Clinical Trial Protocol

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EU Clinical Trial No. **Universal Trial Number**	2023-508998-85-00 U1111-1300-7624	
Boehringer Ingelheim Trial No.	1505-0001	
Boehringer Ingelheim Investigational Medicinal Product	BI 765883	
Title	A first-in-human open label Phase Ia/Ib, multicenter/multiregional, dose escalation study of BI 765883 administered as monotherapy and in combination with gemcitabine and nab-paclitaxel in unselected patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) or patients with PDAC who have relapsed after post-surgery adjuvant therapy	
Lay Title	A study to find a suitable dose of BI 765883 and to test whether it helps people with advanced pancreatic cancer when taken alone or together with chemotherapy	
Clinical Phase	Ia/Ib	
Sponsor	Boehringer Ingelheim Pharma GmbH & Co. KG Boehringer Ingelheim Binger Strasse 173 55218 Ingelheim am Rhein Germany	
Clinical Trial Leader	[redacted] Phone: +[redacted] Email: [redacted]	
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Current Version and Date	Version 4.0, 24-Feb-2025	
Original Protocol Date	15 Dec 2023	Page 1 of **150**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date **Latest revision date**	15 Dec 2023 24-Feb-2025
Boehringer Ingelheim trial number **EU CT number** **Universal trial number**	1505-0001 2023-508998-85-00 U1111-1300-7624
Title of trial	A first-in-human open label Phase Ia/Ib, multicenter/multiregional, dose escalation study of BI 765883 administered as monotherapy and in combination with gemcitabine and nab-paclitaxel in unselected patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) or patients with PDAC who have relapsed after post-surgery adjuvant therapy
Coordinating Investigator	[redacted] Phone: +[redacted]
Trial site(s)	Multicenter conducted in at least 15 sites in 6 countries
Clinical phase	Ia/Ib
Trial rationale	The efficacy of current standard of care options for patients with mPDAC is limited and there is a need to develop new treatment approaches. High expression of both TRAILR2 and CDH3 mRNA is frequently detected in patients with PDAC. BI 765883 is a bi-specific antibody targeting both TRAILR2 and CDH3, and it is designed to selectively induce apoptosis in tumor cells expressing CDH3 via the CDH3-dependent oligomerization of TRAILR2. Ligand-induced oligomerization of TRAILR2 results in the induction of apoptosis. PDAC is a suitable indication for BI 765883. Indeed, *in vivo* efficacy in PDAC patient-derived tumor models (PDX) was demonstrated with BI 765883 monotherapy and, even more prominently, for combinations of BI 765883 with SoC chemotherapeutic agents (gemcitabine, irinotecan), where sustained tumor regressions were observed. Results from this open-label, dose escalation trial will provide basis for further development of BI 765883 in combination with gemcitabine and nab-paclitaxel in

	unselected patients with metastatic PDAC or patients with PDAC who have relapsed within 6 months after post-surgery therapy.
Benefit-risk assessment and ethical considerations	The combination of TRAILR2/CDH3 antibody with chemotherapy is expected to induce the apoptotic signal by the activation of both the intrinsic and the extrinsic apoptosis pathways in cancer cells. However, the nature of dual target (TRAILR2 and CDH3) engagement and the mechanism of action of BI 765883 is not yet tested in humans since this is a first-in-human (FIH) study. The safety and efficacy of BI 765883 have not yet been studied in humans. The preclinical toxicity profile of BI 765883 did not indicate potential for any adverse toxicities and supports the administration of BI 765883 to humans. The proposed starting dose of BI 765883 is 10-fold below the predicted therapeutic dose. Based on preclinical pharmacology data, the proposed starting dose is predicted to have activity of at least ~70% tumor growth inhibition relative to vehicle treated control. The proposed starting dose is expected to provide a meaningful clinical benefit to cancer patients and is supported by multiples of exposure of the no-observed-adverse effect level (NOAEL) from nonclinical toxicology data. The human therapeutic dose is estimated to obtain approximately 90% tumor growth inhibition. Therefore, the selected FIH starting dose is considered to provide an appropriate benefit/risk ratio for cancer patients in Phase I clinical trials. In the context of the unmet medical need for these PDAC patients, the benefit-risk evaluation of BI 765883 in combination with chemotherapy, as supported by the available extensive non-clinical pharmacology and toxicology data, is favorable. Please see the BI 765883 Investigator Brochure for more details.
Trial objective(s)	**Phase Ia (dose escalation):** **The primary objectives** • to determine the safety, tolerability and the MTD for BI 765883 as monotherapy • to determine the safety, tolerability, and MTD for BI 765883 in combination with gemcitabine and nab-paclitaxel **Secondary objectives** • to assess the pharmacokinetic (PK) properties of BI 765883 as monotherapy and as combination therapy after first and after multiple administrations • to evaluate the preliminary efficacy and safety of BI 765883 (as monotherapy)

	• to evaluate preliminary efficacy and safety of BI 765883 in combination with gemcitabine and nab-paclitaxel and define the recommended dose for expansion (RDE) **Phase Ib (dose expansion):** **The primary objectives** • to evaluate preliminary efficacy of BI 765883 in combination with gemcitabine and nab-paclitaxel **Secondary objectives** • to assess the pharmacokinetic (PK) properties of BI 765883 as combination therapy after first and after multiple administrations • to evaluate preliminary efficacy and safety of BI 765883 in combination with gemcitabine and nab-paclitaxel The dose range for further development in Phase II will be determined based on available data, including safety, preliminary efficacy, and PK data from Phase Ia and Phase Ib.
Trial endpoints	**Phase Ia: dose escalation** of BI 765883 as monotherapy and in combination with gemcitabine and nab-paclitaxel. BI 765883 monotherapy/combination therapy: • **Primary endpoint:** - Occurrence of DLTs in the MTD evaluation period for the determination of the MTD • **Secondary endpoints:** - Objective response (OR) defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. OR is defined as the best overall response of complete response (CR) or partial response (PR), recorded from the start of the study treatment until the earliest of disease progression, death, or last evaluable tumor assessment, and before start of subsequent anti-cancer therapy. - RDE for BI 765883 in combination with gemcitabine and nab-paclitaxel (for Phase Ib of this study). The RDE will be based on the totality of the safety, efficacy and PK data observed during the Phase Ia combination dose escalation, provided that the minimal efficacy criterion of at least 2 confirmed

	ORs (per RECIST 1.1) per 10 patients (20%) treated at the same DL is met. - Safety and tolerability based on frequency and severity of AEs according to the Common Terminology Criteria for Adverse Events (CTCAE) - PK parameters of BI 765883 after the first and after multiple administrations of BI 765883: • C_{max}: maximum measured concentration of BI 765883 in serum • AUC_{0-t}: area under the serum concentration time curve of BI 765883 **Phase Ib: dose expansion** - BI 765883 in combination with gemcitabine and nab-paclitaxel: • **Primary endpoint** - Confirmed OR defined by RECIST 1.1 criteria (OR is defined above) • **Secondary endpoints** - Safety and tolerability based on frequency and severity of AEs according to the CTCAE - PK parameters of BI 765883 after the first and after multiple administrations of BI 765883: • C_{max}: maximum measured concentration of BI 765883 in serum • AUC_{0-t}: area under the serum concentration time curve of BI 765883 - Progression-free survival (PFS) PFS is defined as the time from first treatment administration until tumor progression according to RECIST 1.1 or death from any cause, whichever occurs earlier. - Duration of response (DOR) defined as the time from first documented complete response or partial response until the earliest of disease progression or death among patients with objective response

Trial design	Phase Ia is an open-label, non-randomized, FIH, dose escalation study of BI 765883 as monotherapy and in combination with gemcitabine and nab-paclitaxel. Two stepwise dose escalation strategies will be undertaken in parallel to determine the efficacious and safe dose of BI 765883 as combination therapy. Phase Ia of the study will characterize the exposure - safety curve for BI 765883 as monotherapy and as combination therapy administered in patients who have undergone at least 1 line of chemotherapy (≥2L mPDAC patients) by assessing up to 5 dose levels of BI 765883 monotherapy and combination therapy with Bayesian logistic regression modeling (BLRM) overdose control to determine the MTD. PK and efficacy will be evaluated to guide determination of the MTD/RDE. Following identification of the MTD and the RDE for BI 765883 in combination with gemcitabine and nab-paclitaxel in Phase Ia, a Phase Ib open-label, non-randomized, expansion phase at a dose level selected in agreement with the dose escalation committee (DEC) will be conducted to evaluate the safety, preliminary efficacy, and PK data at the RDE in up to 28 evaluable patients, including patients treated with BI 765883 at the RDE in combination with gemcitabine and nab-paclitaxel during the Phase Ia dose escalation part of the study.
Total number of trial patients entered	Up to 99 evaluable patients total Dose escalation: up to 60 evaluable patients Backfill cohorts: 21 evaluable patients Dose expansion: 18 evaluable patients
Diagnosis, main inclusion and exclusion criteria	Patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) or patients with PDAC who have received post-surgery adjuvant therapy and have relapsed within 6 months will be included in this trial. Patients meeting the inclusion criteria below and not meeting any of the exclusion criteria will be eligible to participate. **Key inclusion criteria** • Histologically or cytologically confirmed, advanced unresectable or metastatic PDAC. • Archived tumor tissue from a tissue core biopsy (e.g. paraffin-embedded formalin-fixed tissue blocks) OR fresh tumor tissue available for retrospective biomarker analysis; in both cases, a minimum of at least two core needle biopsies (18 gauge or greater) is required. Only procedures with non-significant risk per the investigator's judgment will be used to obtain any biopsies specified in this study in cases where a fresh tumor biopsy is required.

	• Patients with at least 1 target lesion that can be accurately measured per RECIST version 1.1. • **For monotherapy cohorts only:** Patients who have progressed on or are intolerant to available standard therapy, or for whom no standard therapies with proven benefit exists, according to the local and institutional guidelines. • **For combination cohorts only:** Patients who have progressive metastatic disease after prior platin and/or irinotecan-based first line therapy. Eligible patients for combination therapy as second-line (2L) include patients who have relapsed within 6 months and present with metastatic disease after resection and neo- and/or adjuvant therapy as these patients are considered as frontline failed and are now 2L treatment eligible. • Adequate hepatic, renal, and bone marrow functions • Recovery from AEs (according to CTCAE v 5.0) due to previous anti-cancer therapies to CTCAE grade ≤1, except for alopecia (CTCAE grade 2), endocrinopathies controlled by replacement therapy which must be ≤CTCAE grade 2, and amenorrhea/menstrual disorders which can be any grade. • Eastern Cooperative Oncology Group (ECOG) performance status ≤1. • Male or female patients. Women of childbearing potential (WOCBP) and men able to father a child must be willing 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. **Key exclusion criteria** • Any prior gemcitabine and/or paclitaxel therapy (for combination therapy cohorts). • Known hypersensitivity to the trial medications or their excipients (including gemcitabine and nab-paclitaxel). • Any contraindications to gemcitabine or nab-paclitaxel according to the current approved local labels. • Prior radiotherapy or systemic therapy within 14 days prior to treatment start. • History or presence of cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of ≥III or IV, unstable angina or poorly controlled arrhythmia which are considered as clinically relevant by the Investigator.

	• Myocardial infarction, stroke, or clinically-significant pulmonary embolism within 6 months prior to first drug administration. • Either of the following cardiac criteria: QT interval corrected for heart rate by Fridericia's formula (QTcF) >480 ms or left ventricular ejection fraction (LVEF) <50%. • Women who are pregnant, nursing, or who plan to become pregnant or nurse during the study or within 6 months after the last dose of study treatment. • Major surgery (by investigator's assessment) performed within 28 days prior to treatment start or planned within 3 months after screening. • Presence of uncontrolled or symptomatic brain or subdural metastases. • Any serious concomitant disease or medical condition affecting compliance with trial requirements or which are considered relevant for the evaluation of the efficacy or safety of the trial drug, such as neurologic, psychiatric, infectious disease, active ulcers (gastrointestinal tract, skin), inflammatory bowel disease or bowel infection, or laboratory abnormality that may increase the risk associated with trial participation or trial drug administration, and in the judgment of the Investigator, would make the patient inappropriate for entry into the trial. • Sensory peripheral neuropathy of CTCAE grade ≥2 or grade 1 considered clinically significant (combination therapy).

Trial intervention and test product(s)	**Phase Ia:** BI 765883 in monotherapy and in combination with SoC gemcitabine and nab-paclitaxel **Phase Ib:** BI 765883 in combination with SoC gemcitabine and nab-paclitaxel
Dose and mode of administration	**Phase Ia:** Five DLs are planned for both the monotherapy and for the combination dose escalations (all with intravenous [IV] dosing every 2 weeks [q2w]). Higher dose levels above DL5 may be permitted if the DEC deems DL5 to be tolerable and if the benefit-risk ratio favors further escalation. The dosing schedules for monotherapy and combination therapy will be as follows: • Monotherapy: BI 765883 is administered by IV over 30 minutes (+10 minutes) on Day 1 of each 2-week cycle. • Combination therapy: BI 765883 is administered by IV infusion (over 30 minutes +10 minutes) on Day 1 of each 2-week cycle followed by nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) each administered by IV infusion over a 30-minute period also on Day 1 of each 2-week cycle. Permitted dose modifications: • Patients who experience dose-limiting toxicity (DLT), or Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3 diarrhea or grade 2 diarrhea for > 7 days, grade ≥2 vomiting, grade ≥3 nausea or proteinuria ≥ CTCAE grade 3 should interrupt or delay treatment until recovery to CTCAE grade 1 or to baseline. In such cases, restarting BI 765883 treatment may be considered at a reduced dose (-1 DL). **Phase Ib:** The RDE for the combination therapy, as determined in Phase Ia (dose escalation), will be administered in Phase Ib.
Combination products	Gemcitabine Nab-paclitaxel
Dose and mode of administration	Except for the biweekly dosing schedule, dosing of gemcitabine and nab-paclitaxel is in accordance with the local Summary of Product Characteristics (SmPC) for each drug. The biweekly schedule has been shown to be better tolerated without loss of efficacy than the approved weekly schedule and is preferred for this trial. Gemcitabine and nab-paclitaxel are administered by IV every 2 weeks. No routine premedication will be required for BI 765883 IV infusions. Since premedication is required for gemcitabine and nab-

	paclitaxel, this will be administered prior to the BI 765883 IV infusion.
Duration of treatment	The duration of treatment is until unacceptable toxicity, disease progression, or death, whichever occurs first.
Statistical methods	Phase Ia: Dose escalation is guided by a BLRM with overdose control that will be fitted to binary toxicity outcomes (DLTs). The estimate of parameters will be updated as data are accumulated using the BLRM. Phase Ib: Primary and secondary endpoints will be analyzed descriptively.

FLOW CHART - PHASE IA AND PHASE IB

Trial period	SCR	Treatment period														EoT	Follow-up period	
Cycle number		C1				C2		C3		C4				C5	C6 onwards		Safety follow-up Last IMP +30	Every 3 months after last IMP via phone/in person[1]
Day	D -28 to -1	D1	D2	D3	D8	D1	D8	D1	D8	D1	D2	D3	D8	D1	D1			
Visit window (days)					±2	±2	±2	±2	±2	±2			±2	±2	±2	+14	+5	±14
Informed consent	X																	
Demographics	X																	
Medical history[2]	X																	
IC biobanking (optional)	X																	
Review of in-/exclusion criteria	X	X																
Safety laboratory (hematology, clinical chemistry)[3]	X	X			X	X	X	X	X	X			X	X	X	X	X	
Safety laboratory (urinalysis)	X	X			X	X	X	X	X	X			X	X	X	X	X	
Pregnancy test (WOCBP only)	X	X				X		X		X				X	X[4]	X[4]	X	
Physical examination[5]	X	X				X		X		X				X	X	X	X	
Vital signs[6]	X	X				X		X		X				X	X	X	X	

Trial period	SCR	Treatment period														EoT	Follow-up period	
Cycle number		C1				C2		C3		C4				C5	C6 onwards		Safety follow-up Last IMP +30	Every 3 months after last IMP via phone/in person[1]
Day	D -28 to -1	D1	D2	D3	D8	D1	D8	D1	D8	D1	D2	D3	D8	D1	D1			
Visit window (days)					±2	±2	±2	±2	±2	±2			±2	±2	±2	+14	+5	±14
ECOG performance score	X	X				X		X		X				X	X	X		
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[12]
ECG, 12-lead	X[7]	X				X		X		X				X	X	X	X	
LVEF	X[7]																	
Blood samples for ctDNA [8]		X			X	X								X		X		
Blood for PK analysis[9]		X	X	X	X	X		X		X	X	X	X	X	X[9]	X	X[13]	
Blood for ADA/nAb assessment[9]		X[10]				X		X						X	X[10]	X	X[13]	

Trial period	SCR	Treatment period														EoT	Follow-up period	
Cycle number		C1				C2		C3		C4				C5	C6 onwards		Safety follow-up Last IMP +30	Every 3 months after last IMP via phone/in person[1]
Day	D -28 to -1	D1	D2	D3	D8	D1	D8	D1	D8	D1	D2	D3	D8	D1	D1			
Visit window (days)					±2	±2	±2	±2	±2	±2			±2	±2	±2	+14	+5	±14
PRO-CTCAE		X			X	X	X	X	X	X			X	X	X	X		
Archived tumor tissue (mandatory unless fresh tumor biopsy tissue provided instead)	X																	
Tumor assessment (CT/MRI) by RECIST 1.1 [11]	X													X[11]	X[11]	X		
CA19-9 tumor marker[11]	X													X[11]	X[11]	X		
Administration of BI 765883[6]		X				X		X		X				X	X			
Administration of gemcitabine and nab-paclitaxel COMBINATION COHORTS ONLY		X				X		X		X				X	X			

Trial period	SCR	Treatment period														EoT	Follow-up period	
Cycle number		C1				C2		C3		C4				C5	C6 onwards		Safety follow-up Last IMP +30	Every 3 months after last IMP via phone/in person[1]
Day	D -28 to -1	D1	D2	D3	D8	D1	D8	D1	D8	D1	D2	D3	D8	D1	D1			
Visit window (days)					±2	±2	±2	±2	±2	±2			±2	±2	±2	+14	+5	±14
Termination of all trial medications																X		
Completion of patient participation																	X	
Patient status[14]																		X

ADA = anti-drug antibody; C = cycle; CRS = cytokine release syndrome; CT = computed tomography; ctDNA = circulating tumor DNA; D = Day; ECG = electrocardiogram; Echo-CG = echocardiography. MUGA =multigated acquisition scan. ECOG = Eastern Cooperative Oncology Group; EoT = end of treatment; IC = informed consent; IMP = investigational medicinal product; IRR = infusion-related reactions; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; nAb = neutralizing antibodies; phys = physical; PGx = pharmacogenomics; PK = pharmacokinetics; PRO-CTCAE = Patient Reported Outcomes-Common Terminology Criteria for Adverse Events; RECIST = Response Evaluation Criteria in Solid Tumors; SCR = screening; V = Visit; WOCBP = women of child-bearing potential

EoT: At end of treatment visit (EoT), patients and investigators will be encouraged to complete at least the following assessments: CT scan/MRI, PK, ADA, and safety assessments.

Safety follow-up: The Safety Follow-up visit is to be performed in person 30 days (+ 5 days) after the last dose of study medication. At this visit, all AEs/SAEs/AESIs must be collected along with the other required information as shown in the FLOW CHART.

Follow-up visits every 3 months after last dose of IMP: Additional follow-up visits will be performed every 3 months (+/- 2 weeks) starting 3 months after last dose of study medication. These visits are to obtain further data on safety, anti-cancer treatment, disease progression, and survival, and can be performed via phone contact or in person (at the investigator discretion and/or if in-person assessments are needed).

1 Follow-up for overall survival (all patients) and disease progression (only patients that discontinued early for reasons other than progression).

2 Medical history includes a general medical history, and a detailed oncological disease history will be collected. The oncological history to be reported on the eCRF will include: date of first histological diagnosis; the primary tumor site; staging and grading information; the number and location of metastatic sites; previous treatment for the tumor, including any

surgery, radiotherapy, and/or systemic therapy including start and stop dates and outcome; any known genomic alterations; the date of tumor progression after previous lines of treatment will be recorded if known, including start and end dates and outcome; compliance with inclusion/exclusion criteria.

3 Safety laboratory assessments do not need to be repeated at the C1D1 visit if performed ≤ 72 hours prior to the first IMP administration; however, the results must be available before the start of the infusion in this or any subsequent cycle in order to evaluate the eligibility of the patient to receive treatment.

4 After Cycle 5, pregnancy tests will be performed on Day 1 of every other treatment cycle thereafter (i.e. Day 1 of Cycles 7, 9, 11, etc). At EoT, a pregnancy test will not be required if the last test has been conducted within the last 7 days.

5 Includes measurement of height (cm) (at screening only) and body weight (kg).

6 Patients will remain under surveillance to monitor potential occurrences of IRRs or CRS for at least 6 h after the end of infusion for the administration of BI 765883. Vital signs should be evaluated pre-dose, post-dose, and then every 2 h during the BI 765883 post-infusion observation period. In the absence of IRR/CRS this can be reduced in subsequent administrations (see Sections 4.1.4.1 and 4.2.3.1).

7 ECG or Echo-CG or MUGA (multigated acquisition scan) will be performed at screening to determine if patients meet the exclusion criterion of QTcF >480 ms or LVEF <50%.

8 For exact details on timing of ctDNA sampling, see Table 16.

9 For exact details on timing of PK and ADA sampling, see Table 16.

10 First sample pre-dose on C1D1. For exact details on timing after Cycle 5, see Table 16.

11 Tumor assessment should include CT scans or MRI of the chest, abdomen, pelvis and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. brain, bone). The same radiographic procedure must be used throughout the study. Repeat tumor assessment will be performed at screening, Cycle 5 (Day 1), and every 8 weeks (± 7 days) thereafter, until study discontinuation. Tumor assessment does not need to be performed at the Screening visit if there are valid results available from assessments that were performed as part of routine clinical practice within 28 days prior to start of treatment.
In the event of interruption/delay of treatment, the tumor assessment schedule should not be changed.
In the event of early discontinuation for reasons other than progressive disease, wherever possible, tumor assessment/imaging must be performed at the time of treatment discontinuation, unless it has been done within the past 4 weeks and every 3 months (± 14 days) thereafter until progressive disease or start of subsequent anti-cancer treatment.
CA19-9 tumor marker levels should be measured at baseline and at every protocol specified tumor assessment timepoint.

12 All SAEs/AESIs considered to be unequivocally related to BI 765883 must be collected.

13 Samples for PK and ADA assessments are needed up to safety follow-up at last dose of IMP + 30 days.

14 Patient status: progression/overall survival.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AESI	Adverse event of special interest
ALCOA	Attributable, legible, contemporaneous, original, accurate
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
b.i.d.	Bis in die (twice daily dosing)
BLRM	Bayesian logistic regression model
CA	Competent Authority
CDX	Cell line-derived xenograft
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
CRA	Clinical research associate
CRF	Case report form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract research organization
CRS	Cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical trial protocol
CTR	Clinical trial report
DBL	Database lock
DEC	Dose Escalation Committee
DILI	Drug-induced liver injury
DL	Dose level
EC	Ethics Committee
ECG	Electrocardiogram
Echo-CG	Echocardiography
eCRF	Electronic case report form
eDC	Electronic data capture

eGFR	Estimated glomerular filtration rate
EoR	End of residual effect period
EoS	End of study (corresponds with end of trial)
EoT	End of treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EWOC	Escalation with overdose control
FAP	Fibroblast activation protein
FcR	Fc receptor
FIH	First-in-human
FN	Febrile neutropenia
FUP	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HA	Health authority
HED	Human efficacious dose
HLH	Hemophagocytic lymphohistiocytosis
IA	Interim analysis
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
iPD	Important protocol deviation
IRB	Institutional Review Board
IRR	Infusion-related reactions
IRT	Interactive response technology
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous(ly)
LPLT	Last patient last treatment
LPLV	Last patient last visit
LVEF	Left ventricular ejection fraction

mAb	Monoclonal antibody
MAS	Macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
nAb	Neutralizing anti-drug antibody
NCCN	National Comprehensive Cancer Network
NOAEL	No-observed-adverse effect level
OPU	Operative unit
OS	Overall survival
PD	Pharmacodynamic
PDX	Patient-derived xenograft
PK	Pharmacokinetics
p.o.	Per os (oral)
POCP	Proof of clinical principle
PopPK	Population pharmacokinetics
p.r.n.	As needed
PRO	Patient-reported outcome
q2w	Every 2 weeks
RA	Regulatory authority
RDE	Recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
REP	Residual effect period
SAE	Serious adverse event
SoC	Standard of care
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Half-life time
TGI	Tumor growth inhibition
TLS	Tumor lysis syndrome
t_{max}	Timepoint of maximum plasma concentration
TMF	Trial master file
TPM	transcripts per million

TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
WHO	World Health Organisation
WoC	Withdrawal of consent
WOCBP	Woman of childbearing potential

Terms synonymous with those used in this CTP are listed below.

