treatment with BI 1821736. Replacement of the word '[redacted] with '[redacted] in this section and throughout the CTP.
Rationale for change		Administrative updates to provide clarity.
Section to be changed		Section 4.2.2.3
Description of change		Clarification regarding contraception requirements for male trial participants or male partner of trial participants.
Rationale for change		Inconsistent with restriction listed in Section 4.2.2.2 Restrictions on diet and lifestyle.
Section to be changed		Section 5.1
Description of change		A lesion that is biopsied cannot be selected as a target lesion. Clarification that tumor assessment/imaging will be performed at the time of EOT, regardless of progression at [redacted]
Rationale for change		FDA request. Administrative update to provide clarity.
Section to be changed		Section 5.2.2 (also referenced in Flowchart footnote 6 and Sections 4.1.4.1 and 10.2 Table 11)
Description of change		Addition of pulse oximetry to vital signs.
Rationale for change		French Health Authority request to add to 1456-0001 (VSV-GP) CTP.
Section to be changed		Section 5.2.3
Description of change		Updated to confirm that safety laboratory parameters will be analysed by a local laboratory and not the central laboratory.
Rationale for change		Procedural change for analysis of safety laboratory parameters.
Section to be changed		Section 5.2.5.1
Description of change		Addition of a blood sample for measuring inflammatory cytokines at the time of an [redacted]-related reaction.
Rationale for change		Testing for CRS at the time of an [redacted]-related reaction.
Section to be changed		Section 5.2.5.3
Description of change		Removal of reference to storing and then disposal of remaining samples 5 years after final trial report.

Rationale for change		Testing for $CD4^+$ and $CD8^+$ T cells performed by CRO who will dispose of samples once testing is complete and the results have been successfully transferred to Boehringer Ingelheim.
Section to be changed		Section 5.3.5
Description of change		Addition of population PK modeling section.
Rationale for change		PK data may also be analyzed by applying the population PK approach using a validated software (e.g. NONMEM®).
Section to be changed		Section 5.4.2.1
Description of change		Update to confirm that [redacted] biopsy is mandatory only where clinically feasible and patients may continue treatment if the on-treatment biopsy cannot be collected. Tumor biopsies should be collected from non-target lesions.
Rationale for change		Clarification regarding the collection of the [redacted] biopsy. FDA request.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 5.5
Description of change		Updated to confirm that leftover serum samples collected for IFNα measurements may be biobanked.
Rationale for change		Clarification of which blood samples may be biobanked.
Section to be changed		Section 5.6.3 (also referenced in Flowchart footnote 14 and Section 2.2.2)
Description of change		Updated to include potential VSV-related skin lesion (i.e. mouth vesicles) swabs.
Rationale for change		FDA request.
Section to be changed		Section 6.2.3.1 (also referenced in Flowchart footnote 18)
Description of change		Clarification that tumor assessment/imaging will be performed at the time of EOT, unless it has been done within the past 4 weeks, regardless of progression.
Rationale for change		Administrative update to provide clarity.
Section to be changed		Section 6.2.3.2
Description of change		Updated to confirm that all patients, regardless of whether they progressed on treatment or at the EOT visit, will have follow-up visits to assess for new treatment related AEs and status of ongoing drug-related AEs.
Rationale for change		Clarification that all patients should be followed up after EOT regardless of their progression status.

Section to be changed		Section 7.2.3
Description of change		Update to primary analyses.
Rationale for change		FDA request to limit the dose escalation interval to approximately 3-fold resulting in 3 additional DLs being added.
Section to be changed		Section 7.5
Description of change		The approximate total number of patients treated has been updated to 27 (assuming ~3 patients per dose level).
Rationale for change		The approximate total number of patients treated has been updated due to the addition of 3 DLs.
Section to be changed		Section 10.1, Table 10
Description of change		Additional language was added in footnote b. Addition of 8 hour shedding samples at [redacted] and [redacted] Addition of Footnote f: In case a patient develops any potential VSV-related skin lesions (i.e. mouth vesicles), based on investigator's medical assessment, a swab from a respective lesion should be taken for analysis of viral shedding.
Rationale for change		Language was added to provide clarity FDA request.
Section to be changed		Section 10.4.1
Description of change		Update to the BLRM for the dose escalation.
Rationale for change		FDA request to limit the dose escalation interval to approximately 3-fold resulting in 3 additional DLs being added.

APPROVAL / SIGNATURE PAGE

Document Number: c39898864 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-02

Title: An open-label, Phase I dose escalation and expansion trial to investigate safety and efficacy of BI 1821736 in patients with advanced solid tumors

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	26 Jan 2023 18:48 CET
Author-Statistician	[redacted]	27 Jan 2023 09:15 CET
Approval-Clinical Program [redacted]	[redacted]	27 Jan 2023 09:47 CET
Verification-Paper Signature Completion	[redacted]	03 Feb 2023 16:29 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**