Term	Synonymous term
Trial participant *or* participant	Patient
End of study (EoS)	End of trial
Investigational medicinal product (IMP)	Trial medication (*or* medication), *or* trial drug (*or* drug), *or* trial treatment (*or* treatment), *or* trial intervention, *or* intervention, *or* investigational product

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal solid malignancies: the 7th leading cause of cancer-related deaths worldwide and the 4th leading cause of cancer-related deaths in the US. Notably, 52% of patients are diagnosed as *de novo* metastatic with a 5-year survival rate of 2.6%. In 2022, there were an estimated 407,162 PDAC patients in the 8 major countries including US, Japan, France, Germany, Italy, Spain, the United Kingdom, and China.

The National Comprehensive Cancer Network (NCCN) guidelines recommend FOLFIRINOX as a preferred first-line treatment for patients with metastatic or locally advanced unresectable disease with good performance status. Paclitaxel plus gemcitabine may be considered instead of FOLFIRINOX in patients unlikely to tolerate toxicities associated with FOLFIRINOX. The standard of care (SoC) second-line treatment for patients failing first-line FOLFIRINOX is gemcitabine plus nab-paclitaxel.

Apoptotic cell death can be triggered by external signals (extrinsic apoptotic pathway), including pro-apoptotic FAS- and TRAIL-ligands, homotrimeric proteins that bind to and activate cell surface-anchored death receptors (DR), such as FAS, TRAIL-Receptor 1 (TRAILR1/DR4), or TRAIL-Receptor 2 (TRAILR2/DR5).

The TRAIL (Tumor necrosis factor [TNF]-related apoptosis-inducing ligand) pathway induces apoptosis selectively in cancer cells [R17-4113] and represents a valid opportunity for cancer treatment. However, conventional TRAILR2 agonists have not been successful in the clinic so far due to insufficient agonistic properties or liver toxicity [R17-2985]. Published data suggest that activation of the TRAIL receptor not only depends on binding of the ligand to the receptor, but requires a hyperclustering of receptor-ligand trimers in order to effectively achieve apoptosis induction [R17-2986]. The level of receptor oligomerization/clustering can be highly increased if the ligand is immobilized by binding to the surface of the membrane or via secondary cross-linking [R17-2985].

TRAILR2 expression has been widely demonstrated in several solid cancers including pancreatic and colorectal tumors, lung adenocarcinoma, squamous carcinoma of lung, and head and neck [R18-2092, R18-2740, R18-2741, R18-2742]. In agreement with published data, studies using in-house immunohistochemical (IHC) analysis show expression of TRAILR2 on CRC tumor cells in visceral metastases of human liver. In contrast, TRAILR2 expression was very low or not detectable on healthy liver cells adjacent to the tumor. Due to the lack of Cadherin 3 (CDH3, placental cadherin; P-cadherin) expression in non-neoplastic liver tissue, BI 765883 has the potential for an improved therapeutic window as both TRAILR2 and CDH3 expression support the induction of apoptosis [n00263941; R16-1795]. Screening of a DR5 agonist nanobody across >600 cell lines representing 21 tumor types

identified pancreatic ductal adenocarcinoma (PDAC) as responsive to TRAILR2 agonists [R16-4522].

The tumor necrosis factor receptor superfamily member TRAILR2 is a pro-apoptotic receptor that initiates the apoptotic pathway upon its oligomerization in a wide range of cancers. CDH3 or cadherin-3 or P-cadherin is a calcium-dependent adhesion molecule and member of the classical cadherin superfamily. Examination of public databases (TCGA/GTEx data) shows that high expression levels of both *TRAILR2* and *CDH3* mRNA frequently occur in PDAC. More importantly, evaluation of TRAILR2 and CDH3 protein expression in tumor samples derived from patients with late-stage PDAC shows expression of both targets in all evaluable specimens (TRAILR2, n = 39; CDH3, n = 43) (in-house prevalence data).

1.2 DRUG PROFILE

1.2.1 Mode of action

BI 765883 is a tetravalent bispecific antibody of human IgG1 isotype targeting both TRAILR2 and CDH3 and it is designed to selectively induce apoptosis in CDH3-expressing tumor cells via the CDH3-dependent clustering of TRAILR2. Ligand-induced oligomerization of TRAILR2 results in the induction of apoptosis.

BI 765883 has been developed to provide effective TRAILR2 activation in tumor cells while avoiding activation of the same pathway in the liver due to the lack of CDH3 protein in non-neoplastic liver tissue.

For further details, see the BI 765883 Investigator Brochure (IB) [c39438758].

1.2.2 Key pharmacokinetic characteristics

Study 1505-0001 is a first-in-human (FIH) study. Pharmacokinetic (PK) data are not yet available in humans.

1.2.3 Pharmacokinetic drug interactions

BI 765883 is a therapeutic protein and its clearance is through protein catabolism. BI 765883 is not an immune modulator and is not expected to impact expression and production of cytochrome P450 enzyme or certain drug transporters that may affect indirectly the exposure of co-administered small molecule drugs. Therefore, PK drug interaction between BI 765883 and co-administered drugs is not expected. No *in vitro* drug interaction studies for BI 765883 have been performed [c39438758].

1.2.4 Residual effect period (REP)

The expected REP of BI 765883 is 30 days (+5 days). This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present. The first safety follow-up visit will be conducted at the end of the REP.

1.2.5 Data from non-clinical studies

1.2.5.1 Nonclinical pharmacology

Primary pharmacology studies have demonstrated that BI 765883 is a potent inducer of apoptosis, selectively in TRAILR2/CDH3 expressing tumor cells. A short summary is given below. For further details, see the IB [c39438758].

In vitro sensitivity was tested in proliferation assays for one hundred thirteen cell lines of various tumor origins and with different RNA expression levels of TRAILR2 and CDH3. Sensitivity ranged from very sensitive to insensitive across many of the tumor types, but as of the date of this protocol, no clear threshold for TRAILR2 and CDH3 expression or an additional predictive marker of sensitivity has been identified.

In vivo efficacy of BI 765883 was demonstrated in PDAC patient-derived xenograft (PDX) models. In models expressing *TRAILR2* (≥30 transcripts per million [TPM]) and *CDH3* (≥30 TPM) mRNA, anti-tumor activity could be demonstrated in 8 PDAC PDX models. Bi-weekly (q2w) treatment with 1 mg/kg BI 765883 led to tumor regression in 3 models, tumor stasis in a further 1 model, and 4 additional models displayed moderate tumor growth inhibition (TGI) of about 50-70%. Anticancer activity of BI 765883 monotherapy was not revealed in PDAC PDX models with low (<30 TPM) expression of TRAILR2 and CDH3. Notably, a prominent *in vivo* efficacy in PDAC PDX models was demonstrated for combinations of BI 765883 with SoC chemotherapeutic agents, including gemcitabine, where sustained tumor regressions were observed.

In vivo efficacy of BI 765883 as monotherapy was also tested in the cell line-derived xenograft (CDX) tumor model GP2d (CRC), where a single dose administration of BI 765883 (0.33, 1, 3, and 6 mg/kg, IV) resulted in statistically significant tumor regression (TGI of 117%/121%/119%/and 121%, respectively) compared to control.

In another cell-line derived model, KNS-62 (squamous NSCLC), BI 765883 dosed at 1 mg/kg (and up to 6 mg/kg) significantly, but only moderately delayed tumor growth (TGI of 57%), but nevertheless showed a clear beneficial effect in combination with docetaxel.

1.2.5.2 Nonclinical pharmacokinetics (PK)

Nonclinical PK data are detailed in the IB [c39438758]. In summary, the PK for BI 765883 was investigated in the cynomolgus monkey in a single-dose PK study. BI 765883 demonstrated dose proportional increases in C_{max} and AUC with increasing dose levels (0.3, 1.5 and 10 mg/kg). In the repeat dose toxicology study, the systemic exposure to BI 765883 also increased in an approximately dose-proportional manner with increased dose level (10, 30 and 100 mg/kg/dose). Human PK prediction for BI 765883 IV infusion was performed using single species scaling from cynomolgus monkey to human using a Dedrick plot. The fitted 2-compartment PK parameters were then used in the extended model containing tumor growth which enabled the prediction of the drug effect on tumor inhibition.

Based on the predicted human PK parameters and a mouse xenograft model for PDAC (PATX141), the human therapeutic dose was estimated to be 4 mg/kg every two weeks (q2w) to obtain approximately 90% TGI.

Absorption: In nonclinical studies, BI 765883 has been evaluated via intravenous (IV) and intraperitoneal (IP) administration in animals. Dedicated absorption studies have not been conducted for BI 765883.

Distribution: No dedicated distribution studies have been performed. In the cynomolgus monkey, C_{max} and AUC_{0-168} increased approximately dose-proportionally upon dosing for all dosing groups (0.3, 1.5, and 10 mg/kg) and it is expected that BI 765883 will be mostly distributed to the blood after IV administration in a manner typical of IgG molecules.

Metabolism: BI 765883 is a protein and is expected to undergo protein catabolism in animals and humans to peptides and amino acids. Dedicated metabolism studies have not been conducted for BI 765883.

Excretion: The molecular weight of BI 765883 is approximately 196 kDa, which is above the renal filtration cut-off threshold (approximately 60 kDa). Dedicated excretion studies have not been conducted.

1.2.5.3 Nonclinical toxicology

No evidence of BI 765883-related effects was observed in cynomolgus monkeys on cardiovascular, respiratory, or neurological measurements in the 4-week repeated dose toxicity study. BI 765883 administration IV once per week (q1w) to cynomolgus monkeys for 4 weeks at dose levels up to 100 mg/kg did not cause adverse effects in any of the parameters or organs (including liver) examined in the study. The no-observed-adverse effect level (NOAEL) was 100 mg/kg q1w.

In vitro cytokine release assay results suggest a low potential risk for inducing cytokine release upon BI 765883 treatment in humans.

The predicted human exposure at the proposed starting dose of 0.4 mg/kg q2w is 254- and 428-fold below the C_{max} and AUC_{0-336}, respectively, in monkeys at the NOAEL.

Based on the mode of action, the pharmacological targets, and the non-clinical toxicology data, BI 765883 is considered a low-risk compound for use in clinical studies.

1.2.6 Data from clinical studies

Study 1505-0001 is a FIH study. Clinical data are not yet available.

For a more detailed description of the BI 765883 profile, please refer to the current IB [c39438758].

For information on the SoC products gemcitabine and nab-paclitaxel used in combination with BI 765883 in this study, see the Summary of Product Characteristics (SmPC) or US Package Insert.

1.3 RATIONALE FOR PERFORMING THE TRIAL

The efficacy of the current SoC for patients with mPDAC is limited and there is a need to develop new treatment approaches. PDAC remains one of the most lethal solid malignancies and a leading cause of cancer-related deaths worldwide. Notably, 52% of patients are diagnosed as de novo metastatic, with a 5-year survival rate of 2.6%.

BI 765883 *in vivo* efficacy in PDX PDAC models was demonstrated for the monotherapy setting and even more prominently for combinations of BI 765883 with SoC chemotherapeutic agents, where sustained tumor regressions were observed [c39438758]. This study represents the first use of BI 765883 in humans and the dose escalation design is intended to determine the maximum tolerated dose (MTD) for BI 765883 administered as monotherapy and also when administered in combination with the SoC chemotherapeutic agents (gemcitabine and nab-paclitaxel) for patients with mPDAC. Additionally, the study will evaluate safety, tolerability, PK, and preliminary efficacy assessments in humans. The study is open-label, with no comparator arm, and safety will be monitored throughout the duration of the study by a Drug Escalation Committee (DEC). The DEC will determine when dose levels may be opened in the dose escalation phase and will recommend a recommended dose for expansion (RDE), which will be further evaluated for safety, efficacy, and PK in a second phase of this study. Prior to the initiation of the dose expansion part of the study, the RDE recommendations of the DEC along with a synoptic summary of the safety results from dose escalation will be provided to the regulatory authority.

The study of exploratory biomarkers will be hypothesis-generating. These findings will be used to expand the understanding of the disease mPDAC and BI 765883, e.g. by learning more about the mechanism of action of the BI 765883 or the biology of the disease, thereby allowing correlation of patient subgroups with differential responses to treatment and/or prognosis and supporting subsequent trial designs regarding dose and schedule selection.

In order to be able to address future scientific questions, trial patients will be asked to voluntarily donate biospecimens for banking (please see Section 5.5). If the trial 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 AE, or to gain a mechanistic or genetic understanding of the product's effects and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

The patient population for treatment with BI 765883 as monotherapy will comprise patients with advanced unresectable mPDAC who have failed all available conventional therapies based on local approved standards. The population to be treated with BI 765883 in combination with gemcitabine and nab-paclitaxel (SoC) will comprise unselected patients with 2L mPDAC who have progressive disease after prior platin and/or irinotecan-based first line therapy. Eligible patients for combination therapy as second-line (2L) include patients who have relapsed within 6 months and present with metastatic disease after resection and neo- and/or adjuvant therapy as these patients are considered as frontline failed and are now 2L treatment eligible.

Based on the mechanism of action and available nonclinical data for BI 765883 (described above), this population of patients with advanced mPDAC and limited treatment options may benefit from treatment with BI 765883 as monotherapy or as combination therapy.

1.4.2 Risks

Conventional TRAILR2 antibodies have been extensively tested and well tolerated in the clinic with a well-defined safety profile. The majority of these compounds did not induce dose-limiting toxicities (DLTs) in Phase I with no MTD achieved. Drug-related AEs with such compounds were rare and mostly included mild elevation of AST, ALT and/or pancreatic amylase [R16-1793, R16-1794, R16-4524, R17-2590, R17-2600, R17-2601, R17-2606]. There is limited clinical experience with the second generation of compounds inducing TRAILR2 clustering independently of Fc receptor (FcR) interactions. Phase I data from studies of the TRAILR2 binding tetramer (TAS-266) reported reversible liver toxicity at the first administered dose, which led to discontinuation of clinical development [R16-1795]. A detailed review of this published pre-clinical and clinical data suggested that a relatively high exposure at the starting dose in Phase I contributed to the observed toxicity of this drug [R16-1800]. Another TRAILR2 agonist (ABBV-621) was being investigated in Phase I (NCT03082209), and preliminary data reported non-dose related liver transaminase elevation and other gastrointestinal adverse effects [R20-0970]. Overall, increased ALT and AST were reported as treatment-related AEs in 21% and 17% of patients, respectively (and events of grade ≥3 were reported in 6% and 8% of patients, respectively) [R23-0540]. Phase I data of monotherapy dose escalation of the TRAILR2/CDH17 bispecific BI 905711 showed no DLTs through the highest monotherapy dose tested and the MTD was not determined [data in-house; trial 1412-0001].

The preclinical toxicity profile of BI 765883 did not indicate potential for any adverse toxicities and supports the administration of BI 765883 to humans. The NOAEL in the 4-week cynomolgus monkey study was 100 mg/kg q1w, which provides a safety margin of 254x and 428x the estimated human C_{max} and AUC, respectively, at the proposed starting dose of 0.4 mg/kg in Phase I.

Anticipated risks for adverse events (AEs) based on BI 765883 mode of action, findings in preclinical toxicology studies, and related guidelines for investigators are discussed below.

Injury of tissues expressing CDH3
BI 765883 may potentially cross-link TRAILR2 to CDH3 in non-cancerous tissues and induce apoptosis and injury. CDH3 is expressed in a wide range of non-neoplastic tissues in both humans and cynomolgus monkeys (Section 5.3 of the IB [c39438758]). No signs of injury were observed in preclinical toxicology studies in cynomolgus monkeys up to the highest administered dose (Section 5.3.2 of the IB [c39438758]). There are also nonclinical *in vitro* data suggesting that normal human colon epithelial cells are insensitive to TRAILR2 agonism, but their sensitivity may be increased during inflammation and viral infection [R16-4563, R17-2592]. Patients with inflammatory bowel disease and bowel infection should not participate in initial clinical trials with BI 765883 and are excluded from this trial.

Based on the above considerations, anticipated adverse events of BI 765883 may include nausea, anorexia, diarrhea, vomiting, pancreatitis, an increase in pancreatic lipase/amylase, abdominal pain and/or other gastrointestinal tract related symptoms. Patients should be closely monitored for development of the above-mentioned adverse events and treated symptomatically according to established treatment standards (e.g. with antiemetics, antidiarrheal medication, analgesic medication) as specified in the respective section of the clinical trial protocol and, if deemed necessary, transient or permanent discontinuation may be considered.

Liver injury
The liver is reported to be the most sensitive non-cancerous tissue to TRAILR2-mediated apoptosis [R16-1793, R16-1795]. Human hepatocytes do not express CDH3 and therefore BI 765883-mediated clustering of TRAILR2 in normal liver is not expected to occur. However, possible liver damage induced by BI 765883 cannot be excluded, particularly in combination with chemotherapy and/or in patients with liver metastases. Patients should be monitored closely for aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin increases and clinical symptoms of liver injury, which could potentially require transient or permanent discontinuation of BI 765883 as specified in Section 4.2.3.8. The possibility of their relationship to ADA will be assessed.

Neurological events
A 4-week GLP toxicology study in monkeys showed no neurological effects [n00261479]. While TRAILR2 and CDH3 have been described in the human brain and nerves, particularly in certain pathological conditions [R18-2769], there have been no neurological findings described in human studies with other TRAILR2 agonists up to the highest tested dose levels [R16-1793, R16-1794, R16-4524, R17-2590, R17-2600, R17-2601, R17-2606]. The risk of possible neurological side effects will be closely monitored clinically in human trials. Patients who develop new neurological symptoms or deficits need to undergo neurological status investigation followed by MRI and treatment with BI 765883 must be interrupted or

discontinued. Further provisions about management of study drug in case of neurological adverse events are provided in Section 4.2.3.5. The possibility of their relationship to ADA will be assessed.

Renal injury
Immunostaining for anti-human CDH3 antibody occurred in epithelial cells of the kidney, however in a 4-week GLP toxicology study in monkeys no renal injury was reported at the highest tested dose of 100 mg/kg (Section 5.3.2 of the IB [c39438758]). Patients will be monitored for changes in renal functions by serial measurement of creatinine and urea in blood and protein in urine as specified in the Section 4.2.3.6. Possible relationship of renal adverse events to ADA will be assessed.

Infusion-related reactions
BI 765883 is a humanized bispecific antibody with atypical structure and may lead to infusion-related reactions (IRRs) due to multiple mechanisms. Data from a similar bispecific antibody targeting TRAILR2 and fibroblast activation protein (FAP) indicate 9% of patients experienced grade 1 to 2 IRRs, but no grade 3 or higher infusion-related reaction were reported [R18-1695]. Infusion-related reactions may occur and should be treated by infusion interruption, administration of antihistamine agents and steroids according to severity, as specified in Section 4.2.3.1.

ADA (anti-drug antibodies) related side effects
The consequence of anti-drug antibody (ADA) occurrence for safety is currently unknown. Patients should be closely monitored for development of liver injury, neurological effects, and renal injury for the whole duration of BI 765883 treatment and possible contribution of ADA to these events should be considered.

Cytokine release syndrome (CRS)
In vitro cytokine release assay results suggest a low potential risk for inducing cytokine release upon BI 765883 treatment in humans. Additionally, in whole blood samples from 20 healthy human donors, overall, cytokine release of BI 765883-treated donors was comparable with the negative controls. A subset of donors (9/20) demonstrated higher IL-6 release following treatment with BI 765883. However, these higher values were not statistically significant, occurred sporadically, and there was no clear relationship with concentration of BI 765883. Thus, the increases were unlikely related to the mechanism of action of BI 765883, and the potential risk for inducing cytokine release *in vivo* upon BI 765883-treatment is considered low (Sections 5.3.7.2 and 5.3.8.2 of the IB [c39438758]).

The safety of patients in this study will be monitored by the DEC. For further details of the DEC, see Section 8.7.

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 765883		
Drug-induced liver injury (DILI)	Liver tissue is reported as the most sensitive non-cancerous tissue to TRAILR2 mediated apoptosis [R16-1793, R16-1795]. However human hepatocytes do not express CDH3 and therefore BI 765883-mediated clustering of TRAILR2 in normal liver is not expected to occur.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure trial patients' safety. For guidance on management of DILI, see Section 4.2.3.8
Infusion-related reactions (IRRs)	As with any mAb, hypersensitivity reactions are possible. BI 765883 is a humanized, bispecific antibody with atypical format and may lead to infusion-related reactions due to multiple mechanisms. Data from a similar bispecific antibody targeting TRAILR2 and FAP indicate 9% of patients experienced grade 1 to 2 IRRs, and no grade 3 or higher infusion-related reaction were reported [R18-1695].	IRRs may occur and should be treated by infusion interruption, administration of antihistamine agents and steroids according to severity. Patients with a known hypersensitivity to the trial medications or their excipients are excluded. Patients will remain under surveillance for at least 6 h after the end of infusion for the administration of BI 765883. In the absence of IRR this can be reduced in subsequent administrations. See section 4.2.3.1. Management guidelines for IRRs are provided in Section 4.2.3.1.

Table 1 (cont'd) Overview of trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Renal injury	Immunostaining for anti-human CDH3 antibody occurred in epithelial cells of the kidney, however in a 4-week GLP toxicology study in monkeys no renal injury was reported at the highest tested dose of 100 mg/kg. Although no renal injury observed in monkeys, the risk to humans remains unknown.	Patients will be monitored for changes in renal functions by serial measurement of creatinine and urea in blood and protein in urine as specified in the clinical trial protocol. Possible relationship of renal adverse events to ADA will be assessed.
Cytokine release syndrome (CRS) and immune-mediated reactions	CRS is a supra-physiologic response resulting in the activation or engagement of T cells and/or other immune effector cells, which can be serious or life-threatening. The TRAIL pathway has been implicated in inflammation, in some preclinical experiments, but the clinical relevance of these findings is unknown [R18-2770].	The risk of CRS cannot be excluded, and patients should be followed for possible occurrence of CRS. Patients will remain under surveillance after the end of infusion. Guidelines for the management of study drug in case of CRS are provided in Section 4.2.3.2.
Tumor lysis syndrome (TLS)	BI 765883 induces apoptosis within a short time frame *in vitro* and leads to tumor regression *in vivo* in preclinical models. Theoretically, TLS can occur.	Patients should be monitored for occurrence of TLS particularly after the first administration of study drug. Guidelines for the management of study drug in case of TLS are provided in Section 4.2.3.4.

Table 1 (cont'd) Overview of trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Injury of tissues expressing CDH3	BI 765883 may potentially cross-link TRAILR2 to CDH3 in non-cancerous tissues and induce apoptosis and injury. CDH3 is expressed in a wide range of non-neoplastic tissues in both humans and cynomolgus monkeys. No signs of injury were observed in preclinical toxicology studies in cynomolgus monkeys up to the highest administered dose. There are also nonclinical *in vitro* data suggesting that normal human colon epithelial cells are insensitive to TRAILR2 agonism, but their sensitivity may be increased during inflammation and viral infection.	Patients with inflammatory bowel disease and bowel infection should not participate in initial clinical trials with BI 765883. Anticipated adverse events of BI 765883 may include nausea, anorexia, diarrhea, vomiting, pancreatitis, and increase in pancreatic lipase/amylase, abdominal pain and/or other gastrointestinal tract related symptoms. For guidance on the management of diarrhea, nausea, and vomiting, see Section 4.2.3.3.
Neurological adverse events	A 4-week GLP toxicology study in monkeys showed no neurological effects. Although no neurological effects were observed in monkeys, the risk to humans remains unknown.	The risk of possible neurological side effects will be closely monitored clinically in human trials. Patients who develop new neurological symptoms or deficits need to undergo neurological status investigation followed by MRI and treatment with BI 765883 must be interrupted or discontinued. Further provisions about management of study drug in case of neurological adverse events are provided in Section 4.2.3.5. The possibility of their relationship to ADA will be assessed.
ADA (anti-drug antibodies) related adverse reactions	ADA to BI 765883 were observed in monkeys and were considered an immune response to a humanized monoclonal antibody. BI 765883 may lead to development of ADA in humans, and its occurrence will be explored in this study.	Patients will be followed for development of ADA related adverse reactions, and possible contribution of ADA to adverse reactions will be assessed.

Table 1 (cont'd) 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		
Inflammation of the wall of the vein. Injuring of a nerve while inserting the venous catheter, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.	General risk, acceptable in the framework of trial participation. The same risk applies to IV SoC treatment.	Evaluation of the medical expertise of the trial sites is part of site feasibility assessment. IMP discontinuation criteria, as well as criteria for IMP restart, are implemented for relevant cases.
Tumor biopsy	There is an added risk for pain, swelling, and bleeding for those patients who will undergo tumor biopsies. As the results from the biopsy will provide more information that will assist clinical decisions for future patients, the benefit is assumed to outweigh the risks.	Biopsies will only be performed when deemed safe by the investigator and if the platelet count is sufficient to allow for hemostasis.
Other risks		
Combination therapies gemcitabine and nab-paclitaxel	Refer to the most recent approved local labels.	The investigator must review the label for each therapy and implement any additional required safety monitoring to reduce the risk to the patient.

1.4.3 Discussion

The nature of the target and the mechanism of action of BI 765883 is not yet known in humans since this is a FIH study. Based on nonclinical data, primary pharmacology studies demonstrated that BI 765883 is a potent inducer of apoptosis, selectively in TRAILR2/CDH3 expressing tumor cells. BI 765883 in vivo efficacy in PDX PDAC models was demonstrated for the monotherapy setting and even more prominently for combinations of BI 765883 with SoC chemotherapeutic agents, where sustained tumor regressions were observed.

The proposed starting dose (0.4 mg/kg) is expected to provide a meaningful clinical benefit to cancer patients and is supported by multiples of exposure of the NOAEL from nonclinical toxicology data.

The toxicity profile of BI 765883 does not indicate potential for any severe adverse toxicities and supports the administration of BI 765883 to humans.

In the context of the unmet medical need, anticipated benefit of BI 765883, and available non-clinical and clinical information, the benefit-risk evaluation of the compound(s) is favorable.

Close monitoring of all adverse events has been implemented in the protocol. A Bayesian logistic regression model (BLRM) design will be used in order to escalate the dose into a range where efficacy is expected whilst minimizing the risk of undue toxicity.

The DEC will assess trial data to ensure the overall safety of enrolled patients. The DEC will also provide the investigators and the Sponsor with advice about the overall conduct of the trial (refer to Section 8.7).

The Sponsor will continuously assess the risks and benefits based on accumulating data from all clinical trials with BI 765883. Any significant change in risk-benefit ratio will be communicated to investigators and patients.

In summary, this trial will implement multiple safety measures to mitigate possible risks for participating patients. It is assumed that participation in this study and treatment with BI 765883 in combination with gemcitabine and nab-paclitaxel may potentially provide patients with clinical benefit at an acceptable risk.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

Phase Ia (dose escalation):
Primary objectives

- to determine the safety, tolerability and the MTD for BI 765883 as monotherapy
- to determine the safety, tolerability, and MTD for BI 765883 in combination with gemcitabine and nab-paclitaxel

Secondary objectives

- to assess the pharmacokinetic (PK) properties of BI 765883 as monotherapy and as combination therapy after first and after multiple administrations
- to evaluate the preliminary efficacy and safety of BI 765883 (as monotherapy)
- to evaluate preliminary efficacy and safety of BI 765883 in combination with gemcitabine and nab-paclitaxel and define the recommended dose for expansion (RDE)

For details of the dose escalation and determination of the MTD and RDE, see Section 3.1.1.

Phase Ib (Dose-expansion):
Primary objectives

- to evaluate preliminary efficacy of BI 765883 in combination with gemcitabine and nab-paclitaxel

Secondary objectives

- to assess the pharmacokinetic (PK) properties of BI 765883 as combination therapy after first and after multiple administrations
- to evaluate preliminary efficacy and safety of BI 765883 in combination with gemcitabine and nab-paclitaxel

The dose range for further development in Phase II will be determined based on all available data, including safety, preliminary efficacy, and PK data from Phase Ia and Phase Ib.

The handling of intercurrent events in Phase Ia and Phase Ib is described in Section 7.2.2.

2.1.2 Primary endpoints

Phase Ia: dose escalation
BI 765883 monotherapy/combination therapy

- **Primary endpoint** – dose escalation of BI 765883 as monotherapy and in combination with gemcitabine and nab-paclitaxel:
  - Occurrence of DLTs in the MTD evaluation period for the determination of the MTD (MTD definition described in Section 3.1.1)

Phase Ib: dose expansion
BI 765883 in combination with gemcitabine and nab-paclitaxel

- Primary endpoint
  - Confirmed objective response (OR) as assessed by the investigator defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1)
    - OR is defined as the best overall response of complete response (CR) or partial response (PR), recorded from the start of the study treatment until the earliest of disease progression, death, or last evaluable tumor assessment, and before start of subsequent anti-cancer therapy.

2.1.3 Secondary endpoints

Phase Ia: dose escalation
BI 765883 monotherapy/combination therapy

Secondary endpoints:

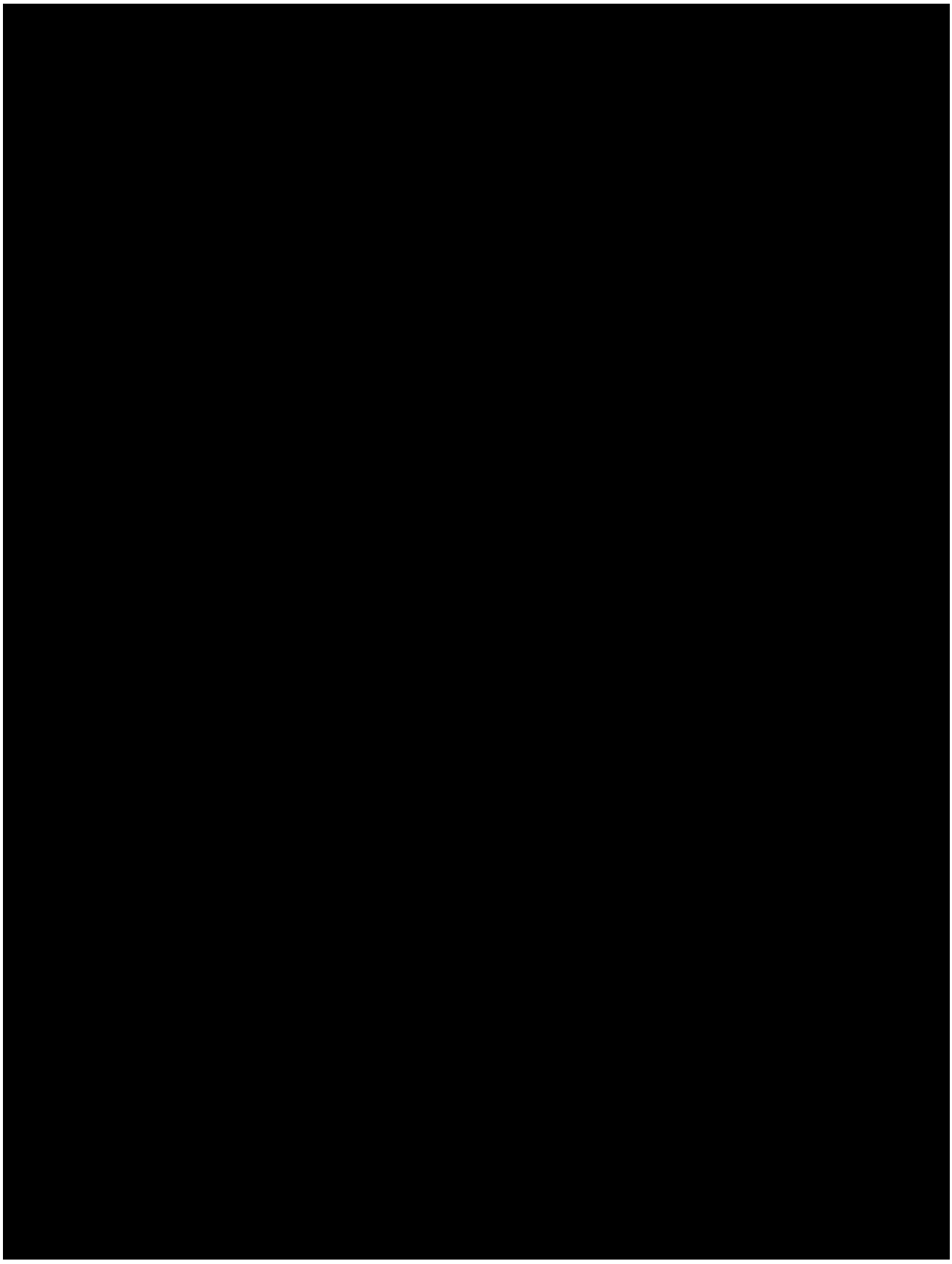
- OR, as defined above
- RDE for BI 765883 in combination with gemcitabine and nab-paclitaxel (for Phase Ib of this study).
  The RDE will be based on the totality of the safety, efficacy and PK data observed during the Phase Ia combination dose escalation, provided that the

minimal efficacy criterion of at least 2 confirmed ORs (per RECIST 1.1) per 10 patients (20%) treated at the same DL is met.

- Safety and tolerability based on frequency and severity of AEs according to the Common Terminology Criteria for Adverse Events (CTCAE)
- PK parameters of BI 765883 after the first and after multiple administrations:
  - C_{max}: maximum measured concentration of the analyte in serum
  - AUC_{0-t}: area under the serum concentration time curve of the analyte

Phase Ib: dose expansion
BI 765883 in combination with gemcitabine and nab-paclitaxel

- Secondary endpoints
  - Safety and tolerability based on frequency and severity of AEs according to the CTCAE
  - PK parameters of BI 765883 after the first and after multiple administrations of BI 765883:
    - C_{max}: maximum measured concentration of the analyte in serum
    - AUC_{0-t}: area under the serum concentration time curve of the analyte
  - Progression-free survival (PFS)
    PFS is defined as the time from first treatment administration until tumor progression according to RECIST 1.1 or death from any cause, whichever occurs earlier.
  - Duration of response (DOR), defined as the time from first documented complete response or partial response until the earliest of disease progression or death among patients with objective response



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is an open-label, Phase Ia/Ib, FIH, multicenter, dose escalation trial of BI 765883 as monotherapy and in combination with gemcitabine and nab-paclitaxel followed by dose expansion cohorts in patients with mPDAC. The study will consist of 2 phases: the dose escalation phase (Phase Ia) and the dose expansion phase (Phase Ib). Further dose optimization will be conducted in future Phase II trials or earlier if required.

3.1.1 Dose escalation (Phase Ia)

Phase Ia is an open-label, non-randomized, FIH, dose escalation of BI 765883 administered as monotherapy and of BI 765883 administered in combination with gemcitabine and nab-paclitaxel.

Two stepwise dose escalation strategies will be undertaken in parallel to determine the efficacious dose of BI 765883 as combination therapy. The stepwise increase in BI 765883 monotherapy and combination therapy is illustrated in Figure 1, below. An active control group is not planned. After the combination dose escalation is complete, or sooner as described in Section 3.3, the DEC will select up to 3 combination cohorts for backfills with an additional 7 patients per cohort to better evaluate efficacy.

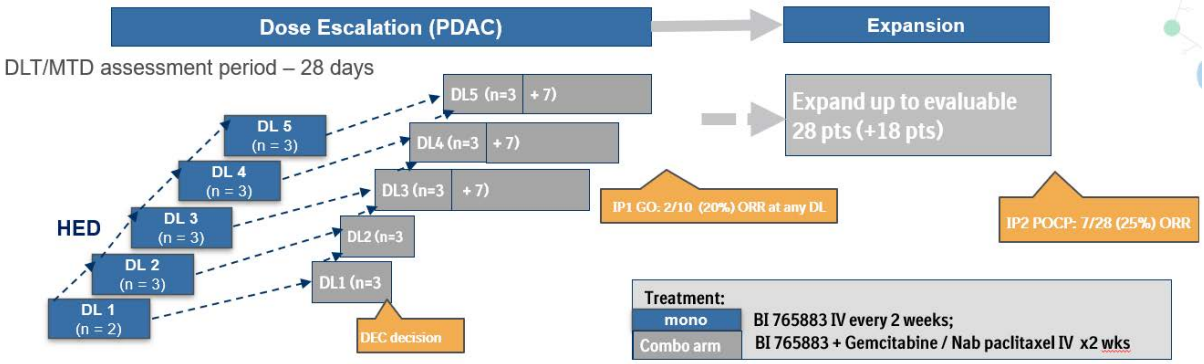


Figure 1 Schematic representation of the stepwise dose escalation (monotherapy and combination therapy) and dose expansion (combination therapy) in the 1505-0001 study

Combo = combination therapy; DEC = Dose Escalation Committee; DL = dose level; DLT = dose-limiting toxicity; HED = human efficacious dose ; IP = inflection point; mono = monotherapy; MTD = maximum tolerated dose; ORR = objective response rate; PDAC = pancreatic ductal adenocarcinoma; POCP = proof of clinical principle; pts = patients

Phase Ia of the study will characterize the exposure - safety curve for BI 765883 as monotherapy and as combination therapy administered in patients who have undergone at least 1 line of chemotherapy (≥2L mPDAC patients). Multiple dose levels of BI 765883 monotherapy and combination therapy will be assessed with Bayesian logistic regression

modeling (BLRM) and overdose control in order to achieve the primary objective of determining the MTD. PK and efficacy will also be evaluated to guide determination of the MTD/RDE.

The MTD evaluation period is defined as the first two treatment cycles; i.e. from Cycle 1 Day 1 (C1D1) up to and including the day before C3D1, or to the end of the REP in case of discontinuation before the start of C3. DLTs observed during the MTD evaluation period will be considered for the MTD determination (see below). However, all adverse events (AEs) and serious adverse events (SAEs) meeting DLT criteria (Table 10) that are observed in all treatment cycles will be considered when determining an RDE for Phase Ib and a recommended dose range for future development in Phase II.

The number of patients with DLTs per dose level observed within the MTD evaluation period will be the basis for defining the MTD according to the BLRM method. Dose escalation is guided by a BLRM with overdose control that will be fitted to binary toxicity outcomes (DLTs; for a list of DLTs, see Table 10). The estimate of parameters will be updated as data are accumulated using the BLRM.

To determine the MTDs for both BI 765883 monotherapy and for BI 765883 in combination with gemcitabine and nab-paclitaxel, the BLRM updates estimates of the probability of observing a DLT in the MTD 28-day evaluation period for each dose level as patient information becomes available. At any time in the study, it will not be permitted to escalate to a dose that does not fulfil the escalation with overdose control (EWOC) principle.

At the end of the dose escalation, the toxicity probability at each dose level will be calculated to determine an estimate of the MTD if applicable. The MTD is defined as the highest dose with less than 25% risk of the true DLT rate being equal or above 33% during the MTD evaluation period (for further details, see Section 7.2.3.1). An RDE will also be determined during the dose escalation phase.

Dose reductions will be permitted for BI 765883 for the dose escalation phase as described in Section 4.1.2. The duration of treatment in Phase Ia is until the development of progressive disease or until other criteria for stopping medication are met.

During Phase Ia dose escalations, a minimum of 48 h must have elapsed between the first dose of one patient and the first dose of the next subsequent patient within a dose level. The requirement of a minimum of 48 h between patient dosing is not applicable for backfill patients. Following completion of each dose level (monotherapy or combination therapy), the DEC will assess available study data to ensure the overall safety of the patients treated at each DL, before opening the next monotherapy or combination therapy dose level. Based on the accumulated data, the DEC will recommend the next dose level of BI 765883 to be assessed and will also provide the Investigators and the Sponsor with advice about the overall conduct of the study.

3.1.2 Dose expansion (Phase Ib)

Phase Ib is an open-label, non-randomized, expansion phase that will allow evaluation of safety, preliminary efficacy, and PK data at the RDE. Following identification of the MTD and the RDE for BI 765883 in combination with gemcitabine and nab-paclitaxel during Phase Ia, a Phase Ib expansion phase at a dose level will be selected to allow these assessments of this combination therapy in up to 28 evaluable patients.

The RDE for BI 765883, from Phase Ia, will be administered on Day 1 of each 2-week cycle followed by nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) each administered by IV infusion over a 30 minute period on Day 1 of each 2-week cycle.

Dose reductions will be permitted for BI 765883 as described in Section 4.1.2 for the dose escalation (Phase Ia) and also for the dose expansion (Phase Ib). The duration of treatment in Phase Ib is until the development of progressive disease or until other criteria for stopping medication are met.

3.1.3 Enrolment stopping rules

All safety information will be carefully analyzed by the sponsor.

Enrolment will also be temporarily stopped if any of the following events occur:

1. A clinically relevant AE occurs that is associated with evidence suggesting a reasonable possibility that the investigational drug caused the AE and the AE occurs at a frequency or with severity that suggest that the risk-benefit profile of the investigational drug should be reassessed.
2. One patient experiences a grade 4 Cytokine Release Syndrome and/or grade 4 hypersensitivity reaction and/or grade 4 infusion related reaction.
3. Study drug related death (other than death related to progressive disease) that occurs within 30 days of study drug administration.
4. More than 20% of patients experience grade 3 or 4 hepatic toxicity. The study may be discontinued if these adverse events are determined to be related to BI 765883.
5. More than 33% of patients experience any grade 3 or 4 adverse events related to BI 765883. The study may be discontinued based on the findings of this evaluation and the determination of a causal relationship to the study drug.
6. More than 15% of patients discontinue treatment due to toxicity (other than hepatic toxicity). A detailed safety review will be conducted to assess the causes of discontinuation and to determine the future course of the study, which may include modifications to the protocol or discontinuation of the trial.

Criteria #4, 5 and 6 above will be applied once the patients from at least 2 dose levels of monotherapy and combination therapy cohorts have completed assessment period.

If the sponsor, in consultation with the DEC, determines that the above criteria are met, the enrolment to the trial will be temporarily stopped to allow for in-depth analysis of the safety profile of BI 765883 plus the combination therapy, as appropriate. The benefit-risk profile will be re-assessed by the DEC to determine if the trial should be continued as planned, or permanently discontinued or will continue with modification to the trial 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 765883 plus gemcitabine and nab-paclitaxel treatment remains positive. The DEC will also consider and provide guidance for the management of patients who are already receiving study treatment. The outcome of the analysis and the recommendations will be shared with all involved Health Authorities prior to a planned re-start of enrolment. In case the benefit-risk assessment is no longer considered positive, the trial will be discontinued.

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

The present study is a FIH dose escalation study in patients with mPDAC who have undergone at least 1 line of chemotherapy who do not have SoC treatment options based on local approved standards and, in combination with gemcitabine and nab-paclitaxel (SoC), in unselected patients with 2L mPDAC who have progressive disease after prior platin and/or irinotecan-based first line therapy. Current SoC as per NCCN guidelines for the treatment of advanced or metastatic pancreatic ductal adenocarcinoma includes platinum-based combination chemotherapy in first line patients with good performance status (PS), followed by combination treatment of nab-paclitaxel and gemcitabine [NCCN guidelines PDAC 2.2023; R23-4062].

In Phase Ia, the selection of dose levels and patient cohort size will be based on the decisions of 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 BLRM for Phase I trials has also been advocated by the EMA guideline on small populations [R07-4856] and by the FDA [R13-4881].

Before the start of Phase Ib, a dose selection (RDE) will be conducted, considering the full safety and efficacy profile, including all available data within and beyond the MTD evaluation period. It is foreseen that the lowest dose with sufficient therapeutic activity will be selected for further development in Phase Ib in combination with current SoC treatment nab-paclitaxel and gemcitabine.

To decrease the burden for patients, follow-up visits will be conducted remotely after the 30-day follow-up visit has been completed, during which all relevant trial information will be collected in a structured questionnaire and/or interview. If requested by a trial patient or

deemed necessary by the investigator at any time, an on-site trial visit can be conducted, either in place of or in addition to a prespecified remote visit. Similarly, site personnel should be ready to address any concerns, questions, or event reporting from patients outside the prespecified follow-up time points.

3.3 SELECTION OF TRIAL POPULATION

This is an international, multicenter trial.

Patients in Phase Ia are planned to be enrolled in approximately 15 sites. For Phase Ib, patients are planned to be entered at sites that participate in the dose escalation part of the study as well as additional sites that will be initiated as needed to fulfill the planned enrolment. If participating sites are unable to recruit patients, additional sites may be opened, and under-performing sites may be closed.

The total number of patients will depend on the number of dose levels to be tested and the size of the dose escalation cohorts. For Phase Ia (dose escalation), up to 60 evaluable patients are planned to be enrolled in the monotherapy and combination therapy dose escalation cohorts. For the backfill and dose expansion parts (Phase Ib), assuming the DEC decides to recruit additional patients to 3 dose levels for early efficacy checking, and 1 DL satisfies the interim efficacy criterion, this leads to up to 39 evaluable patients (21 evaluable patients for backfill cohorts [7 patients for 3 dose levels], plus 18 evaluable patients for the 1 dose level that has passed the interim efficacy criterion) that are planned to be enrolled in the combination therapy backfill and dose expansion parts. In case of patients being not evaluable for MTD or efficacy assessments per RECIST version 1.1, they may be replaced; therefore extra patients would be needed. In total, up to 99 evaluable patients may be enrolled in the study.

Screening of patients for this trial is competitive; however in Phase Ia, recruitment slots will be assigned by the Sponsor. Treatment in the monotherapy and combination cohorts will be started sequentially. Monotherapy will start first. Once the first dose level in monotherapy has been determined to be safe by the DEC, the first dose level of treatment in the combination cohort may be initiated. Further details on recruitment slot allocation will be provided in the slot allocation plan.

Screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial. Any patients already in screening at this time will be allowed to continue to receive treatment if eligible.

A log of all patients enrolled in 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 or not. The following information, at minimum, will be collected, including for patients who are determined to be ineligible for enrolment: patient number, visit date, demographics,

eligibility criteria, information on AEs (if applicable), concomitant treatment relevant for the AE.

If retrospectively it is found that a trial patient has been entered in error (i.e. 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 as to whether continued trial participation is possible.

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.

A patient who has been declared as a "screening failure" may be re-screened once. In this situation, patients will be handled as new patients i.e. sign a new informed consent, allocate a new patient number, and undergo full screening assessments to assess eligibility.

3.3.1 Main diagnosis for trial entry

The patient population for this trial includes patients with histologically or cytologically confirmed, advanced unresectable or metastatic PDAC. Patients meeting the inclusion criteria below and not meeting any of the exclusion criteria will be eligible to participate.

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

3.3.2 Inclusion criteria

Applicable to both Phase Ia and Phase Ib patients:

1. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
2. Of legal adult age (according to local legislation) at screening.
3. Male or female patients. Women of childbearing potential (WOCBP; see definition in Section 4.2.2.3) and men able to father a child must be willing 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 use is provided in Section 4.2.2.3.
4. Histologically or cytologically confirmed, advanced unresectable or metastatic PDAC.
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤1.
6. Life expectancy ≥3 months in the opinion of the investigator.
7. Archived tumor tissue from a tissue core biopsy (e.g. paraffin-embedded formalin-fixed tissue blocks), OR fresh tumor tissue available for retrospective biomarker analysis; in both cases, a minimum of at least two core needle biopsies (18 gauge or greater) is required. Only non-significant risk procedures per the investigator's judgment will be

used to obtain any biopsies specified in this study in cases where a fresh tumor biopsy is required.

8. Patients with at least 1 target lesion that can be accurately measured per RECIST version 1.1.
9. **For monotherapy cohorts only:** Patients who have progressed on or are intolerant to available standard therapy, or for whom no standard therapies with proven benefit exists, according to the local and institutional guidelines.
10. **For combination cohorts only:** Patients who have progressive metastatic disease after prior platin and/or irinotecan-based first line therapy. Eligible patients for combination therapy as second-line (2L) include patients who have relapsed within 6 months and present with metastatic disease after resection and neo- and/or adjuvant therapy as these patients are considered as frontline failed and are now 2L treatment eligible.
11. Adequate hepatic, renal, and bone marrow functions as defined below:
    - Total bilirubin ≤1.5 x institutional upper level of normal (ULN)
    - Alanine transaminase (ALT) and aspartate transaminase (AST) ≤2.5 x institutional ULN or ≤5 x institutional ULN for patients with known liver metastases
    - Estimated glomerular filtration rate (eGFR) ≥45 mL/min (≥0.045 L/min) measured or calculated using the applicable Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Caucasian and Black: R12-1392; Japanese: R22-1536; other races: R22-1535)
    - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L (≥1.5 x 10^3/µL or ≥1500/mm^3)
    - Platelets ≥100 x 10^9/L (≥100 x 10^3/µL or ≥100 x 10^3/mm^3)
    - Hemoglobin ≥9.0 g/dL (≥90 g/L or ≥5.6 mmol/L) without transfusion within previous week
    - Serum lipase ≤1.5 x institutional ULN
12. Significant or symptomatic amounts of ascites should be drained prior to Day 1.
13. Recovery from AEs (according to CTCAE v 5.0) due to previous anti-cancer therapies to CTCAE grade ≤1, except for alopecia (CTCAE grade 2), endocrinopathies controlled by replacement therapy which must be ≤CTCAE grade 2, and amenorrhea/menstrual disorders which can be any grade.

3.3.3 Exclusion criteria

Applicable to both Phase Ia and Phase Ib patients:

1. Previous exposure to trial drug (BI 765883).
2. Any prior gemcitabine and/or paclitaxel therapy (for combination therapy cohorts).
3. Known hypersensitivity to the study medications or their excipients (including gemcitabine and nab-paclitaxel).
4. Any contraindications to gemcitabine or nab-paclitaxel according to the current approved local labels (combination therapy).
5. 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).

6. Any serious concomitant disease or medical condition affecting compliance with trial requirements or which are considered relevant for the evaluation of the efficacy or safety of the trial drug, such as neurologic, psychiatric, infectious disease, active ulcers (gastro-intestinal tract, skin), inflammatory bowel disease or bowel infection, or laboratory abnormality that may increase the risk associated with trial participation or trial drug administration, and in the judgment of the Investigator, would make the patient inappropriate for entry into the trial.
7. Prior radiotherapy or systemic therapy within 14 days prior to treatment start
8. History or presence of cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of ≥III or IV, unstable angina or poorly controlled arrhythmia which are considered as clinically relevant by the Investigator.
9. Myocardial infarction, stroke, or clinically significant pulmonary embolism within 6 months prior to first drug administration.
10. Either of the following cardiac criteria: QT interval corrected for heart rate by Fridericia's formula (QTcF) >480 ms or left ventricular ejection fraction (LVEF) <50%.
11. Women who are pregnant, nursing, or who plan to become pregnant or nurse during the study or within 6 months after the last dose of study treatment.
12. Major surgery (by investigator’s assessment) performed within 28 days prior to treatment start or planned within 3 months after screening.
13. Presence of uncontrolled or symptomatic brain or subdural metastases. Inclusion of patients with brain metastases who have completed local therapy and are considered stable by the investigator, or with newly identified asymptomatic brain metastases at screening will be allowed. Use of corticosteroids is allowed if the dose was stable for at least 1 week before the baseline CT/MRI.
14. Sensory peripheral neuropathy of CTCAE grade ≥2 or grade 1 considered clinically significant (combination therapy).
15. 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.
16. 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 patient).
17. Any condition not covered by any of the other exclusion criteria which, in the investigator’s opinion, might jeopardize the patient’s safety or compliance with the protocol.
18. Any vulnerable person (defined as: pregnant or breastfeeding women; persons deprived of their liberty; minors; persons that may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests; persons unable to explicitly give consent; patients who are under judicial protection and patients who are legally institutionalized), as per local regulation.
19. Previous or concomitant malignancies, other than the one treated in this trial within the last 5 years with the exception of the following:
    - Effectively treated non-melanoma skin cancers
    - Effectively treated carcinoma in situ of the cervix

- Effectively treated ductal carcinoma in situ
- Other effectively treated malignancy that is considered cured by local treatment

20. Patients with history of human immunodeficiency virus (HIV) infection who meet one or more of the following criteria:
    - CD4+ count < 350 cells/µL
    - Viral load > 400 copies/mL (local lab assessment)
    - Not receiving antiretroviral therapy
    - Receiving established antiretroviral therapy for less than 4 weeks prior to the start of study treatment
    - 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 diseases specialist or an HIV/infectious diseases specialist must be consulted prior to inclusion. For patients with known HIV, results from CD4+ count and viral load testing within a year of screening can be used to determine eligibility.
21. Patients with chronic hepatitis B virus (HBV) infection with active disease who meet the criteria for anti HBV therapy (according to local/institutional standard) and patients currently receiving antiviral treatment or patients with a history of hepatitis C virus (HCV) infection who meet one or both of the following criteria:
    - Currently receiving curative antiviral treatment
    - HCV viral load is above the limit of quantification (HCV RNA positive)

3.3.4 Discontinuation of trial patients from treatment or assessments

Trial patients may discontinue trial drug 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.

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

The decision to discontinue trial drug or withdraw consent to trial participation and the reason (if provided) must be documented in the trial patient files and CRF. If applicable, consider the requirements for AE collection and reporting (see Section 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

If a trial patient discontinues treatment but agrees to remain in the trial, they should attend further trial visits to ensure their safety and to collect important trial data.

An individual trial patient will discontinue trial drug if:

- The patient wants to discontinue study treatment without the need to justify the decision. The trial 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 the investigator, 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 needs to take concomitant medication that interferes with the investigational medicinal product
- The patient can no longer receive BI 765883 and gemcitabine for medical reasons such as surgery, AEs, other diseases, or pregnancy. If only nab-paclitaxel is discontinued, the patient may continue treatment with BI 765883 and gemcitabine. If only BI 765883 is discontinued, the patient may continue treatment with gemcitabine and nab-paclitaxel.
- Has radiological (or clinical) documentation of progressive disease on the current treatment (see Section 5.1) unless the investigator documents that the patient will continue treatment beyond initial RECIST progression due to clinical benefit.
    - The patient may continue treatment beyond initial RECIST progression if:
        - The patient is clinically benefiting
        - The criteria described below are met
        - It is agreed between the Investigator and the Sponsor
        - The patient has signed an informed consent describing this circumstance
    - Criteria required to continue treatment beyond RECIST-defined radiological progression of disease:
        - Absence of clinical symptoms or signs indicating clinically significant disease progression
        - No decline in performance status
        - Absence of rapid disease progression or threat to vital organs or critical anatomical sites [e.g. CNS metastasis, respiratory failure due to tumor

compression, spinal cord compression] requiring urgent alternative medical intervention

- No significant, unacceptable or irreversible toxicities related to study treatment

If a patient becomes pregnant during the trial, trial treatment must be stopped immediately. The patient will be followed up until delivery or termination of pregnancy.

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.

Patients will also be replaced if they are non-evaluable for RECIST v. 1.1 response assessment if they are needed either (1) to assess the OR rate for the 10 evaluable patients/cohort in the Phase Ia combination cohorts that had backfills or (2) to assess the OR rate for the 28 evaluable patients treated at the RDE.

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 trial patient wants to withdraw consent, the investigator should be involved in the discussion with the trial 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 (see Section 3.3.4.1).

Any blood, serum, plasma, blood cells, urine, or tumor samples collected prior to withdrawal of consent to trial participation (WoC) has been confirmed will still be used in the analysis of study results, unless patients inform their doctor that it is preferred these samples be destroyed.

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. 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

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

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

3.3.4.4 Replacement of patients

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

- Patients who withdraw consent or who are lost from follow-up or discontinue for any other reason other than DLT before completing the first two cycles of study treatment
- Patients who have received less than 70% of the planned BI 765883 doses during first two cycles of study treatment and do not experience a DLT
- Patients who miss 2 or more partial or complete visits during the first two cycles of study treatment, with missing PK and safety parameters needed to accurately assess DLT and MTD determination
- Patients found to be non-eligible after starting study treatment based on a case-by-case basis

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.

Of note, the dose escalation will be determined based on all the safety information of all treated patients including those who will not be included in the BLRM analysis.

Patients who experience a DLT during the MTD evaluation period as well as patients who withdraw after the MTD evaluation period will not be replaced.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the investigational medicinal products during Phase Ia and Phase Ib

Table 2 BI 765883

Substance:	BI 765883
Pharmaceutical formulation:	Powder for solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	100 mg/vial (30 mg/mL)
Posology:	Single administration every 2 weeks, on Day 1 of each 2-week treatment cycle
Mode of administration:	Intravenous
Solvent/diluent	Solvent: Water for injection Diluent: Sodium chloride 9 mg/mL (0.9%) solution for injection

In combination therapy cohorts, gemcitabine and nab-paclitaxel are administered in combination with BI 765883 (Table 3).

Table 3 Gemcitabine and nab-paclitaxel (combination therapy cohorts only)

Substance:	Gemcitabine	Nab-paclitaxel (paclitaxel formulated as albumin bound nanoparticle)
Pharmaceutical formulation:	Concentrate for solution for infusion	Powder for dispersion for infusion
Source:	[redacted]	[redacted]
Unit strength:	2000 mg/52.6 mL	100 mg of paclitaxel formulated as albumin bound nanoparticles to be dissolved in 20 mL
Posology:	Single administration every 2 weeks, on Day 1 of each 2-week treatment cycle	Single administration every 2 weeks, on Day 1 of each 2-week treatment cycle
Mode of administration:	Intravenous	Intravenous
Solvent/diluent	Sodium chloride 9 mg/mL (0.9%) solution for injection	Sodium chloride 9 mg/ml (0.9%) solution for infusion

4.1.2 Selection of doses in the trial and dose modifications

4.1.2.1 Dose escalation

In Phase Ia, the starting dose of BI 765883 is 0.4 mg/kg, administered every 2 weeks (q2w dosing). This dose level is 10-fold below the predicted therapeutic dose of 4 mg/kg q2w ($C_{max,ss}$ = 175.8 µg/mL, $AUC_{0\text{-}inf}$ = 27280 µg*h/mL). Based on nonclinical efficacy data from PDAC/ PDX animal models, a starting dose of 0.4 mg/kg q2w with a predicted activity of 70% TGI is proposed for this Phase I clinical trial [n00299708, n00303858]. The proposed starting dose is expected to provide a meaningful clinical benefit to cancer patients and is supported by multiples of exposure of the NOAEL from nonclinical toxicology data. Therefore, the selected FIH starting dose is considered to provide an appropriate benefit/risk ratio for cancer patients in Phase I clinical studies.

Five DLs are planned for both the monotherapy and for the combination dose escalations (all with q2w dosing):

- DL1 = 0.4 mg/kg (starting dose)
- DL2 = 1.3 mg/kg
- DL3 = 4.0 mg/kg (predicted human efficacious dose [HED])
- DL4 = 8.0 mg/kg
- DL5 = 16 mg/kg

Higher dose levels above DL5 may be permitted if the DEC deems DL5 to be tolerable and if the benefit-risk ratio favors further escalation.

In the monotherapy dose escalation, the planned sample size is n = 3 for all cohorts (except the first cohort where n = 2) unless a DLT occurs, in which case, the cohort will be expanded as determined by the DEC (e.g. to n = 6). If 2 DLTs occur, further patients in this cohort or higher dose cohorts are not permitted as the MTD will have been exceeded.

During Phase Ia dose escalations, a minimum of 48 h must have elapsed between the first dose of one patient and the first dose of the next subsequent patient within a dose level. The requirement of a minimum of 48 h between patient dosing is not applicable for backfill patients. The dose escalations (monotherapy and combination cohorts) will be staggered so the monotherapy dose escalation comes first and no combination cohort will be tested without prior determining sufficient safety of the corresponding monotherapy cohort using the same dose of BI 765883. Following completion of each dose level (monotherapy or combination therapy), the DEC will assess available study data to ensure the overall safety of the patients and before opening the next monotherapy or combination therapy dose level.

If the first monotherapy cohort (DL1) is determined by the DEC to be safe and tolerable, 2 sets of dose escalations will then proceed in parallel: 1) enrolment of 3 new patients into the combination cohort at DL1; and 2) simultaneous enrolment of 3 new patients into the

monotherapy cohort at DL2. Each combination cohort begins with enrolment of 3 patients with the latter option of 7 additional patients in combination backfill cohorts at DL3 – DL5 as described below.

Nab-paclitaxel combined with gemcitabine is a standard of care in the treatment of advanced/metastatic PDAC [R23-4062]. Different schedules exist. According to the label the recommended dose of nab-paclitaxel in combination with gemcitabine is 125 mg/m^2 administered intravenously over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. However in cross trial comparisons a biweekly schedule of both drugs has shown comparable efficacy and improved safety and has therefore been chosen for combination with BI 765883 [R23-4049, R23-4050].

After the combination dose escalation is complete, or sooner as described below, the DEC will recommend up to 3 combination cohorts for backfills with 7 additional patients each to make a total of 10 patients per cohort to better evaluate efficacy. If all combination cohorts are deemed safe and tolerable, then the combination backfill cohorts will begin at DL3, the estimated HED, and at any higher DLs deemed safe and tolerable up to the MTD. In order to save time, enrolment of 7 patients into each of the backfill combination cohorts does not need to wait until all combination dose escalation cohorts are enrolled and may begin enrolment at DL3 once combination cohort DL3 is deemed safe by the DEC. After the combination dose escalation and combination backfill cohorts are completed, the DEC will recommend one DL (RDE) for the Phase Ib expansion phase. The RDE must meet the efficacy criterion of at least 2 confirmed ORs/10 patients (20%). If no combination cohort demonstrates at least 2 ORs/10 patients (20%), then the study and project will proceed to termination. Any on-treatment patients benefitting at that time will be allowed to remain on study.

BI 765883 dosing schedule
The dosing schedules for monotherapy and combination therapy will be as follows:

- Monotherapy: BI 765883 is administered intravenously (IV) over 30 minutes (+10 minutes) on Day 1 of each 2-week cycle.
- Combination therapy: BI 765883 is administered by IV infusion (over 30 minutes +10 minutes) on Day 1 of each 2-week cycle followed by nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) each administered by IV infusion over a 30-minute period also on Day 1 of each 2-week cycle.

Permitted dose modifications:

- Patients who experience DLT(s) or any BI 765883 related CTCAE grade 3 to 4 AE should interrupt or delay treatment until recovery to CTCAE grade 1 or to baseline. In such cases, restarting BI 765883 treatment may be considered at a reduced dose (-1 DL).
- No more than 2 dose reductions will be allowed.

The duration of treatment in Phase Ia is until unacceptable toxicity, disease progression, or death, whichever occurs first.

Dose modifications for gemcitabine and nab-paclitaxel are permitted as outlined in the local SmPC for gemcitabine and nab-paclitaxel (see also Table 5).

4.1.2.2 Dose expansion (Phase Ib)

Phase Ib is an open-label, non-randomized, expansion phase that will allow evaluation of safety, preliminary efficacy, and PK data at the RDE. Following identification of the MTD and the RDE for BI 765883 in combination with gemcitabine and nab-paclitaxel, an expansion phase at the RDE dose level will allow these assessments of this combination therapy in up to 28 evaluable patients.

BI 765883 dosage
The RDE for BI 765883 from Phase Ia will be administered via IV infusion (over 30 minutes +10 minutes) on Day 1 of each 2-week cycle followed by nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) each administered by IV infusion over a 30-minute period on Day 1 of each 2-week cycle.

Dose reductions will be permitted as described above for the dose escalation phase. The duration of treatment in Phase Ib is until unacceptable toxicity, disease progression, or death, whichever occurs first.

4.1.3 Method of assigning trial patients to treatment groups

Recruitment into the trial will be conducted in a controlled manner. Patient numbers will be assigned via Interactive Response Technology (IRT) upon registration of screening. In both Phase Ia and Phase Ib, each eligible patient will be assigned and receive the appropriate dose for their assigned cohort.

In both Phase Ia and Phase Ib, the BI 765883 dose level will be assigned via the IRT.

Each medication vial will have a unique medication number. The medication number assigned will be documented in the CRF. Note that the medication number is different from the patient number (the latter is generated during screening via the IRT system).

The IRT system will be used to screen patients, create a patient number, perform treatment assignment, and manage initial/re-supply ordering of supplies of study treatments and of the SoC combination therapy.

4.1.4 Drug assignment and administration of doses for each trial patient

4.1.4.1 BI 765883

BI 765883 will be prepared and handled according to the 1505-0001 "Instructions for Preparation and Administration of BI 765883 powder for solution for infusion" which will be filed in the ISF. Each patient will receive the appropriate trial medication and dose for their assigned dose cohort.

BI 765883 (and combination therapy where appropriate) for each dose cohort will be assigned via IRT for each treatment cycle. Upon notification that a patient will be treated in the study, the pharmacy will prepare the trial medication at the assigned dosage for administration to the patient.

The C1 D1 dose of BI 765883 will be calculated using the C1 D1 weight or weight up to 3 days prior as the reference weight. If the patient's weight changes by ≤10% compared to the reference weight, the dose (in mg) may remain the same for subsequent cycles. If the weight changes by >10% the dose will be recalculated and the new weight will be used as the reference weight.

All trial medications (including gemcitabine and nab-paclitaxel) will be given as an IV infusion by authorized site staff in a specialized unit where emergency care can be provided. Appropriate drugs and medical equipment to treat anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

No routine premedication will be required for BI 765883 IV infusions. Refer to Section 4.2.1.3 for premedication for the combination therapy and Section 4.1.4.2 for the order of administration. The BI 765883 IV infusion should take place over 30 minutes (+10 minutes) unless there is a necessity of administration rate reduction according to the protocol (e.g. in case of infusion-related reaction). Total storage time for ready-to-use solution at room temperature should not exceed 150 minutes between preparation and end of infusion time.

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 the 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.

If a patient misses a visit during which there is treatment administration planned (e.g. due to AEs), the visit should be rescheduled as soon as possible and the delayed visit documented with the actual date and the reason for the delay. The scheduling of subsequent visits should be adapted accordingly, keeping the original intervals. Response assessment should be

maintained as originally planned, wherever possible. However, alteration of the tumor assessment schedule to align with clinical assessments and to avoid additional visits / patient burden is allowed. The next dose of treatment may be delayed for up to 28 days until the criteria for receiving further treatment (Section 4.1.4.3) are met.

Additional information on BI 765883 use will be provided in a pharmaceutical manual.

Observation period for CRS/IRR

- Patients will remain under surveillance for at least 6 hours after the end of infusion after the first, second and third administrations of BI 765883. During the post-infusion observation period, body temperature, pulse rate and blood pressure will be measured at the end of the infusion and every 2 hours (± 15 minutes) thereafter.
- If no adverse signs or symptoms, e.g. infusion-related reactions, are observed during the first 3 administrations, the duration of the post-infusion observation period may be reduced to 4 hours for subsequent administrations. Body temperature, pulse rate and blood pressure will be measured at the end of the infusion, then after 2 and 4 hours (± 15 minutes).
- After 6 administrations in the absence of infusion-related reactions, the post-infusion observation period can be reduced to 2 hours at the investigator's discretion. Body temperature, pulse rate and blood pressure will be measured at the end of the infusion, then after 2 hours (± 15 minutes).

4.1.4.2 Gemcitabine and nab-paclitaxel

For patients treated with BI 765883 in combination with gemcitabine and nab-paclitaxel, the order of administration on Day 1 of each 2-week cycle is premedication for chemotherapy (in accordance with institutional standards) followed by BI 765883 followed by nab-paclitaxel followed by gemcitabine.

Dosing of gemcitabine and nab-paclitaxel will be in accordance with the SmPC for gemcitabine and nab-paclitaxel.

Immediately before the BI 765883 IV infusion, patients will receive chemotherapy premedication (in accordance with institutional standards; acceptable common premedication examples are dexamethasone and ondansetron to prevent nausea). After the BI 765883 infusion, patients will receive nab-paclitaxel, which is injected by IV at 125 mg/m^2 for 30 minutes, followed by IV gemcitabine at 1000 mg/m^2 for 30 minutes.

4.1.4.3 Criteria for receiving further treatment

Eligibility for further treatment should be confirmed prior to dosing on D1 of each cycle prior to administration of BI 765883 by confirming the patient has not met any criteria for protocol

discontinuation as described in Section 3.3.4.1 or experienced any AE requiring treatment discontinuation (Section 4.2.3).

To continue treatment the following criteria must be met:

- Total bilirubin ≤ 1.5 x institutional ULN
- ALT and AST ≤2.5 x institutional ULN or ≤5 x institutional ULN for patients with known liver metastases
- Serum creatinine ≤1.5 x institutional ULN. If creatinine is >1.5 x ULN, patient is eligible if concurrent eGFR is ≥45 mL/min (≥0.045 L/min) (measured or calculated by applicable CKD-EPI formula) [R12-1392, R22-1535, R22-1536]
- ANC ≥1.5 x 10^9/L (≥1.5 x 10^3/µL or ≥1500/mm^3)
- Platelets ≥100 x 10^9/L (≥100 x 10^3/µL or ≥100 x 10^3/mm^3)
- Hemoglobin ≥8.5 g/dL (≥85 g/L or ≥5.3 mmol/L) without transfusion within previous week
- Serum lipase ≤1.5 x institutional ULN
- Absence of worsening (any CTCAE grade) or new neurological signs/symptoms CTCAE grade > 1
- Absence of progressive disease unless the investigator documents that the patient will continue treatment beyond progression due to clinical benefit (after agreement with Sponsor).

If the 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 for up to 28 days until the criteria are met. Dose modification may be appropriate (see below, Section 4.1.4.4).

If treatment with BI 765883 is discontinued, the patient may discontinue gemcitabine and nab-paclitaxel and may be treated with SoC, at the discretion of the investigator, outside of this trial. Alternatively, if BI 765883 treatment is discontinued, the patient can continue treatment with gemcitabine and nab-paclitaxel within this trial.

4.1.4.4 Dose modifications

Individual patients must not receive a higher dose than assigned to them at the start of the trial. Dose escalation is allowed in cases where the dose has been reduced in error. At the time the recommended dose for expansion is determined by DEC, patients that are on any other dose levels may be adapted to the recommended dose at investigator's discretion. The dose cannot be escalated if the dose has been previously reduced for toxicity reason(s).

BI 765883
Patients who experience DLT(s) or any AEs outlined in Section 4.2.3 should interrupt or delay treatment until recovery to CTCAE grade 1 or to baseline (Table 4). In such cases, restarting BI 765883 treatment may be considered at a reduced dose (-1 DL). No more than 2 dose reductions will be allowed.

Table 4 Dose reduction scheme for BI 765883

Dose level	First occurrence	Second occurrence	Third occurrence
1	Discontinue BI 765883 treatment	n/a	n/a
2	Reduce to DL 1	Discontinue BI 765883 treatment	n/a
3	Reduce to DL 2	Reduce to DL 1	Discontinue BI 765883 treatment
4	Reduce to DL 3	Reduce to DL 2	Discontinue BI 765883 treatment
5	Reduce to DL 4	Reduce to DL 3	Discontinue BI 765883 treatment
Further dose levels in case decision to go beyond DL5	Reduce to next lower DL according to BLRM	Reduce further to next lower DL according to BLRM	Discontinue BI 765883 treatment

BLRM = Bayesian logistic regression model; DL = dose level; n/a = not applicable

If treatment with BI 765883 is discontinued, the patient may discontinue gemcitabine and nab-paclitaxel and may be treated with SoC, at the discretion of the investigator, outside of this trial. Alternatively, if BI 765883 treatment is discontinued, the patient can continue treatment with gemcitabine and nab-paclitaxel within this trial.

Gemcitabine and nab-paclitaxel
Dose reductions or treatment delays for gemcitabine and nab-paclitaxel are to be performed as described by Mita et al, 2019 [R23-3401] and in the Summary of Product Characteristics [SmPC] for Abraxane®.

SmPC recommendations for D8 and D15 dosing are not applicable for this trial since gemcitabine and nab-paclitaxel are administered using a biweekly schedule (see recommendations for D1 of each treatment cycle, described above).

The treatment is to be delayed in cases of 1 or more of the following at pre-dosing on D1 of any cycle: white blood cell count (WBC) count >12 000/mL, ANC <1500/mm^3, hemoglobin level <8.5 g/dL, platelet count <100 000/mm^3, total bilirubin level >2.0 mg/dL, AST and ALT levels >150 U/L, creatinine level >1.5 mg/dL, peripheral neuropathy, or febrile neutropenia (FN).

Subsequent doses of both nab-paclitaxel and gemcitabine are to be reduced if ANC reaches ≤1000/mm^3 and/or platelet count reaches ≤75 000/mm^3 at D8 or pre-dosing on D1 of the subsequent cycle (throughout the study).

Dose reductions due to non-hematological toxicities will be performed as follows: if CTCAE grade >2 exanthema or CTCAE grade >3 oral mucositis or CTCAE grade >3 diarrhea

develops, both nab-paclitaxel and gemcitabine will be reduced, and if CTCAE grade >3 peripheral neuropathy develops, only nab-paclitaxel will be reduced. Dose modifications for gemcitabine and nab-paclitaxel are summarized in Table 5.

If more than 2 dose reductions are required for either nab-paclitaxel or gemcitabine the patient must discontinue that treatment. If dosing with nab-paclitaxel is discontinued, treatment may continue with BI 765883 and gemcitabine. If treatment with gemcitabine is discontinued, the patient also has to discontinue BI 765883 and nab-paclitaxel and may be treated with SoC, at the discretion of the investigator, outside of this trial.

Table 5 Dose modifications for nab-paclitaxel and gemcitabine

Dose level	Nab-paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
Reduced dose level 1	100	800
Reduced dose level 2	75	600
Additional dose reduction required	Discontinue	Discontinue

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable; this is an open-label FIH dose escalation and dose expansion trial with no comparator group. Treatment allocation will not be concealed throughout the trial. Dosing during dose escalation is controlled with BLRM modeling.

4.1.5.2 Emergency unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

All study treatments (BI 765883 and for combination cohorts additionally nab-paclitaxel/gemcitabine) will be provided by Boehringer Ingelheim or a designated CRO. The trial treatments will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites. For details of packaging and the description of the label, refer to the ISF.

The labels for all three trial drugs will be prepared according to EU Regulation No. 536/2014, Annex 6, Section D.8, omitting certain particulars with the following justifications:

- The investigator name was omitted from the label due to the IRT System.
- The visit number is not relevant for the label because the product will remain at the clinical site.
- The "keep out of reach of children" statement was omitted from the label because the product will remain at the clinical site.

Should local regulations outside the EU require these particulars, they will be added to the country-specific label text.

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

4.1.7 Storage conditions

Drug supplies must be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label.

A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the CRA (as provided in the list of contacts), must be contacted immediately.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB/IEC
- 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 by the investigator
- Availability of the proof of a medical license for the Principal Investigator
- Availability of FDA Form 1572 (for USA)

Investigational drugs are not allowed to be used outside the context of this protocol and 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, inventory at the site, use by each trial patient, and the return to the sponsor or warehouse/drug distribution center or alternative disposal of unused products in alignment with the sponsor, if

applicable. If applicable, the sponsor or warehouse/drug distribution center 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 IMP and trial patients. The investigator or designee will maintain records that adequately document that trial patients were provided the doses specified by this clinical trial protocol and reconcile all IMPs received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator or designee must verify that all unused or partially used IMP supplies have been returned and that no remaining IMP supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

4.2.1.1 Auxiliary medicinal products

Not applicable.

4.2.1.2 Emergency procedures

There are no special emergency procedures to be followed.

Rescue medications to reverse the actions of BI 765883 or gemcitabine and nab-paclitaxel are not available. Potential adverse events should be treated symptomatically with concomitant medications to provide adequate supportive care as clinically necessary. Section 4.2.3 provides guidance for management of adverse events.

Radiotherapy for local symptom control of non-target lesions may be allowed during the study treatment period if agreed between the investigator and Sponsor.

4.2.1.3 Premedication

No routine premedication will be required for BI 765883 IV infusions. Since premedication is required for gemcitabine and nab-paclitaxel, this will be administered prior to BI 765883 IV infusion (see Section 4.1.4.2 for the order of administration). See Section 4.2.3.1 for premedication requirements for all subsequent treatment infusions of BI 765883 after symptoms of an IRR ≥ grade 2 occur.

Premedication for combination therapy gemcitabine and nab-paclitaxel must be given in accordance with the local approved label.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The following recommendations are provided for medications or therapies during the treatment period:

- BI 765883 is a therapeutic protein and its clearance is through protein catabolism. BI 765883 is not an immune modulator and is not expected to impact expression and production of cytochrome P450 enzyme or certain drug transporters that may affect indirectly the exposure of co-administered small molecule drugs. Therefore, no drug-drug interaction is expected for BI 765883.
- Paclitaxel is catalyzed, in part, by CYP2C8 and CYP3A4. Therefore, CYP2C8 or CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) should be avoided because efficacy may be compromised because of lower paclitaxel exposures. Caution should be exercised when administering paclitaxel concomitantly with CYP2C8 or CYP3A4 inhibitors (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure.
- No drug-drug interactions (DDI) are known for gemcitabine (no DDI studies have been performed).

Please refer to the current SmPC for gemcitabine and nab-paclitaxel for further information.

Anti-cancer treatment
No experimental or approved anti-cancer treatment (other than gemcitabine and nab-paclitaxel for combination cohorts) including chemotherapy, targeted therapy, immunotherapy, hormone therapy (except as stated below), or radiotherapy is allowed throughout the study treatment period. Radiotherapy for local symptom control of non-target lesions may be allowed if agreed between the investigator and Sponsor.

Anticoagulants
Therapy with factor Xa inhibitors, direct thrombin inhibitors, and warfarin is allowed. Patients receiving warfarin must have their international normalized ratio (INR) values closely monitored according to institutional guidelines.

The use of heparin (including flushing and locking of intravenous catheters) or low molecular weight heparin (LMWH) is permitted during study treatment. However, BI 765883 and heparin should not be mixed or infused through the same IV line.

Hematopoietic growth factors
Hematopoietic growth factor agents are not allowed for use as primary prevention during the first two 14-day cycles. Thereafter, hematopoietic growth factor agents may be used according to institutional standard.

Erythropoietic therapy is allowed when used in accordance with the American Society of Clinical Oncology/American Society of Hematology or the NCCN guidelines. In Japan, erythropoietic therapy is not approved for anemia caused by cancer chemotherapies.

COVID-19 vaccination and other preventive measures
The decision on COVID-19 vaccination of a BI study patient must be taken based on an individual benefit-risk assessment by the investigator after thorough discussion with the patient. This assessment should consider the approved labels of the respective vaccines as well as the provisions given in the protocol, including the time point when the vaccination should be given or a potential delay of the vaccination or of the study treatment.

The package insert for approved COVID-19 vaccinations should be carefully reviewed for local guidance considering acute moderate/severe febrile illness, and the risk of an anaphylactic reaction to the vaccine. Furthermore, the diminished response to the vaccine needs to be considered for immunocompromised conditions which may be observed in BI 765883 treated patients.

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

4.2.2.2 Restrictions on diet and lifestyle

There are no restrictions regarding diet and lifestyle.

For PK assessments, no restrictions regarding food or water intake are required.

4.2.2.3 Contraception requirements

Women of childbearing potential (WOCBP; trial patient or female partner of trial patient):
A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Tubal ligation is not a method of permanent sterilization. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Throughout the trial and for a period of at least 6 months after the last dose of study treatment, WOCBP (as defined above; trial patient or female partner of trial patient) and men able to father a child (non-vasectomized men) must use highly effective methods of birth

control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided below:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral [approved in Japan], intravaginal [unapproved in Japan], transdermal [unapproved in Japan]).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable) [unapproved in Japan].
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomy with documented absence of sperm
- Consistent and correct use of condoms combined with an additional highly effective female method of contraception (e.g., hormonal contraception, IUD, or IUS)

If not using one of the methods of highly effective birth control listed above, then trial patients must abstain from male-female sex. Complete abstinence (refraining from heterosexual intercourse) is considered a highly effective method of contraception only if it is in line with the preferred and usual lifestyle of the trial patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to trial IMP, and withdrawal are not acceptable methods of contraception.

Breast feeding should be interrupted from the start of study treatment through 6 months after the last study treatment.

4.2.3 Dose modification and management of adverse events

4.2.3.1 Management of infusion-related reactions

Infusion-related reactions (IRRs) involve the immune system; however, they can have different mechanisms. Some are allergic in nature and are usually mediated by immunoglobulin E while others are not classical allergic reactions (so-called anaphylactoid reactions e.g. caused by cytokine release). Although infusion reactions can be allergic or non-allergic, clinical symptoms are difficult to distinguish and require rapid assessment and immediate management to avoid severe adverse events, including fatality.

If an infusion-related reaction of ≥ CTCAE grade 3 occurs, trial treatment must be permanently discontinued.

If symptoms of an infusion-related reaction of CTCAE grade 2 occur that do not qualify as DLT, according to Table 10, the infusion should be temporarily stopped. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Upon recovery, the following guidance must be followed.

- If at least 50% of the planned dose of BI 765883 was administered, no further BI 765883 will be administered until the next scheduled dose.
- If less than 50% of the planned dose of BI 765883 was administered due to an IRR, a further dose of 50% of the intended total dose may be administered at the earliest on the following day and after recovery to baseline for at least 24 hours. The remaining solution from the original dose must be discarded, and a new kit must be dispensed to prepare the dose of 50% of the intended total dose. Administration may occur within up to 2 days after the original planned dose (Subsequent treatments [gemcitabine and nab-paclitaxel] should be also delayed so that the interval between BI 765883 dosing is 14 days). Refer to Table 16 for details regarding PK collection if the patient experiences an IRR.
- During the first re-exposure, patients must remain under observation for at least 6 hours post start of infusion. If required, patients may be hospitalized for a longer observation period at the investigator's discretion.
- Premedication must be used for all subsequent treatment infusions. The recommended premedication is:
  - Acetaminophen/paracetamol 650 mg - 1000 mg oral, or equivalent
  - Antihistamine oral or IV, equivalent to diphenhydramine 50 mg IV
  - Glucocorticoid IV, equivalent to prednisolone 50-100 mg
- The infusion rate for further treatment cycles may be adapted according to Investigator decision, but any adaption of the infusion rate must be agreed with the sponsor. Total storage time for ready-to-use solution at room temperature should not exceed 150 minutes between preparation and end of infusion time. See Section 4.1.4.

If infusion reactions and/or hypersensitivity reactions occur in a substantial proportion of treated patients without premedication, the DEC may decide that all future patients treated in the trial must receive premedication (as described above) prior to BI 765883 infusion; the dosage and schedule of premedication will be aligned and will take into account any local clinical standards. Such a decision will be communicated to all investigators in writing.

Premedications should be recorded in the eCRF.

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

Cytokine release syndrome (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 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 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.
Patients must remain under observation for potential signs and symptoms of CRS (e.g. hypotension, rash, tachypnea, hypoxia, tachycardia, fever, nausea, fatigue, headache, myalgias and malaise) for at least 6 hours following the end of infusion of BI 765883. If no signs or symptoms of CRS are observed during the first 3 administrations, the duration of observation may be reduced to 4 hours for subsequent administrations. After 6 administrations, in the absence of potential signs and symptoms of CRS, the observation period can be reduced to 2 hours at Investigator's discretion. During all post infusion observation periods, body temperature, pulse rate and blood pressure must be monitored as described in Section 5.2.2.

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 standards [R19-0311, R20-2020], best medical judgement, and local guidelines. Supportive therapy including antipyretics, intravenous fluids, and low dose vasopressors may be used. In patients who do not respond to these treatments, corticosteroids and/or interleukin 6 receptor antagonists [R15-0031, R18-1685 , R18-1686] may be required and patients should be monitored closely, preferably in an intensive care unit.

In the event of CTCAE ≥ grade 3 CRS, study treatment must be permanently discontinued. In the event of CTCAE grade 2 CRS, the guidance for handling a CTCAE grade 2 IRR must be followed (Section 4.2.3.1).

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.

4.2.3.3 Management of diarrhea, nausea, and vomiting

The occurrence, severity and duration of diarrhea, vomiting and nausea, and the outcomes of these events must be documented in detail in the eCRF. Further tests and examinations (e.g. colonoscopy, gastroscopy) should be performed according to the severity of the symptoms in order to document and obtain more information about the extent of possible

injury due to BI 765883. If severe injury to gastrointestinal tissues is excluded, these events could be managed symptomatically according to Table 6 and Table 7.

Table 6 Management of diarrhea

CTCAE grade	**Action for anti-diarrheal treatment**
Grade 1 and grade 2 < 7 days	Anti-diarrheal treatment according to the local standard e.g. loperamide p.r.n. and hydration
Grade 2 > 7 days despite optimal medical management	Anti-diarrheal treatment according to the local standard e.g. loperamide p.r.n, and hydration, interrupt BI 765883 treatment and once diarrhea resolves to grade ≤ 1 resume at the next lower dose level according to Section 4.1.4.4
Grade ≥3	Anti-diarrheal treatment according to the local standard e.g. loperamide p.r.n, and hydration, interrupt BI 765883 treatment and once diarrhea resolves to grade ≤ 1 resume at the next lower dose level according to Section 4.1.4.4

Table 7 Management of nausea and vomiting

CTCAE grade	**Action for anti-emetic treatment**
Nausea grade 1	Anti-emetic treatment may be considered according to the local standard e.g. metoclopramide p.r.n.
Nausea grade 2 and/or Vomiting grade 1	Start anti-emetic treatment according to local standard of care e.g. metoclopramide or 5-HT_3 receptor antagonist. If ineffective, patients should be treated according to treatment of vomiting ≥2 or nausea CTCAE Grade ≥ 3 as shown below.
Vomiting grade ≥2 and/or Nausea grade ≥ 3	Anti-emetic treatment according to local standard of care e.g.: with 5-HT_3 receptor antagonist and/or corticosteroid, interrupt BI 765883 treatment and once vomiting/nausea resolves to grade ≤ 1, resume at the next lower dose level according to Section 4.1.4.4

4.2.3.4 Tumor lysis syndrome

All patients have to be assessed for clinical or laboratory suspicion of tumor lysis syndrome (TLS). To prevent tumor lysis syndrome, patients should remain appropriately hydrated throughout the administration period. In case TLS is observed, patients should be managed according to local or available guidelines [R10-4517].

4.2.3.5 Neurological adverse events

A 4-week GLP toxicology study in monkeys showed no neurological effects [n00261479]. While expression of both TRAILR2 and CDH3 has been reported in the human brain and

nerves, particularly in certain pathological conditions [R18-2769], there have been no neurological findings described in human studies with other conventional TRAILR2 agonists up to the highest tested dose levels [R16-1793, R16-1794, R16-4524, R17-2590, R17-2600, R17-2601, R17-2606]. Patients in this trial shall be monitored for possible neurological toxicity. Patients who develop worsening or new neurological signs/symptoms CTCAE grade ≥ 2 should undergo full neurological investigation including a brain MRI. Treatment with BI 765883 must be interrupted or permanently discontinued unless alternative etiology is documented e.g. new metastases in the CNS, metabolic disturbances, sepsis, infection, hypoxia, tumor lysis syndrome, trauma, adverse effect of concomitant medications. Additional workup may be performed if clinically indicated, e.g. lumbar puncture.

4.2.3.6 Renal adverse events

In a 4-week GLP toxicology study in monkeys no renal injury was reported at the highest tested dose of 100 mg/kg. Patients will be followed periodically for kidney function by measurement of serum creatinine and a qualitative urine protein.

Patients with a 2+ or greater protein reading on a urine dipstick should be followed by a 24-hour urine collection for a quantitative protein.

Patients with proteinuria ≥ CTCAE grade 3 (>3.5 g/24 hours) should interrupt BI 765883. Continuation of treatment with BI 765883 at a reduced dose may be considered if proteinuria recovers to ≤ grade 1 within 3 weeks.

4.2.3.7 Pancreatic adverse events

Increase in pancreatic lipase/amylase has been observed with TRAILR2 antibodies. While most of these increases were mild in intensity, imaging must be performed in case of amylase or lipase elevation grade ≥ 3, in order to rule out pancreatitis.

4.2.3.8 Liver injury

The liver is reported to be the most sensitive non-cancerous tissue to TRAILR2-mediated apoptosis [R16-1793, R16-1795]. Human hepatocytes do not express CDH3 and therefore BI 765883-mediated clustering of TRAILR2 in normal liver is not expected to occur. However, possible liver damage induced by BI 765883 cannot be excluded, particularly in combination with chemotherapy and/or in patients with liver metastases. Patients should be monitored closely for AST, ALT, and bilirubin increases and clinical symptoms of liver injury, which could potentially require transient or permanent discontinuation of BI 765883.

Trial patients should be monitored for possible hepatic injury. Management and criteria for liver injury, including potential DILI are described in Section 5.2.6.1.4.

4.2.3.9 General management of toxicities

Toxicities not covered within Sections 4.2.3.1 to 4.2.3.8 (above) will be handled according to the instructions in Table 8. For the definition of a DLT, refer to Section 5.2.7.

Table 8 General management of toxicities

Event	First occurrence	Second occurrence	Third occurrence
Nonhematological toxicity grade fulfilling the criteria for DLT (see Section 5.2.7)	Hold BI 765883 treatment until recovery to grade ≤ 1 or baseline; start supportive measures according to standards of the institution Patient may be eligible to continue BI 765883 treatment at a lower dose - see Section 4.1.4.4	Hold BI 765883 treatment until recovery to grade ≤ 1 or baseline; start supportive measures according to standards of the institution A second dose reduction is permitted. Patient may be eligible to continue BI 765883 treatment at a lower dose - see Section 4.1.4.4	Permanently discontinue treatment Start supportive measures according to standards of the institution
Hematological toxicity fulfilling criteria for DLT (see Section 5.2.7)	Hold BI 765883 treatment until recovery to grade ≤ 1 or baseline; start supportive measures according to standards of the institution (e.g. G-CSF, antibiotics, platelet transfusion) Perform complete blood count at least twice per week until improvement to a lower grade Patient may be eligible to continue BI 765883 treatment at a lower dose - see Section 4.1.4.4	Hold BI 765883 treatment until recovery to grade ≤ 1 or baseline; start supportive measures according to standards of the institution (e.g. G-CSF, antibiotics, platelet transfusion) Perform complete blood count at least twice per week until improvement to a lower grade A second dose reduction is permitted. Patient may be eligible to continue BI 765883 treatment at a lower dose - see Section 4.1.4.4	Permanently discontinue treatment Start supportive measures according to standards of the institution

4.3 TREATMENT COMPLIANCE

BI 765883, gemcitabine and nab-paclitaxel will be administered as IV infusions at the clinical site under the supervision of trained site personnel. Therefore, actual dosing is expected to follow the protocol. The doses 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 and progression will be evaluated by investigator review in this study according to Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1) [R09-0262].

Tumor assessment will be performed per institutional practice. Only the overall response and disease progression will be collected in the eCRF.

Tumor assessments should include computed tomography (CT) scans or MRI of chest, abdomen, and pelvis. If clinically indicated, imaging of any other known or suspected sites of disease (e.g. brain, bone) should be performed.

Scans will be collected and stored centrally.

5.2 ASSESSMENT OF SAFETY

Safety will mainly be evaluated by severity and incidence of AEs, graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [R18-1357]. Criteria for DLT are described in Section 5.2.7.

5.2.1 Physical examination and body weight

A complete physical examination will be performed as per institutional practice. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

Measurement of height (cm) and body weight (kg) and the evaluation of ECOG performance score will be performed at the time points specified in the FLOW CHART.

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

Body weight measurements should be done on the same scale for each patient. In order to get comparable body weight values, body weight measurements should be performed per the following:

- shoes and coat/jackets should be taken off
- pockets should be emptied of heavy objects (i.e. keys, coins, etc.)

5.2.2 Vital signs

Vital signs will be evaluated as per institutional practice at the required time points prior to blood sampling. This includes systolic and diastolic blood pressure, body temperature, and pulse rate (electronically or by palpation count for 1 minute) in a seated position after

2 minutes of rest. The results must be included in the source documents available at the site. Patients will remain under surveillance to monitor potential occurrences of IRRs or CRS for at least 6 h after the end of infusion for the administration of BI 765883. Vital signs should be evaluated pre-dose, post-dose, and then every 2 h during the BI 765883 post-infusion observation period. In the absence of IRR/CRS this can be reduced in subsequent administrations (see Section 4.2.3.1).

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 9 and will be performed by a local laboratory as per institutional practice. The site will file the respective reference ranges in the ISF.

Patients do not have to be fasted for the blood sampling for safety laboratory tests. Instructions regarding sample collection, sample handling/processing, and sample shipping are provided in the laboratory manual in the ISF.

It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6).

In case a treatment course is delayed due to an adverse event (AE), the patient should visit the site at least once a week for assessment of safety laboratory and adverse events. More frequent visits may be appropriate as assessed by the investigator.

Additional parameters may be measured if they are part of the standard panel of the institution laboratory. 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 AE.

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 eDC system). The amount of blood taken from the trial patient concerned will be increased due to this additional sampling. The site will transfer the results of the analysis to the Sponsor or delegate.

Table 9 Safety laboratory tests

Functional laboratory group	Test name
Hematology	Hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count including differential (absolute), RBC indices, reticulocytes, platelet count
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin time (PT) or, if applicable, international normalised ratio (INR)
Biochemistry	Glucose, blood urea nitrogen (BUN) or urea, creatinine, eGFR (calculated using applicable CKD-EPI formula* [R12-1392, R22-1535, R22-1536] inorganic phosphate, sodium, potassium, calcium, total protein, albumin, uric acid, lipase, amylase, total bilirubin (indirect and direct in case of elevated total or if required per local guidelines), C-reactive protein (CRP) Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), lactate dehydrogenase (LDH) Note: Creatinine can be assessed by any of these methods: • CREE (enzymatic serum creatinine assay), • CREJIDMS (IDMS standardized Jaffe), or • CREJ (non-IDMS standardized Jaffe). * The eGFR will be derived from the serum creatinine value, age, sex, and race using the CKD-EPI equation. The race must be collected because the CKD-EPI equation uses race as an adjustment factor and therefore it is required for accurate estimation.
Pregnancy testing	A human chorionic gonadotropin (HCG) urine pregnancy test needs to be obtained at the time points indicated in the FLOW CHART in patients of childbearing potential; a HCG blood test may replace the urine test. A serum pregnancy test should be performed at screening if urine test is positive.
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analyzed by routine analysis and reported as semiquantitative measurements. In case of pathological findings, further evaluation should be performed, and results documented.[2]
Infectious disease[1]	HBV-DNA (quantitative) Hepatitis C: HCV-RNA (quantitative) HIV1 and HIV2 antibody (qualitative) Results for hepatitis virus infection obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date.

1 At Screening visit, patients are to be tested for hepatitis B and C virus infection. HIV testing is only required at screening for patients with unknown HIV status. See Section 3.3.3 for exclusion criteria for patients with HIV, HBV, or HCV.

2 In case of a 2+ or greater urine protein by urine dipstick is found, a 24-hour urine should be collected for a quantitative protein.

5.2.4 Electrocardiogram

The 12-lead ECG must be administered at time points shown in the FLOW CHART by a qualified technologist, and results will be recorded. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. 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 ECG with findings should be documented in the patient's medical record.

At the screening visit only, LVEF (left ventricular ejection fraction), measured by MUGA (multigated acquisition scan) or echocardiography (Echo-CG) can be used to access eligibility instead of a 12-lead ECG.

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

Not applicable.

5.2.6 Assessment of adverse events

Data and information necessary for the thorough assessment of AEs, SAEs, and AESIs will be reported to the sponsor via eCRF. This may include specific data and information not prospectively specified in this protocol.

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 trial 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 unfavorable 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 on the appropriate eCRF(s) and Boehringer Ingelheim SAE form:

- Worsening of the underlying disease if certain conditions are met (see Section 5.2.6.2.4)
- Worsening of pre-existing conditions other than the underlying disease
- Changes in vital signs, ECG, physical examination findings, and/or laboratory test results, if 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 as medical history in the eCRF only.

5.2.6.1.2 Serious adverse event

An SAE is defined as any AE that 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 hospitalization or prolongation of existing hospitalization
- 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 jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse

A suspected unexpected serious adverse reaction (SUSAR) is an untoward and unintended response to a study drug. A SUSAR should be considered as unexpected if the nature, seriousness, severity, or outcome of the reaction is not consistent with the reference safety information of the investigational drug (e.g. the investigator's brochure, or the corresponding defined local label such as the summary of product characteristics).

For Japan only: An event that possibly leads to disability will be handled as “deemed serious for any other reason” and, therefore, reported as an SAE.

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. 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 IMP 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; see Section 5.2.6.2.2.

The following are considered as AESIs:

- Drug-induced liver injury (DILI)
- Infusion-related reactions
- Dose-limiting toxicities (DLTs)

Potential severe DILI
A potential severe DILI that requires follow-up is defined by any of the following alerts (alterations) of hepatic laboratory parameters that occur after the first dose of IMP:

For patients with normal ALT and AST levels at baseline:

1. AST or ALT elevation ≥3 × ULN combined with an elevation of total bilirubin ≥2 × ULN measured in the same sample, or in samples drawn within 30 days of each other, OR
2. AST or ALT elevation ≥10 × ULN

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

1. 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
2. AST or ALT elevation ≥5 fold the baseline value

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

1. 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
2. AST or ALT elevation ≥3 fold the baseline value

These laboratory findings constitute a hepatic injury alert, and patients showing any of these laboratory abnormalities need to be followed up according to the “DILI Checklist” provided in the eDC.

In case of clinical signs or symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analyzed, 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.

For further details, see Figure 2, below.

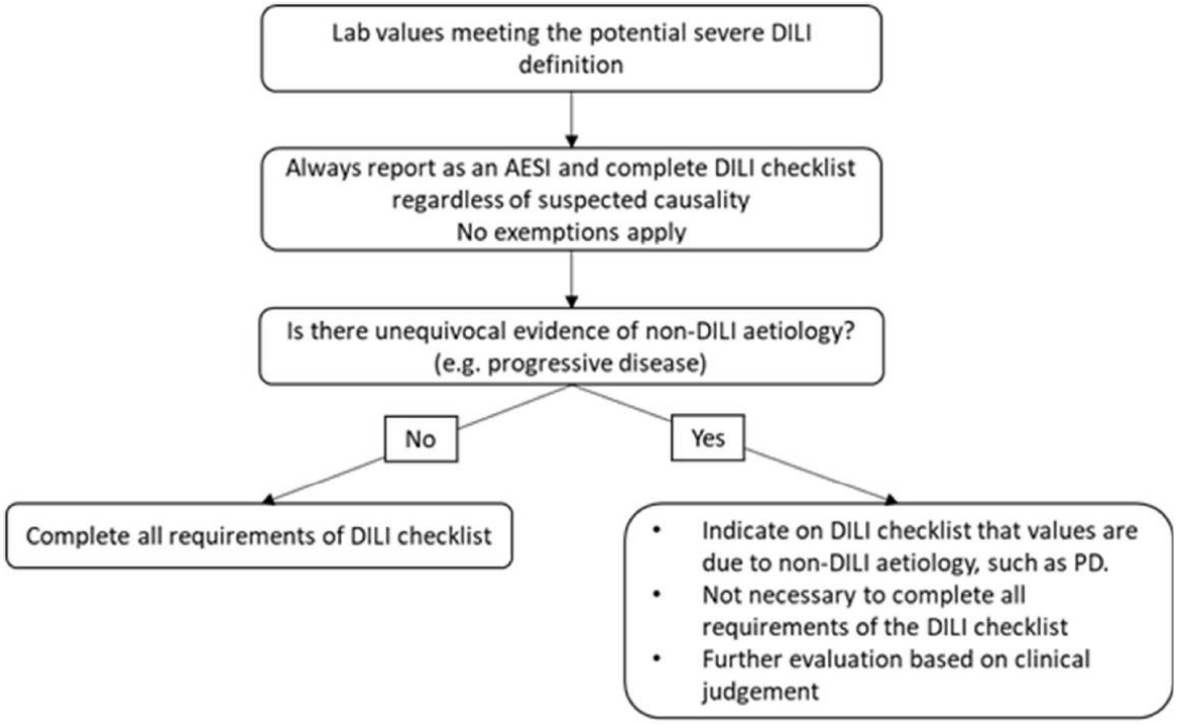


Figure 2 Potential severe DILI reporting

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
- Cytokine-release syndrome (CRS)
- Any other event which the investigator considers as a potential infusion-related reaction.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of AEs should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the AE and trial medication 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 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 trial drug exposure
- Evidence that the event is reproducible when the trial drug is reintroduced
- No medically sound alternative etiologies 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 no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of trial drug exposure is evident (e.g. pretreatment cases, diagnosis of cancer or chronic disease within days/weeks of trial drug administration; an allergic reaction weeks after discontinuation of the IMP concerned)
- Continuation of the event despite the withdrawal of the trial drug, 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 trial drug concerned
- Disappearance of the event even though trial IMP treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

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

The following must be collected and documented:

- From signing informed consent onwards until the individual patient's end of trial (usually the End of Study Visit; please see Section 6.2.3):
  all AEs (serious and non-serious) and all AESIs
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer of new histology, IMP-related SAEs, and IMP-related AESIs of which the investigator may become aware by any means of communication, e.g. phone call

The rules for AE 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 that are relevant for the reported SAE or AESI on the AE eCRF and on the SAE eCRF to the sponsor's unique entry point immediately (within 24 hours of becoming aware of the event). The country-specific process will be described in the ISF. On specific occasions, the investigator could inform the sponsor upfront via telephone in addition.

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

Should the EDC system not be available for more than 24 hours, reporting must occur via the Boehringer Ingelheim paper SAE forms.

5.2.6.2.3 Pregnancy

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

Similarly, potential IMP exposure during pregnancy must be reported if a partner of a male trial patient 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 IMP 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 (Parts A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for 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 AE/SAE reporting

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

- Non-serious, asymptomatic disease progression which is unrelated to trial medication is exempted from AE reporting. In this case, disease progression will only be recorded on the response assessment page of the CRF.
- In other cases of disease progression, the signs and symptoms (and not the term ‘disease progression’ itself) will be reported on the AE CRF and reported via the SAE form if applicable.
- If signs and symptoms are attributable to a diagnosis (other than ‘disease progression’), reporting the diagnostic term is preferable e.g. pulmonary embolism rather than dyspnea, intestinal obstruction rather than abdominal pain.
- Lab values meeting the potential severe DILI definition in Section 5.2.6.1.4 must always be reported as AESI, even if the most likely cause is disease progression. No exemption to AE reporting applies.

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

5.2.7 Dose-limiting toxicity (DLT)

Any of the following AEs will be classified as DLTs, unless unequivocally due to underlying malignancy or an extraneous cause (Table 10).

Table 10 Dose-limiting toxicities

Category	Criteria and CTCAE grade defining a DLT
HEMATOLOGIC	• Grade 4 neutropenia or lymphopenia lasting >7 days • Grade 4 anemia or thrombocytopenia • Grade ≥3 neutropenia with documented infection. • Grade ≥3 febrile neutropenia defined as ANC <1000/mm^3 and a single temperature of ≥38.3ºC (101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than 1 hour; or where there are life-threatening consequences or urgent intervention indicated • Grade 3 thrombocytopenia <50 000/mL (<50 x10^9/L, <50 x10^3/µL) associated with bleeding excluding grade 1 epistaxis • Grade 4 thrombocytopenia (platelet count <25 000/mL)
NON-HEMATOLOGIC LABORATORY	• Any grade 3 or 4 non-hematologic laboratory value unless being grade 3 asymptomatic laboratory abnormalities that resolve within ≤7 days. • A DILI is always considered a DLT (for DILI criteria, see Section 5.2.6.1.4)
NON-LABORATORY	• Any grade 4 non laboratory toxicity possibly related to study therapy. • Any grade 3 non laboratory toxicities possibly related to study therapy, except for the following adverse events: 1. Fatigue/asthenia present at baseline that worsens on study and lasts less than 7 days 2. Grade 3 vomiting/nausea or diarrhea which persists for less than 48 hours after start of adequate treatment • Any other toxicity considered significant enough to be qualified as DLT in the opinion of the investigator, and confirmed by the DEC, will be reported as a DLT
AEs leading to dose reductions or treatment discontinuations or delays	• Any toxicity of grade 2 or higher leading to dose reduction • Any treatment emergent AE that leads to either treatment discontinuation or treatment delay for more than 14 days during the DLT observation period
DEATHS	• Any grade 5 toxicity not clearly due to the underlying disease or extraneous causes

Dose-limiting toxicities (DLTs) will be recorded throughout the trial. Any DLT must be reported as an AESI to the Sponsor's Pharmacovigilance Department by the Investigator or designee within 24 hours of first knowledge regardless of the relationship to the study drug and regardless of seriousness (serious and non-serious). All DLTs will be agreed upon by the DEC after review of the data from each cohort. Only DLTs occurring in the first 2 cycles are necessary for dose-escalation decisions made by the DEC. DLTs observed during the MTD evaluation period will be considered for MTD determination. However, all AEs and SAEs meeting criteria of DLT observed in all treatment cycles will be considered for determining a dose range for future development in Phase II.

Replacement of patients for DLT evaluation during MTD evaluation period
For the definition of DLT, it is essential that patients are sufficiently treated according to supportive care standards described in Section 4.1.4.1. Patients with AEs that do not qualify as DLT, that have not been sufficiently exposed to trial medication, would not qualify for DLT evaluation and need to be replaced if this occurs in the first two cycles. Dose escalation will be determined based on all safety information of all treated patients including those who do not complete the first two cycles for reasons other than a DLT. Criteria for replacement of patients during the MTD evaluation period are described in Section 3.3.4.4.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Blood samples for PK and ADA analysis of BI 765883 will be collected at the time points specified in the FLOW CHART and Table 16.

5.3.1 Assessment of pharmacokinetics and immunogenicity

The evaluation of BI 765883 concentrations, PK parameters and immunogenicity will be performed according to the applicable BI procedures and will be specified in the TSAP.

Preliminary PK and immunogenicity analyses may be performed as necessary, e.g. for DEC decisions. In contrast to the final analysis, the preliminary analyses will be based on planned sampling times, and the outputs will not be validated. Minor discrepancies between preliminary and final results may therefore occur. Please refer to Section 7.2.8.

PK data may additionally be analyzed using a population PK approach. Modeling activities will be planned and documented separately according to internal and external guidelines and SOPs.

5.3.2 Methods of sample collection

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

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

For quantification of BI 765883 concentrations, blood will be taken from an antecubital or forearm vein from the contralateral arm of drug administration (sample collection from arm that does not receive IMP) at the time points and time schedules specified in the PK Flow Chart (Table 16).

After completion of the trial, the samples may be used for further methodological investigations, e.g. for stability testing or further investigations to characterize ADA response or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte or ADA/nAbs will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations, but not later than 5 years following signature of the final Clinical Trial Report (CTR).

[redacted]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

If the data allow, the relationship between drug exposure (e.g. AUC or C_{avg}) and clinical anti-tumor activity or efficacy data, as well as safety and tolerability endpoints, are planned to be investigated. Population pharmacokinetics (PopPK) analyses, graphical explorations on exposure-response relationships, as well as exposure-response modeling, as applicable, are planned to be performed based on preliminary data from the ongoing study and updated as new data become available. If limited dose-response relationships are detected, further PK-PD evaluations or modeling activities might be omitted. Modeling activities will be planned and documented separately according to internal and external guidelines and SOPs.

[redacted]

5.4.1 Drug interaction biomarkers

Not applicable. Please refer to Section 1.2.

5.4.2 Handling of samples and biomarker data

Detailed instructions on sampling, preparation, processing, and shipment of the samples are provided in the laboratory manual. For sampling time points, see the FLOW CHART and/or Appendix 10.1. Sampling time points and periods may be adapted during the trial based on information obtained during trial conduct (e.g. as a result of preliminary PK/biomarker data), including addition or reduction of samples and visits, as long as the total blood volume taken from each patient at each visit does not exceed approximately 50 mL. Such changes would be implemented via non-substantial CTP Amendments.

This section refers to exploratory biomarkers and a brief description of the biomarker analyses to be performed is also provided below.

Samples can be analyzed in a staged approach, and decisions for further analysis may depend on the results of prior analyses. This may also imply that not all collected samples will be analyzed, especially in case of termination of the project/trial.

Should other biomarkers become relevant in the context of the trial and/or based on new information in the scientific literature or early trial analysis, these may also be explored from the available specimens.

The study samples will be discarded after completion of any investigations, but not later than 2 years after the final trial report has been signed. Any leftover samples or derived material

from pre-specified analyses (e.g. RNA, DNA, and blood) may be used for method development/validation but will be destroyed no later than 2 years after the final trial report has been signed. Exceptions are remainders of study samples for which a patient has voluntarily accepted a biobanking option and has provided a signed ICF (see Section 5.5).

Biomarker analyses will be performed by Boehringer Ingelheim or by a laboratory authorized by Boehringer Ingelheim.

Analytical results for the biomarker analyses will be described in an analytical report.

5.4.3 Tumor tissue samples

Provision of an archived tumor sample from a tissue core biopsy (e.g. paraffin-embedded formalin-fixed tissue blocks) that is at least two core needle biopsies (18 gauge or greater) is mandatory at screening for all patients. If an archival biopsy is not available, a fresh tumor biopsy should be obtained. Only non-significant risk procedures per the investigator's judgement will be used to obtain any biopsy specified in this study.

The archival tumor material will preferably be provided as an embedded block and less preferably as mounted tissue sections as detailed in the lab manual. The required number of tissue slides or tumor tissue volume will be specified in the Laboratory Manual.

Tumor tissues will be used for the retrospective determination of protein expression, including, but not limited to, CDH3, TRAILR2, and P16. Protein expression will be measured by an IHC assay using FFPE tumor material. If feasible, these data will be used for retrospective correlation with treatment response in Phase Ia and Phase Ib or clinical outcome and will help to determine possible patient selection criteria.

Tumor tissues will be used for the exploratory retrospective measurement of gene expression and determination of cancer-related mutations. The purpose of this analysis will be to study the biology of the tumors at baseline (prior to first treatment). If feasible, these data will be used for retrospective correlation with treatment response or clinical outcome in Phase Ia and Phase Ib.

5.4.4 Blood samples for the quantification of circulating tumor DNA (ctDNA)

Blood samples will be used for the determination of circulating tumor DNA (ctDNA) levels in patient's plasma at baseline and at several time points on treatment. Collection of ctDNA is mandatory. Genomic profiling of ctDNA in plasma is aimed at understanding the patient's tumor genomic composition, potential resistance mechanisms and exploratory monitoring of changes in ctDNA mutations comparing baseline and on-treatment samples. Genes to be analyzed within the gene panel include, but are not limited to, KRAS, TP53, and SMAD4.

5.5 BIOBANKING

Biobanking will be performed only in countries where allowed by local laws and regulations. Participation in biobanking is voluntary and not a prerequisite for participation in the trial.

Biobanking will occur only after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

The following biomarker samples specified in Section 5.4 (Assessment of biomarkers) will be banked:

- Remainders of (FFPE) tissues collected at screening or derivatives thereof (e.g. RNA, DNA)
- Remainders of plasma samples taken at any time point.

5.6 OTHER ASSESSMENTS

5.6.1 Patient-reported outcomes

Patient-reported outcomes (PRO) are considered important to prescribers, patients and health care decision-makers when evaluating the clinical utility of a medical intervention. The information collected using PRO instruments can lend supportive arguments to the clinical activity or tolerability of a therapy and describe the extent to which patients' physical, emotional and social well-being are affected by treatment.

Patient-reported symptom data will be measured with the Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [R18-2068]. The PRO-CTCAE system has been developed by the US National Cancer Institute to complement the CTCAE by providing patient-reported data on symptomatic toxicities experienced while undergoing cancer treatment. While the CTCAE asks the physician to report the severity of the symptom based on a 5-point grading system (mild, moderate, severe, life-threatening, death), the PRO-CTCAE asks the patients to rate between 1 and 3 symptom attributes, including presence, amount, frequency, severity and/or interference with daily life.

Questionnaires will be completed at the time points specified in the FLOW CHART. Paper questionnaires should be completed at the site by patients prior to seeing the clinician, prior to clinical assessment, prior to any treatment at the clinic, and before provision of any new information about their disease status so that the responses are not influenced (biased). The responses recorded on the questionnaires will not be recorded as adverse events. Adverse events are collected during protocol specified study visits with the clinician. The questionnaire generally takes about 10 minutes to complete. Patients will receive the questionnaire in their native language in countries where validated translations exist. The answered questionnaires will be entered into the CRF by the site personnel.

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]. 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.
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6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients must satisfy all inclusion and exclusion criteria prior to treatment administration (see Section 3.3). Details of any patient who is screened for the study but is found ineligible must be entered in an enrolment log (see ISF) and documented in the eCRF. All patients are to 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.

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 the 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.

If a patient is hospitalized for administrative reasons to allow study treatment and PK sampling this will not be considered an SAE, unless any other criteria for an SAE are fulfilled.

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

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

Refer to the FLOW CHART and Section 5 for details on the procedures performed at each visit.

6.2.1 Screening period

Following informed consent, the patient will undergo screening assessments as indicated in the FLOW CHART. The assessments required during the screening period do not need to be conducted on the same day but must be conducted within a time interval of 28 days prior to the Cycle 1 Day1.

Screening assessments may be repeated as long as they fall within the 28-day screening visit window. If more than one screening assessment is available, the latest assessment prior to the start of treatment must be used to assess eligibility.

A patient who has been declared as a "screening failure" may be re-screened once. In this situation, patients will be handled as new patients i.e. sign a new informed consent, allocate a new patient number, and undergo full screening assessments to assess eligibility. Tumor assessments performed prior to informed consent as part of routine clinical practice can be accepted if they meet the requirements of the protocol. For example, during the screening period, a tumor assessment does not need to be performed if there are valid results available from assessments which were performed within 28 days prior to start of treatment.

Demographics to be collected during the screening period
During the screening visit, demographics information will be collected. This includes:

- Age on the day of informed consent (in years).
- Sex (male, female in order to describe the subject`s sex at birth),
- Gender identity (male, female, other in order to describe how the subject self identifies regardless of their genotypic or phenotypic sex)
- For women: of childbearing potential yes/no in order to characterize the patient population and as a basis for contraception requirements.
- Ethnicity and race in order to sufficiently characterize the patient population and to support possible subgroup analyses unless not acceptable according to local regulations.

Baseline conditions
Baseline conditions and concomitant therapies present during screening will be recorded in the eCRF.

Medical history:
A general medical history and a detailed oncological disease history will be collected.

The oncological history to be reported on the eCRF will include:

- Date of first histological diagnosis
- The primary tumor site
- Staging and grading information at diagnosis and at screening
- The number and location of metastatic sites
- Previous treatment for the tumor, including any surgery, radiotherapy, and/or systemic therapy including start and stop dates and outcome (best OR and DOR)
- Any known genomic alterations such as but not limited to BRAF, KRAS, HER2, BRCA, and the immune markers status (i.e. microsatellite instability and/or DNA mismatch repair deficiency).
- The date of tumor progression after previous lines of treatment will be recorded if known, including start and end dates and outcome (best OR and DOR).

6.2.2 Treatment period(s)

If a patient is eligible for trial participation, the Cycle 1 Day 1 assessments will be performed as noted in the FLOW CHART. Safety laboratory assessments do not need to be repeated at the C1D1 visit if performed ≤ 72 hours prior to the first IMP administration; however, the results must be available before the start of the infusion in order to evaluate the eligibility of the patient to receive treatment.

Treatment cycles are 14 days in duration. Subsequent visits and assessments during the treatment period are performed as described in the FLOW CHART.

See Section 4.1.4.3 for criteria for receiving further treatment.

Patients may continue on treatment for unlimited cycles until criteria for stopping treatment are met (See Section 3.3.4.1).

PK, biomarkers, other specialty samples collected for reasons other than safety may be discontinued if the sponsor decides that sufficient information has been collected.

6.2.3 Follow-up period and trial completion

The post treatment period will consist of an end of treatment (EoT) visit, a 30-day safety follow-up visit, which is also the end of residual effect period (EoR), as well as follow-up visits for disease progression (PD) and overall survival (OS).

If needed, in the opinion of the investigator, additional visits may be scheduled after the EoT visit for continued safety monitoring.

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

6.2.3.1 End of treatment (EoT) visit

The EoT visit will be performed as soon as possible, but not later than 14 days after permanent discontinuation of trial medication for any reason, or e.g. when the investigator decided with the patient to permanently discontinue the trial medication or became aware that the trial medication had been terminated. The EoT assessments will be performed instead of the next planned visit as noted in the FLOW CHART.

6.2.3.2 End of Residual Effect Period (EoR)

The EoR visit (safety follow-up visit [FUP] #1) should occur no earlier than 30 days (+5 days) after the last dose of treatment in order to evaluate safety. Assessments will be performed as noted in the FLOW CHART.

6.2.3.3 Follow-up

The end of the trial is referred to as the end of the study (EoS) to avoid possible confusion with end of treatment (EoT). The EoS is defined as the date of the last visit of the last patient in the whole study, including the safety follow-up.

All patients will be followed-up for survival status at approximately every 3 months (±14 days) after the last dose of IMP until:

- Death
- Withdrawal of consent
- Lost to follow-up or
- Completion of the whole trial

In addition to follow-up for survival status, follow-up for disease progression via tumor assessments will continue for patients that discontinue early from the study for reasons other than progressive disease. This follow-up will continue until disease progression or the start of subsequent anti-cancer treatment.

The follow-up visits for survival status will be performed in person, by telephone or via written correspondence. If a patient cannot be contacted for survival status, information may also be obtained by other means in accordance with informed consent language and local regulations (e.g. contact with patients' health care providers, public sources, e.g. death registry, obituary listing, etc) when it is available and verifiable. The last follow-up visit will be considered the "end-of-trial" visit.

The following patient status information will be collected during the FUP time points for survival status:

- Date of contact
- Further anti-cancer treatment including surgery and radiotherapy: regimen and drug name, start and stop dates.
- All SAEs/AESIs considered to be unequivocally related to BI 765883 must be collected. For each reportable drug-related SAEs/AESIs, the investigator should provide the information with regard to concomitant medication and the medication administered to treat the adverse events on the appropriate CRF pages and the SAE form including trade name, indication and dates of administration
- Outcome event (e.g. death: record date of and reason for outcome event/death [if applicable])

6.2.3.4 Trial completion for an individual patient

A patient is considered to have completed the trial in case any of the following applies:

- Completion of planned follow-up period
- Lost to follow-up
- Refusal to be followed-up
- Death

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This trial will be conducted as an open-label study to determine the MTD of BI 765883 as monotherapy and MTD/RDE of BI 765883 in combination with gemcitabine and nab-paclitaxel. Additionally, the safety and efficacy of BI 765883 in monotherapy and in combination with gemcitabine and nab-paclitaxel will be evaluated.

The monotherapy and combination therapy dose-finding will be guided by a Bayesian 2-parameter logistic regression model with overdose control [R13-4806; R13-4803] independently.

In the combination therapy, the chemotherapy component dose level is fixed and only the BI 765883 doses will be escalated. There by, the Bayesian 2-parameter model, the prior derivation and the operating characteristics will be the same for both mono- and combination therapies.

The model is given as follows:

$$\text{logit}(\pi_d) = \log(\alpha) + \beta * \log(d/d^*),$$
where $\text{logit}(\pi) = \log(\pi/(1-\pi))$

π_d represents the probability of having a DLT in the MTD evaluation period at dose d, $d^* = 8$ mg/kg is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose d^*, and $\theta = (\log(\alpha), \log(\beta))$ with $\alpha, \beta > 0$ is the parameter vector of the model.

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

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

The BLRM recommends a dose for the next dose cohort with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the doses fulfilling EWOC criterion. Applying the EWOC criterion, it should be unlikely (<25% posterior probability) that the DLT rate at that dose will exceed 0.33. However, the maximum allowable dose increment for the subsequent cohort will be no more than 225% (0.4 mg/kg to 1.3 mg//kg).

The MTD will be considered reached if one of the following criteria is fulfilled:

the posterior probability of the true DLT rate in the target interval (0.16, 0.33) of the MTD is above 0.5
OR
at least 12 patients have been treated in Phase Ia, of which at least 6 at the MTD.

The DEC may recommend stopping the dose escalation phase after the criterion for MTD is fulfilled.

Since a Bayesian approach is applied, a prior distribution f(θ) for the unknown parameter vector θ needs to be specified. This prior distribution will be specified as a mixture of three multivariate normal distributions, i.e.:

$a(\theta) = a_1 f_1(\theta) + a_2 f_2(\theta) + a_3 f_3(\theta)$

with

a_i, i = 1, 2, 3 the prior mixture weights ($a_1 + a_2 + a_3 = 1$)

and

$f_i(\theta) = MVN(\mu_i, \Sigma_i)$

Where MVN is the multivariate normal distribution of the i-th component with mean vector μ_i and covariance matrix Σ_i, where

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

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

<u>Prior derivation for monotherapy and combination therapy:</u>

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 0.4 mg/kg, would equal 0.01, and the median DLT rate, at the anticipated MTD of 16 mg/kg, would equal 0.20. This yields $\mu_1 = (-1.39\text{-}0.08)$. The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11} = 1.0$, $\sigma_{1,22} = 1$ and $\rho_1 = 0$, respectively. The prior weight a_1 for the first component was chosen as 0.9.

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 0.4 mg/kg, would equal 0.10, and the median DLT at the anticipated MTD of 16 mg/kg would equal 0.60. These assumptions yield $\mu_2 = (0.41, -0.29)$. The standard deviations and correlations were set identical to the weakly informative prior, i.e. $\sigma_{2,11} = 2$, $\sigma_{2,22} = 1$ and $\rho_2 = 0$, respectively. The prior weight a_2 for the second component was chosen as 0.05.

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 0.4 mg/kg, would equal 0.01, and the median DLT at the anticipated MTD of 16 mg/kg would equal 0.1. These assumptions yield $\mu_3 = (-2.20,0.31)$, i.e. basically a flat curve. The standard deviations and correlations were set to $\sigma_{3,11} = 5$, $\sigma_{3,22} = 0.01$, therefore almost fixing the slope parameter to its mean. The correlation was set to 0, i.e. $\rho_3 = 0$. The prior weight a_3 for the third component was chosen as 0.05.

A summary of the prior distribution is provided in Table 11. Additionally, the prior probabilities of DLTs at different doses, as well as the corresponding probability of under-, targeted and over toxicity, are shown in Table 12. As can be seen from the table, the prior medians of the DLT probabilities are in-line with the prior medians derived from the weakly informative prior derivation, and the uncertainty around the medians is large, showing the low amount of information this prior provides. A detailed evaluation of the model using hypothetical data scenarios (separately for monotherapy and combination therapy) and operating characteristics is provided in Appendix 10.2.

Table 11 Summary of prior distribution

Prior component	Mixture weight	Mean vector	SD vector
1: Weakly informative.	0.900	(-1.39, -0.08)	(1.0, 1)
2: High toxicity	0.050	(0.41, -0.29)	(2, 1)
3: Low toxicity	0.050	(-2.20, 0.31)	(5, 0.01)

SD = standard deviation

Table 12 Prior probabilities of DLTs at selected doses

combination Dose (mg/kg + mg/m^2/ mg/m^2)	Monotherapy dose (mg/kg)	Probability of true DLT rate in			**Mean**	**SD**	Quantiles		
		[0-0.16)	**[0.16-0.33)**	**[0.33-1)**			**2.5%**	**50%**	**97.5%**
0.4 + 1000/125	0.4	0.933	0.038	0.029	0.048	0.118	0	0.009	0.369
1.3 + 1000/125	1.3	0.892	0.067	0.041	0.07	0.136	0	0.024	0.484
4.0 + 1000/125	4.0	0.796	0.134	0.07	0.114	0.159	0.001	0.061	0.635
8.0 + 1000/125	8.0	0.604	0.255	0.141	0.181	0.18	0.012	0.124	0.758
16.0 + 1000/125	16.0	0.348	0.28	0.372	0.321	0.261	0.02	0.24	0.969

DLT = dose-limiting toxicity; SD = standard deviation

7.1 NULL AND ALTERNATIVE HYPOTHESES

The statistical analyses in this trial are descriptive and exploratory. No confirmatory testing is performed and hence no null and alternative hypotheses are defined.

7.2 PLANNED ANALYSES

7.2.1 General considerations

No per protocol set will be used in the analysis. However, important protocol deviations (iPDs) will be summarized. Adherence to the protocol will be assessed by the trial team. iPDs categories will be specified in the iPD specification document. iPDs will be identified at trial oversight meetings and documented in the iPD log. The iPD categories will be updated as needed.

For determination of the MTD, only MTD evaluable patients with be considered. For analyses of secondary and further endpoints, all patients in the treated set (i.e. patients treated with at least one dose of trial medication) will be used if not specified differently. Any other analysis set will be defined in the TSAP.

Descriptive statistics of PK parameters will be calculated if N≥2.

7.2.2 Handling of intercurrent events

The expected intercurrent events of interest in this trial are:

- treatment discontinuation during the MTD evaluation period

- progressive disease during the MTD evaluation period
- death where the death event is not a DLT during the MTD evaluation period
- dose reduction during the MTD evaluation period
- any events that cause missed visits during the MTD evaluation period

The primary characterization will be based on the initial dose administered to the patient and the strategy for handling intercurrent events will be a combined composite and principal stratum approach. Table 13 provides an overview of the intercurrent events and the respective handling strategies for the primary analysis of the dose escalation part.

Table 13 Overview of intercurrent events and handling strategies for the primary analysis of dose escalation part

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
A dose administration of <70% of the full planned dose of any drug during the MTD evaluation period due to other reason than DLT or AE	Principal stratum
Dose reduction during the MTD evaluation period due to a DLT	Composite
Any events other than DLT that cause missed visits during the MTD evaluation period*	Principal stratum

* Patient is not observed for full MTD evaluation period.

A modified while-on-treatment strategy will be used to handle these intercurrent events for the primary analysis. This is the effect of treatment while patients take it, except for non-permanent treatment discontinuation (i.e. breaks from treatment) or insufficient extent of adherence (e.g. missing multiple doses of study medication). Disease relapse, progression, death, start of subsequent anti-cancer therapy, loss to follow-up, or withdrawal of consent will be handled using the while-on-treatment strategy as defined in ICH E9(R1). Permanent treatment discontinuation and breaks from treatment/insufficient extent of adherence will be handled using the treatment policy as defined in ICH E9(R1). Table 14 provides an overview of the intercurrent events and the respective handling strategies for the analysis of the primary endpoint remission rate.

Table 14 Overview of intercurrent events and handling strategies for the primary analysis in dose expansion part

Intercurrent events	Modified while on treatment
Treatment discontinuation	Treatment policy
Subsequent anti-cancer therapy before progression	While-on-treatment
Disease progression	While-on-treatment
Death	While-on-treatment
Lost to follow up	While-on-treatment
Withdrawal of consent	While-on-treatment
Extent of adherence	Treatment policy

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 endpoint analyses

7.2.3.1 Main analyses

Dose escalation (Phase Ia)

This trial will be performed open label.

The primary objective in Phase Ia is to determine the MTD and the recommended dose for expansion (RDE) of BI 765883 in combination with gemcitabine and nab-paclitaxel.

No formal statistical tests will be performed, and no hypotheses will be tested. A BLRM with overdose control will be used to guide dose escalation and determination of the MTD and/or RDE of BI 765883 alone and in combination with gemcitabine and nab-paclitaxel. For determination of the MTD, only MTD-evaluable patients will be considered. The set of evaluable patients for MTD is defined as the treated set population excluding patients that are non-evaluable for analysis of the MTD.

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

- Patients who withdraw consent or who are lost to follow-up or for any other reason other than DLT before completing the first 2 cycles of study treatment
- Patients who have received less than 70% of the planned BI 765883 doses during first 2 cycles of study treatment and do not experience a DLT

- Patients who miss 2 or more partial or complete visits during the first 2 cycles of study treatment, with missing PK and safety parameters needed to accurately assess DLT and MTD determination
- Patients found to be non-eligible after starting study treatment based on a case-by-case basis

Non-evaluable patients will be replaced.

In the case of concurrent monotherapy and combination therapy dose escalations, the dose escalations will be guided by a BLRM with overdose control modeling approach to independently model the escalations in both groups. Primary BLRM analyses will only include DLTs that occur within the MTD evaluation period.

The MTD is defined as the highest dose with less than 25% risk of the true DLT rate being equal or above 0.33 (EWOC criterion).

The Bayesian logistic regression model (BLRM) is formulated as follows:

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

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

The BLRM-recommended dose for the next dose cohort is the dose level with the highest posterior probability of the DLT rate falling in the target interval of [0.16, 0.33) among the doses fulfilling the EWOC principle. With the EWOC criterion, it should be unlikely (i.e. posterior probability <25%) that the DLT rate at the recommended dose will exceed 0.33. The maximum allowable dose increment for each escalation step shall not be more than 225%.

The MTD will be considered reached if one of the following criteria is fulfilled:

- the posterior probability of the true DLT rate in the target interval [0.16, 0.33) of the MTD is above 0.5
- OR at least 12 patients have been treated in Phase Ia, of which at least 6 at the MTD.

The DEC may recommend stopping the dose escalation phase after the criterion for MTD is fulfilled.

When the combination therapy MTD/RDE has been identified or accumulated safety data for more DLs, the DEC may decide which DL will be used for the recruitment of additional patients to backfill cohorts (to make a total of 10 patients for that DL) to confirm early

efficacy. When all patients have finished the observation period for OR, a minimum of 2 out of 10 patients (20%) with OR will be required as an interim efficacy criterion to continue in expansion part for that DL. Among any DL satisfying this condition of 2 OR/10 patients, the DEC will select one of these DLs for expansion by adding 18 more patients to make 28 RECIST-evaluable patients. A final efficacy 'go' decision will be made if a 25% confirmed OR rate is reached.

Dose expansion part:
After the first 6 patients have been treated for at least 2 cycles, the DEC will assess the overall safety profile and confirm the RDE of BI 765883 in combination with gemcitabine and nab-paclitaxel.

The primary endpoint in the dose-expansion part is objective response (OR) derived from the data of all cycles. The OR based on RECIST 1.1 criteria will be analyzed descriptively in terms of OR rate, defined as the proportion of patients with objective response (best overall response of confirmed CR or confirmed PR). Details will be specified in the trial statistical analysis plan (TSAP).

7.2.3.2 Sensitivity analyses

There is no pre-defined sensitivity analysis. More details on sensitivity analyses will be specified in the TSAP.

Additional sensitivity analysis may be considered; for example, adding safety data from patients in backfill cohorts to re-run the BLRM, to confirm whether the MTD/RDE can still be considered safe.

7.2.3.3 Subgroup analyses

Not applicable.

7.2.4 Secondary endpoint analyses

Secondary endpoints for Phase Ia and Phase Ib (dose escalation and dose expansion) will be analyzed descriptively. PK analysis will descriptive, and in accordance with relevant BI procedures.

If data allow, the PK parameters C_{max} and $AUC_{(0-t)}$, of BI 765883 will be assessed in terms of dose proportionality in each DL of Phase Ia (i.e. BI 765883 given as monotherapy or in combination with gemcitabine and nab-paclitaxel). Attainment of steady state will be analyzed by a repeated measures linear model for trough concentrations with dose as an additional covariate, if feasible. Details of these analyses will be further specified in the TSAP.

Secondary time-to-event endpoints will be analyzed by Kaplan-Meier estimates. Other secondary endpoints will be analyzed descriptively. Details of the secondary endpoint analyses will be specified in the TSAP.

7.2.6 Safety analyses

AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard Boehringer Ingelheim summary tables and listings will be produced. All AEs with an onset between start of treatment and end of the REP, a period of 30 (+5) days after the last dose of trial drug, will be assigned to the on-treatment period for evaluation.

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

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs, i.e. all AEs occurring between the start of treatment and the end of the REP. AEs that start before first IMP intake and deteriorate under treatment will also be considered ‘treatment-emergent’.

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

Laboratory data will be analyzed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarized. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of trial 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 with findings before the start of treatment.

7.2.7 Other Analyses

Not applicable.

7.2.8 Interim Analyses

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

For efficacy, after the dose escalation phase, the dose expansion phase might be terminated early due to futility if lack of efficacy signal (in terms of OR, PFS and PD-modulation) observed among evaluable patients. If any DLTs are observed in patients enrolled in dose expansion phase the BLRM will be run to confirm if the dose level still fulfills the overdose risk control.

No formal interim analysis is planned for PK and immunogenicity.

Preliminary, exploratory analyses of PK and if applicable of immunogenicity will be performed prior to database lock during study conduct based on all evaluable data at the time of the analyses. These may be used to support later dose escalations (higher doses) and e.g. in case the information is needed to inform other activities during the development of substance such as concomitant treatment restrictions in other trials. In contrast to the final calculations, the preliminary, exploratory analyses will be based on planned sampling times rather than on actual times. Therefore, minor deviations of preliminary and final results may occur. No formal preliminary PK and immunogenicity report will be written.

7.3 HANDLING OF MISSING DATA

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

Pharmacokinetic parameters
Handling of missing PK data will be performed according to the relevant BI internal procedure.

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

7.4 RANDOMIZATION

Dose escalation (Part A) - monotherapy and combination therapy
No randomization will be performed. Patients will be assigned to escalation arms as described in Section 3.1.

Dose expansion (Part B) – combination therapy
No randomization of patients will be performed. Patients will be assigned to combination therapy as described in Section 3.1.

7.5 DETERMINATION OF SAMPLE SIZE

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

For the dose escalation part, assuming 5 DLs of BI 765883 will be tested with 3-6 patients per dose level, this leads to a maximum of 30 evaluable patients that are planned to be enrolled in the monotherapy dose escalation cohorts. For combination therapy, a maximum of 30 evaluable patients are needed assuming 3-6 patients per dose level. For the backfill and dose expansion parts, assuming the DEC decides to recruit additional patients to 3 dose levels for early efficacy checking, and 1 DL satisfies the interim efficacy criterion, this leads to approximately 39 evaluable patients (7 evaluable patients for 3 dose levels, 18 evaluable patients for 1 dose level passed interim efficacy criterion) that are planned to be enrolled in the combination therapy backfill and dose expansion parts.

In case of patients being not evaluable for MTD or efficacy assessments per RECIST version 1.1, they may be replaced, therefore extra patients would be needed. In total, up to 99 evaluable patients may be enrolled in the study.

A justification of the sample size for the expansion part is based on assumed true OR rate. The probabilities of observing an OR rate of ≥25% based on various assumptions of the underlying true OR rate are summarized in Table 15. Assuming a true OR rate of 30% at a DL, a sample size of 28 patients (10 patients from previous dose escalation and backfill, 18 patients from expansion part) leads to a probability of 71% of observing an OR rate of ≥25% and a probability of 16% to stop for futility at inflection point 1 (IP1). With the same sample size, the probability of observing a false positive signal, i.e. to observe an OR rate of ≥25% in a dose level when the true underlying OR rate is 6% to 12%, is ≤2%. The choice of an OR rate of 25% as a benchmark was chosen to provide a clinically meaningful improvement in

OR rate, considering the SoC OR rate is approximately 8.5% to 13.3% [R23-3400; R23-3401] and pancreatic cancer experts estimate a current response rate less than 10% in their practice.

Table 15 Probability of observing ORR ≥25% under different assumptions

Assumed true OR rate for each dose level	Prob. (%) of observing an OR rate <25%	Prob. (%) of observing an OR rate ≥25%	Prob. (%) to stop for futility at IP1
Negative scenario:			
6%	100%	0%	90%
12%	98%	2%	66%
Intermediate scenario:			
20%	72%	28%	37%
25%	48%	52%	25%
Positive scenario:			
30%	29%	71%	16%
35%	15%	85%	9%

IP = inflection point; OR = objective response; prob. = probability

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 GCP, relevant Boehringer Ingelheim SOPs, EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997), and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP, or applicable regulations will be treated as 'protocol deviation'.

Data protection within the EU will be handled in accordance with the EU GDPR stipulated in Regulation (EU) 2016/679.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the treating physician of the trial 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 finalization of the clinical trial report.

The certificate of insurance cover is made available to the investigator and the trial 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 participation in the trial, written informed consent must be obtained from each patient according to ICH GCP and the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent form 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.

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

The trial patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the trial patient's own free will with the informed consent form after confirming that the trial patient understands the contents. The investigator or 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 be necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial patient protection and reliability of the results, as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative 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 designee, IRB/IEC, or regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

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

8.3.1 Source documents

A detailed description of the transmission of electronic data (i.e. data flow) is provided in the data management plan.

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 safety review (i.e. CT/MRI, ECG) may be collected. 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 been properly removed or redacted from all copies of the patient's source documents.

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

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

- Patient identification: 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 IMP
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory] and end date [if available])
- SAEs (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)
- Prior to allocation of a trial patient to a treatment in a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial patient meets all inclusion criteria and does not meet any exclusion criteria. The absence of

records (either medical records, verbal documented feedback of the patient, or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator/institution will allow site trial-related monitoring, audits, IRB/IEC review, and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes and 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 CRFs 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.

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 the contract or local requirements valid at the time of the end of the trial (whichever is longer).

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

Boehringer Ingelheim is responsible for fulfilling their legal and regulatory reporting obligation in accordance with regulatory requirements.

SAE/AESIs are processed in the global safety database and assessed for sponsor causal relationship, as well as the expectedness of the event according the reference safety information. Individual case safety reports are subsequently reported according to local regulations. SUSARs will be reported to the EMA via E2B transmission of individual case safety reports to the Eudrovigilance CT Module.

A suspected unexpected serious adverse reaction (SUSAR) is an untoward and unintended response to a study drug. A SUSAR should be considered as unexpected if the nature, seriousness, severity, or outcome of the reaction is not consistent with the reference safety information of the investigational drug (e.g. the investigator's brochure, or the corresponding defined local label such as the summary of product characteristics).

Exemptions from expedited reporting are described in Section 5.2.6.2.4.

8.5 STATEMENT OF CONFIDENTIALITY AND TRIAL PATIENT PRIVACY

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred
- The patient must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.
- The patient must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, appropriate IRB/IEC members, and inspectors from regulatory authorities
- The sponsor has implemented privacy and security controls designed to help protect patients' personal data, including information security controls, firewalls, incident detection, and secure transfer measures
- In the event of an accidental or unlawful destruction, loss, alteration, unauthorized disclosure, or access to personal data ("breach"), the sponsor has implemented procedures and measures to promptly address and mitigate any risk to the patient. In the event of a breach, the sponsor will notify the appropriate regulatory authorities and/or the patient(s) in accordance with applicable data protection law.
- The contract between sponsor and trial sites specifies the responsibilities of the parties related to data protection, including the handling of data security breaches and respective communication and cooperation of the parties
- Information technology systems used to collect, process, and store trial-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access
- A Data Protection Impact Assessment established that data protection and mitigation measures in place by the sponsor are suitable to limit residual risk to the levels of "negligible" or "limited".

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 must be in accordance with the separate biobanking informed consent

- The Boehringer Ingelheim internal facilities storing biological samples from clinical trial patients, as well as the external banking facility, are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, including 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 **first act of recruitment** represents the **start of the trial** and is defined as the date when the first trial patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last trial patient in the whole trial ("last patient completed") or when all patients have been discontinued from study treatment and have been followed up for overall survival for at least 12 weeks after treatment discontinuation.

The "**last patient last treatment"** (LPLT) date is defined as the date on which the last trial patient in the whole trial is administered the last dose of trial drug (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial IMP 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 sponsor will prepare a clinical trial report within 1 year from the end of trial.

The sponsor will notify the IEC/competent authority in each participating EU member state about all required trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all trial patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within

1 year from the end of a clinical trial as a whole, regardless of the country of the last trial patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim.

In EU/EAA countries, the trial is sponsored by [redacted]

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

Oncologists experienced in the treatment of patients with mPDAC and in conducting Phase I trials will be considered as principal investigators.

In Phase Ia, a DEC composed of participating investigators 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, next cohort size and RDE. Further details are contained in the DEC charter.

In Phase Ib, the DEC will continue to monitor emerging safety and efficacy data of the trial. Still, efficacy data for the confirmatory dose cohorts 1, 2, and 5 will be only reviewed at the timepoints for efficacy analyses as specified in this CTP.

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 Boehringer Ingelheim web portal, Clinergize, to access documents provided by the sponsor.

Boehringer Ingelheim 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, Clinical Research Associates (CRAs), and investigators of participating countries

In the participating countries, the trial will be performed by the respective local or regional Boehringer Ingelheim organization (Operative Unit [OPU]) in accordance with applicable regulations and Boehringer Ingelheim SOPs, or by a Contract Research Organization (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 Boehringer Ingelheim according to Boehringer Ingelheim SOPs.

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

Central and local laboratory services, a central imaging service, and an IRT vendor will be used in this trial. Details will be provided in the IRT manual and central laboratory manual, available in the ISF.

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10. APPENDICES

10.1 TIME SCHEDULE FOR PHARMACOKINETIC (PK), BIOMARKER, AND ANTI-DRUG ANTIBODY (ADA, nAb) BLOOD SAMPLING IN PHASE IA AND PHASE IB

Table 16 Time schedule for PK, biomarker, and ADA and nAb blood sampling in Phase IA and Phase IB

Cycle/Day (C)/(D)		Visit	Visit No.	Time relative to BI 765883 infusion	CRF Time /PTM (hours)	Time window[1]*	PK	ADA/ nAb	ctDNA
1	1	C1_D1	101	Before start of BI 765883 infusion[2]	-0:05	-1:00 h	X	X	X
				Start of infusion	0:00				
				Immediately after end of infusion	0:30 [3]	+5 min	X		
				5 hours after start of infusion	5:00 [3]	±1 h	X		
	2	C1_D2	102	24 hours after start of infusion	24:00	±1 h	X		
	3	C1_D3	103	48 hours after start of infusion	48:00	±1 h	X		
	8	C1_D8	108	168 hours after start of infusion	168:00	±24 h	X		X
2	1	C2_D1	201	Before start of infusion[2]	-0:05	-1:00 h	X	X	X
				Start of infusion	0:00				
				Immediately after end of infusion	0:30	+5 min	X		
3	1	C3_D1	301	Before start of infusion[2]	-0:05	-1:00 h	X	X	
				Start of infusion	0:00				
				Immediately after end of infusion	0:30	+5 min	X		
4	1	C4_D1	401	Before start of infusion[2]	-0:05	-1:00 h	X		
				Start of infusion	0:00				
				Immediately after end of infusion	0:30 [3]	+5 min	X		
				5 hours after start of infusion	5:00 [3]	± 1 h	X		
	2	C4_D2	402	24 hours after start of infusion	24:00	±1 h	X		
	3	C4_D3	403	48 hours after start of infusion	48:00	±1 h	X		
	8	C4_D8	408	168 hours after start of infusion	168:00	±24 h	X		
5	1	C5_D1	501	Before start of infusion[2]	-0:05	-1:00 h	X	X	X
				Start of infusion	0:00				
				Immediately after end of infusion	0:30	+5 min	X		
9, 13, 17, etc	1	C9_D1, etc	901, etc	Before start of infusion[2]	-0:05		X[4]	X[4]	
EoT		EoT	9960	At any time point during visit	N/A		X[5]	X[5]	X
FUP		EoR	9961	At any time point during visit	N/A		X	X	

ADA = anti-drug antibody; C = cycle; CRF = case report form; ctDNA = circulating tumor DNA; D = day; EoR = end of residual effect period; EoT = end of treatment; FUP = follow-up; nAb = neutralizing antibody; PK = pharmacokinetics; PTM = planned time; V = visit

PK samples should be drawn from the opposite arm to the one in which the infusion was administered.

* The timing of all samples should be as close as possible to the planned time. In case of a delay, samples should still be collected.

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

2 Pre-dose samples (PTM -0:05) to be drawn within 1 hour before BI 765883 infusion.

3 In the event that infusion duration exceeds 90 min, the subsequent actual time points for the 0:30 and 5:00 PTM PK blood collection should be adjusted accordingly.

4 PK and ADA/nAb samples to be drawn before BI 765883 infusion (PTM -0:05) on Day 1 in Cycles 1, 2, 3, 5, and every fourth cycle thereafter.

5 If the patient discontinues treatment, the pre-dose sampling scheduled for Day 1 of the next cycle needs to be performed at the EoT visit.

10.2 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

A BLRM with overdose control will be used to guide dose escalation in the monotherapy and combination therapy arms of the trial independently. The model is introduced in Section 7, which also specifies the priors for the model. After patients in each cohort have completed at least one cycle of treatment, the prior distribution will be updated through Gibbs sampling procedures with the accumulated DLT data from the MTD evaluation period. Posterior probabilities for the rate of DLTs will be summarized from the BLRM. Selection of the next dose in each arm will be based on these probabilities as well as on other safety and laboratory data.

The purpose of this statistical appendix is to present performance metrics (operating characteristics) that illustrate the precision of the design in estimating the MTD under various dose-toxicity relationships (Table 19) through computer simulation. These results are summarized in Table 20. For simplicity reasons, a cohort size of 3 patients who are all evaluable starting at 0.4 mg/kg BI 765883 (monotherapy), respectively at 0.4 mg/kg BI 765883 + 1000 mg/m^2 gemcitabine and 125 mg/m^2 nab-paclitaxel (combination therapy), is assumed for calculation of the operating characteristics. For simplicity, the monotherapy arm will be referred to as Arm A and the combination therapy arm as Arm B in the following tables throughout this section.

In addition, recommendations of the next dose level in monotherapy arm by the 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 17 with first cohort size of 2 patients with 0.4 mg/kg BI 765883 dose. Similarly, the hypothetical outcome scenarios (see Table 18) for combination therapy arm with first cohort size of 3 patients with 0.4 mg/kg BI 765883 + 1000 mg/m^2 gemcitabine and 125 mg/m^2 nab-paclitaxel dose. The recommended next dose is computed as defined in Section 7, i.e. as the dose with the highest probability of having a DLT rate in the target interval (0.16-0.33) among the 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. Additionally, the recommended next dose can at most be the next planned dose in the escalation scheme stated in Figure 1, even if the EWOC criterion would allow higher doses.

Hypothetical data scenarios – Monotherapy

Hypothetical data scenarios are shown in Table 17 for Arm A. These scenarios reflect potential on-trial data constellations and related escalation as allowed by the model and the escalation limit specified in Section 7. For each scenario and each arm, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target dose and over-dosing are shown.

For instance, Scenarios 1 and 2, illustrate different situations that could occur after the first cohort of 2 patients were treated at the starting dose 0.4 mg/kg in the monotherapy arm. In Scenario 1, it is assumed that none of the patients suffered DLT, which leads to the EWOC criterion allowing all doses up to 8 mg/kg for the next cohort. However, as per the maximum increment, the dose could at most be the next planned dose in the escalation scheme, so that the recommended next dose is 1.3 mg/kg. In contrast to this, if one of the patients at 0.4 mg/kg experienced a DLT (Scenario 2), the BLRM would allow a dose of 1.3 mg/kg for the next cohort.

Scenarios 3 and 4 illustrate different situations with the first cohort of 4 patients were treated at the starting dose 0.4 mg/kg in the monotherapy arm. In Scenario 3, it is assumed that one of the patients suffered DLT, which leads to the EWOC criterion allowing all doses up to 4 mg/kg for the next cohort. However, as per the maximum increment, the dose could at most be the next planned dose in the escalation scheme, so that the recommended next dose is 1.3 mg/kg. In contrast to this, if two of the patients at 0.4 mg/kg experienced a DLT (Scenario 4), the BLRM would not allow any dose and recommend stopping the trial. However, if 6 patients were treated at the starting dose 0.4 mg/kg and if two of the patients experienced a DLT (Scenario 5), the BLRM would allow a dose of 1.3 mg/kg for the next cohort.

Scenarios 6 through 10 illustrate varied situations with first cohort of 2 or 4 patients were treated at the starting dose 0.4 mg/kg and the second cohort of 3 patients were treated at the dose of 1.3 mg/kg in the monotherapy arm. In Scenario 6, it is assumed that none of the patients suffered DLT in both cohorts, which leads to the EWOC criterion allowing all doses up to 8 mg/kg for the next cohort. However, as per the maximum increment, the dose could at most be the next planned dose in the escalation scheme, so that the recommended next dose is 4 mg/kg. Whereas in Scenario 7, it is assumed that one of the three patients suffered DLT in second cohort of 1.3 mg/kg dose only, which leads to the EWOC criterion allowing to go to the next dose of 4 mg/kg for the next cohort.

Scenarios 8, 9 and 10 illustrate three situations in which the first cohort of 4 patients treated with 0.4 mg/kg dose followed by a second cohort of 3 patients treated with 1.3 mg/kg dose. In Scenario 8, one of the four patients experienced a DLT in 0.4 mg/kg dose cohort and none of the patients in 1.3 mg/kg dose cohort experienced a DLT. This leads to the EWOC criterion allowing all doses up to 8 mg/kg for the next cohort. However, as per the maximum increment, the dose could at most be the next planned dose in the escalation scheme, so that

the recommended next dose is 4 mg/kg. Whereas in Scenario 9, it is assumed that one of the three patients suffered DLT in second cohort of 1.3 mg/kg dose along with one of the 4 patients experienced a DLT in the first cohort, which leads to the EWOC criterion allows to go to the next dose of 4 mg/kg for the next cohort. In contrast if two of the three patients suffered DLT in second cohort of 1.3 mg/kg dose along with one of the 4 patients experienced a DLT in the first cohort (Scenario 10), the BLRM would not allow any dose and recommend stopping the trial.

Scenarios 11 and 12 consider a situation that may occur after the first three cohorts of 2, 3 and 3 patients have been treated with 0.4, 1.3, and 4 mg/kg doses, respectively. Scenario 11 assumes that none of the patients suffered a DLT in these three cohorts. The EWOC criteria allows to go the next dose cohort of 8 mg/kg. Even with one out of the three patients suffering with a DLT in the third cohort (Scenario 12), the EWOC criteria allows to go to the next dose cohort of 8 mg/kg.

Scenarios 13, 14 and 15 consider a situation that may occur after the first three cohorts of 4, 3 and 3 patients have been treated with 0.4, 1.3, and 4 mg/kg doses, respectively. Scenario 13 assumes that one patient out of four patients in the first cohort of 0.4 mg/kg dose and none of the patients suffered a DLT in the next two cohorts. The EWOC criteria allows to go up to the dose of 16 mg/kg for the next cohort. However, as per the maximum increment, the dose could at most be the next planned dose in the escalation scheme, so that the recommended next dose is 8 mg/kg. If the Scenario 13 was assumed with one out of the three patients suffering with a DLT in the third cohort (Scenario 14), the EWOC criteria allows to go to the next dose cohort of 8 mg/kg. In contrast if two of the three patients suffered DLT in third cohort of 4 mg/kg dose along with one of the 4 patients experienced a DLT in the first cohort (Scenario 15), the EWOC criterion do not allow to go to the next dose or the current third dose but allow to go to the second dose of 1.3 mg/kg.

Scenarios 16 and 17 consider a situation that may occur after the first four cohorts of 2, 3, 3 and 3 patients have been treated with 0.4, 1.3, 4 and 8 mg/kg doses, respectively. Scenario 16 assumes that none of the patients suffered a DLT in these four cohorts. The EWOC criteria allows to go the next dose cohort of 16 mg/kg. In contrast, with one out of the three patients suffering with a DLT in the fourth cohort only (Scenario 17), the EWOC criteria do not allow to go to the next dose cohort of 16 mg/kg but suggest recommending 8 mg/kg as top allowed dose.

Similarly, Scenarios 18 and 19 consider a situation that may occur after the first four cohorts of 4, 3, 3 and 3 patients have been treated with 0.4, 1.3, 4 and 8 mg/kg doses, respectively. Scenario 18 assumes that one out of the four patients in the first cohort of 0.4 mg/kg dose and none of the patients suffered a DLT in the next three cohorts. The EWOC criteria allows to go the next dose cohort of 16 mg/kg. In contrast, with one out of the three patients suffering with a DLT in the fourth cohort along with one of the 4 patients experienced a DLT in the first cohort (Scenario 19), the EWOC criteria do not allow to go to the next dose cohort of 16 mg/kg but suggest recommending 8 mg/kg as top allowed dose.

Scenarios 20 and 21 consider a situation that may occur after all the five cohorts of 2, 3, 3, 3 and 3 patients have been treated with 0.4, 1.3, 4, 8 and 16 mg/kg doses, respectively. Scenario 20 assumes that none of the patients suffered a DLT in these five cohorts. The EWOC criteria allows the current dose of 16 mg/kg as the top dose. In contrast, with one out of the three patients suffering with a DLT in the fifth cohort only (Scenario 21), the EWOC criteria do not allow to continue with current dose cohort of 16 mg/kg but suggest recommending 8 mg/kg as top allowed dose.

Table 17 Hypothetical data scenarios - Monotherapy

Scenario	Arm	Observed Data			Current dose: P(OD[$])	Next recommended dose*[§]	Interval probabilities of next recommended dose*		
		Dose A: mg/kg	#Patients	# DLTs			P(UD[$])	P(TD[$])	P(OD[$])
1	**A**	0.4	2	0	0.005	8 (1.3*)	0.935	0.051	0.014
2	**A**	0.4	2	1	0.153	1.3 (0.4*)	0.496	0.27	0.234
3	**A**	0.4	4	1	0.054	4 (1.3*)	0.632	0.267	0.101
4	**A**	0.4	4	2	0.315	NA[§]	0.237	0.315	0.448
5	**A**	0.4	6	2	0.129	1.3	0.344	0.416	0.24
6	**A**	0.4 1.3	2 3	0 0	0.003	8 (4*)	0.881	0.1	0.019
7	**A**	0.4 1.3	2 3	0 1	0.051	4	0.53	0.33	0.139
8	**A**	0.4 1.3	4 3	1 0	0.031	8 (4*)	0.582	0.335	0.082
9	**A**	0.4 1.3	4 3	1 1	0.152	1.3	0.459	0.389	0.152
10	**A**	0.4 1.3	4 3	1 2	0.419	NA[§]	0.168	0.413	0.419
11	**A**	0.4 1.3 4	2 3 3	0 0 0	0.003	8	0.745	0.207	0.048
12	**A**	0.4 1.3 4	2 3 3	0 0 1	0.041	8	0.442	0.391	0.167
13	**A**	0.4 1.3 4	4 3 3	1 0 0	0.025	16 (8*)	0.574	0.354	0.073
14	**A**	0.4 1.3 4	4 3 3	1 0 1	0.119	8	0.293	0.467	0.240
15	**A**	0.4 1.3 4	4 3 3	1 0 2	0.348	1.3	0.404	0.453	0.143
16	**A**	0.4 1.3 4 8	2 3 3 3	0 0 0 0	0.011	16	0.493	0.265	0.242

Table 17 (cont'd) Hypothetical data scenarios - Monotherapy

Scenario	Arm	Observed Data			Current dose: P(OD[$])	Next recommended dose*[§]	Interval probabilities of next recommended dose*		
		Dose A: mg/kg	#Patients	# DLTs			P(UD[$])	P(TD[$])	P(OD[$])
17	**A**	0.4 1.3 4 8	2 3 3 3	0 0 0 1	0.082	8	0.588	0.331	0.082
18	**A**	0.4 1.3 4 8	4 3 3 3	1 0 0 0	0.031	16	0.553	0.356	0.091
19	**A**	0.4 1.3 4 8	4 3 3 3	1 0 0 1	0.108	8	0.434	0.458	0.108
20	**A**	0.4 1.3 4 8 16	2 3 3 3 3	0 0 0 0 0	0.045	16	0.744	0.210	0.045
21		0.4 1.3 4 8 16	2 3 3 3 3	0 0 0 0 1	0.256	8	0.800	0.191	0.009

*In case the maximum allowed dose based on the EWOC criterion exceeds the maximum increments, 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 Sponsor and DEC.
[$]OD/UD/TD: overdosing (DLT rate ≥ 0.33), underdosing (DLT rate < 0.16), target dosing (0.16 ≤ DLT rate <0.33).

Hypothetical data scenarios – Combination Therapy

Hypothetical data scenarios are shown in Table 18 for Arm A with the first cohort of 3 patients treated with 0.4 mg/kg of BI 765883 (dose A) + 1000 mg/m^2 gemcitabine + 125 mg/m^2 nab-Paclitaxel (dose B). Since dose B is fixed for all the dose escalations, only Dose A is varied in these scenarios. These scenarios reflect potential on-trial data constellations and related escalation as allowed by the model and the escalation limit specified in Section 7. For each scenario and each arm, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target dose and over-dosing are shown.

For instance, Scenarios 1, 2, and 3, illustrate different situations that could occur after the first cohort of 3 patients were treated at the starting dose (0.4 mg/kg + dose B) in the combination therapy arm. In Scenario 1, it is assumed that none of the patients suffered DLT, which leads to the EWOC criterion allowing all doses up to (8 mg/kg +dose B) for the next cohort. However, as per the maximum increment, the dose could at most be the next planned dose in the escalation scheme, so that the recommended next dose is (1.3 mg/kg + dose B). However, if one of the patients at (0.4 mg/kg + dose B) experienced a DLT (Scenario 2), the BLRM would allow all doses up to (8 mg/kg + dose B) for the next cohort. However, as per the maximum increment, the dose could at most be the next planned dose in the escalation scheme, so that the recommended next dose is (1.3 mg/kg + dose B). In contrast to this, if two of the patients at (0.4 mg/kg + dose B) experienced DLTs (Scenario 3), the BLRM would not allow any dose and recommend stopping the trial.

Scenarios 4 and 5 illustrate different situations with the first cohort of 6 patients were treated at the starting dose (0.4 mg/kg + dose B) in the combination therapy arm. In Scenario 4, it is assumed that one of the patients suffered DLT, which leads to the EWOC criterion allowing all doses up to (8 mg/kg + dose B) for the next cohort. However, as per the maximum increment, the dose could at most be the next planned dose in the escalation scheme, so that the recommended next dose is (1.3 mg/kg + dose B). In contrast to this, if two of the patients at (0.4 mg/kg + dose B) experienced DLTs (Scenario 5), the BLRM would allow a dose of (1.3 mg/kg + dose B) for the next cohort.

Scenarios 6 through 10 illustrate varied situations with first cohort of 3 or 6 patients were treated at the starting dose (0.4 mg/kg + dose B) and the second cohort of 3 patients were treated at the dose of (1.3 mg/kg + dose B) in the combination therapy arm. In Scenario 6, it is assumed that none of the patients suffered DLT in both cohorts, which leads to the EWOC criterion allowing all doses up to (8 mg/kg + dose B) for the next cohort. However, as per the maximum increment, the dose could at most be the next planned dose in the escalation scheme, so that the recommended next dose is (4 mg/kg + dose B). Similarly in Scenario 7, it is assumed that one of the three patients suffered DLT in second cohort of (1.3 mg/kg + dose B) dose only, which leads to the EWOC criterion allowing all doses up to (8 mg/kg + dose B) for the next cohort. However, as per the maximum increment, the dose could at most be the next planned dose in the escalation scheme, so that the recommended next dose is (4 mg/kg + dose B).

Scenarios 8, 9 and 10 illustrate three situations in which the first cohort of 6 patients treated with (0.4 mg/kg + dose B) dose followed by a second cohort of 3 patients treated with (1.3 mg/kg + dose B) dose. In Scenario 8, one of the six patients experienced a DLT in (0.4 mg/kg + dose B) dose cohort and none of the patients in (1.3 mg/kg + dose B) dose cohort experienced a DLT. This leads to the EWOC criterion allowing all doses up to (8 mg/kg + dose B) for the next cohort. However, as per the maximum increment, the dose could at most be the next planned dose in the escalation scheme, so that the recommended next dose is (4 mg/kg + dose B). Whereas in Scenario 9, it is assumed that one of the three

patients suffered DLT in second cohort of (1.3 mg/kg + dose B) dose along with one of the 6 patients experienced a DLT in the first cohort, which leads to the EWOC criterion do not allow to go to the next dose of (4 mg/kg + dose B) for the next cohort. Since the next cohort overdose probability of 0.251 is very close to 0.25 threshold, the DEC may allow to enrol additional patients at the current dose. In contrast if two of the three patients suffered DLT in second cohort of 1.3 mg/kg + dose B dose along with one of the 6 patients experienced a DLT in the first cohort (Scenario 10), the EWOC criterion do not allow to go to the next dose or the current second dose but remain with the first dose of (0.4 mg/kg + dose B).

Scenarios 11 and 12 consider a situation that may occur after the first three cohorts of 3, 3 and 3 patients have been treated with (0.4, 1.3, and 4 mg/kg in combination with dose B) doses, respectively. Scenario 11 assumes that none of the patients suffered a DLT in these three cohorts. The EWOC criteria allows to go the next dose cohort of (8 mg/kg + dose B). Even with one out of the three patients suffering with a DLT in the third cohort (Scenario 12), the EWOC criteria allows to go to the next dose cohort of (8 mg/kg + dose B).

Scenarios 13, 14 and 15 consider a situation that may occur after the first three cohorts of 6, 3 and 3 patients have been treated with (0.4, 1.3, and 4 mg/kg in combination with dose B) doses, respectively. Scenario 13 assumes that one patient out of six patients in the first cohort of (0.4 mg/kg + dose B) dose and none of the patients suffered a DLT in the next 2 cohorts. The EWOC criteria allows to go up to the dose of (16 mg/kg + dose B) for the next cohort. However, as per the maximum increment, the dose could at most be the next planned dose in the escalation scheme, so that the recommended next dose is (8 mg/kg + dose B). If the Scenario 13 was assumed with one out of the three patients suffering with a DLT in the third cohort (Scenario 14), the EWOC criteria allows to go to the next dose cohort of 8 mg/kg + dose B). In contrast if two of the three patients suffered DLT in third cohort of (4 mg/kg + dose B) dose along with one of the 6 patients experienced a DLT in the first cohort (Scenario allow to go to the second dose of (1.3 mg/kg + dose B).

Scenarios 16 and 17 consider a situation that may occur after the first four cohorts of 4, 3, 3 and 3 patients have been treated with (0.4, 1.3, 4 and 8 mg/kg in combination with dose B) doses, respectively. Scenario 16 assumes that none of the patients suffered a DLT in these four cohorts. The EWOC criteria allows to go the next dose cohort of (16 mg/kg + dose B). In contrast, with one out of the three patients suffering with a DLT in the fourth cohort only (Scenario 17), the EWOC criteria do not allow to go to the next dose cohort of (16 mg/kg + dose B) but suggest recommending (8 mg/kg + dose B) as top allowed dose.

Similarly, Scenarios 18 and 19 consider a situation that may occur after the first four cohorts of 6, 3, 3 and 3 patients have been treated with (0.4, 1.3, 4 and 8 mg/kg in combination with dose B) doses, respectively. Scenario 18 assumes that one out of the six patients in the first cohort of (0.4 mg/kg + dose B) dose and none of the patients suffered a DLT in the next three cohorts. The EWOC criteria allows to go the next dose cohort of (16 mg/kg + dose B). Similarly, with one out of the three patients suffering with a DLT in the fourth cohort along with one of the 6 patients experienced a DLT in the first cohort (Scenario 19), the EWOC criteria allows to go to the next dose cohort of (16 mg/kg + dose B).

Scenarios 20 and 21 consider a situation that may occur after all the five cohorts of 3, 3, 3, 3 and 3 patients have been treated with (0.4, 1.3, 4, 8 and 16 mg/kg in combination with dose B) doses, respectively. Scenario 20 assumes that none of the patients suffered a DLT in these five cohorts. The EWOC criteria allows the current dose of (16 mg/kg + dose B). as the top dose. In contrast, with one out of the three patients suffering with a DLT in the fifth cohort only (Scenario 21), the EWOC criteria do not allow to continue with current dose cohort of (16 mg/kg + dose B). but suggest recommending (8 mg/kg + dose B). as top allowed dose.

Table 18 Hypothetical data scenarios – Combination therapy

Scenario	Observed Data Dose B: 1000 mg/m² Gemcitabine + 125 mg/m² nab-Paclitaxel			Current dose: P(OD[$])	Next recommended dose*§	Interval probabilities of next recommended dose*		
	Dose A: mg/kg	#Patients	# DLTs			P(UD[$])	P(TD[$])	P(OD[$])
1	0.4	3	0	0.002	8 (1.3*)	0.948	0.043	0.009
2	0.4	3	1	0.092	4 (1.3*)	0.571	0.274	0.155
3	0.4	3	2	0.464	NA§	0.167	0.254	0.579
4	0.4	6	1	0.024	8 (1.3*)	0.705	0.233	0.062
5	0.4	6	2	0.129	1.3	0.344	0.416	0.240
6	0.4 1.3	3 3	0 0	0.002	8 (4*)	0.969	0.029	0.002
7	0.4 1.3	3 3	0 1	0.041	8 (4*)	0.792	0.168	0.041
8	0.4 1.3	6 3	1 0	0.018	8 (4*)	0.819	0.162	0.018
9	0.4 1.3	6 3	1 1	0.106	1.3	0.530	0.364	0.106
10	0.4 1.3	6 3	1 2	0.349	0.4	0.436	0.426	0.139
11	0.4 1.3 4	3 3 3	0 0 0	0.003	8	0.755	0.201	0.043
12	0.4 1.3 4	3 3 3	0 0 1	0.034	8	0.447	0.388	0.165
13	0.4 1.3 4	6 3 3	1 0 0	0.023	16 (8*)	0.600	0.323	0.077
14	0.4 1.3 4	6 3 3	1 0 1	0.101	8	0.326	0.459	0.215
15	0.4 1.3 4	6 3 3	1 0 2	0.292	1.3	0.473	0.434	0.093

Table 18 (cont'd) Hypothetical data scenarios – Combination therapy

Scenario	Observed Data Dose B: 1000 mg/m² Gemcitabine + 125 mg/m² nab-Paclitaxel			Current dose: P(OD[$])	Next recommended dose*[§]	Interval probabilities of next recommended dose*		
	Dose A: mg/kg	#Patients	# DLTs			P(UD[$])	P(TD[$])	P(OD[$])
16	0.4 1.3 4 8	3 3 3 3	0 0 0 0	0.015	16	0.521	0.245	0.234
17	0.4 1.3 4 8	3 3 3 3	0 0 0 1	0.076	8	0.576	0.347	0.076
18	0.4 1.3 4 8	6 3 3 3	1 0 0 0	0.03	16	0.562	0.348	0.090
19	0.4 1.3 4 8	6 3 3 3	1 0 0 1	0.099	16	0.297	0.454	0.249
20	0.4 1.3 4 8 16	3 3 3 3 3	0 0 0 0 0	0.048	16	0.740	0.212	0.048
21	0.4 1.3 4 8 16	3 3 3 3 3	0 0 0 0 1	0.252	8	0.836	0.154	0.010

*In case the maximum allowed dose based on the EWOC criterion exceeds the maximum increments, 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 Sponsor and DEC.
[$]OD/UD/TD: overdosing (DLT rate $\geq$ 0.33), underdosing (DLT rate < 0.16), target dosing (0.16 $\leq$ DLT rate <0.33).

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model by illustrating the precision of the design in estimating the MTD. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation. In the combination therapy, the chemotherapy component dose level is fixed and only the BI 765883 doses will be escalated. There by, the Bayesian 2-parameter model, the prior derivation and the operating characteristics will be the same for both mono- and combination therapies.

Table 19 describes 5 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the model. These scenarios reflect a wide range of possible cases as follows:

Scenario 1: Realistic scenario
Scenario 2: low-toxicity scenario
Scenario 3: high-toxicity scenario
Scenario 4: too-toxic scenario
Scenario 5: non-logistic dose-toxicity scenario

Table 19 Assumed true dose-toxicity scenarios for Arms A (monotherapy) and B (combination therapy) BI 765883 + 1000 mg/m^2 gemcitabine and 125 mg/m^2

Scenario	Arm		Dose [mg/kg BI 765883 (+ mg/m^2 gemcitabine/ mg/m^2 nab-paclitaxel)]				
			0.4 (+ 1000/125)	1.3 (+ 1000/125)	4 (+ 1000/125)	8 (+ 1000/125)	16 (+ 1000/125)
1	A	P(DLT)	0.01	0.10	**0.25**	0.40	0.50
	B		0.01	0.10	**0.25**	0.40	0.50
2	A		0.01	0.03	0.06	0.08	**0.17**
	B		0.01	0.03	0.06	0.08	**0.17**
3	A		**0.25**	0.35	0.40	0.44	0.50
	B		**0.25**	0.35	0.40	0.44	0.50
4[1]	A		0.40	0.45	0.55	0.70	0.80
	B		0.40	0.45	0.55	0.70	0.80
5	A		0.01	0.05	0.14	**0.28**	0.37
	B		0.01	0.05	0.14	**0.28**	0.37

Numbers in bold represent assumed toxicity probabilities lying in the target toxicity interval [0.16, 0.33].
1 For Scenario 4, 0.2 mg/kg dose with 25% true DLT probability was added to the simulation condition in order for the R package to run (which needs at least one provisional dose level with true DLT probability in the target range).

For each of these scenarios, 1000 trials were simulated. Each cohort consisted of 3 patients. For a trial simulation, the number of patients with DLT were simulated independently for cohorts of patients according to the DLT rates specified in the dose-toxicity scenario. Using this, the posterior of the BLRM was computed and used to decide on the dose level for the next cohort of patients. As per Figure 1 and the rules for dose escalation specified in Section 4, the dosing steps considered in the simulation are 0.4 mg/kg, 1.3 mg/kg, 4 mg/kg, 8 mg/kg, and 16 mg/kg mg in monotherapy and 0.4 mg/kg + 1000 mg/m^2 and 125 mg/m^2, 1.3 mg/kg + 1000 mg/m^2, and 125 mg/m^2, 4 mg/kg + 1000 mg/m^2 and 125 mg/m^2, 8 mg/kg +

1000 mg/m^2 and 125 mg/m^2, and 16 mg/kg + 1000 mg/m^2 and 125 mg/m^{2}in combination therapy. Dose escalation occurred as per the following rule:

- Escalate to the dose among the considered dose levels which maximises the probability of the targeted toxicity region among the doses satisfying the overdose criterion, provided that this dose is at most one dosing step above the current dose (as per Figure 1)
- If the dose which maximises the probability of the targeted toxicity region among the doses satisfying the overdose criterion is larger than the next planned dosing step as per Figure 1, escalate to the next planned dosing step instead (i.e., no dose can be skipped)

The first cohort in the monotherapy arm is assumed to be treated at the dose 0.4 mg/kg, while the first cohort in the combination therapy arm is assumed to be treated at 0.4 mg/k + 1000 mg/m^2, and 125 mg/m^2, where it is assumed that the monotherapy and combination therapy arms can start independent of each other.

The MTD was considered reached if (per arm) at least 12 patients have been evaluated in the trial arm, a dose level is the model's recommendation for the next dose cohort two times in a row, and for this dose the posterior probability of targeted toxicity was at least 50% or at least 6 patients have been treated at this dose in the respective arm of the trial. In this case, the dose satisfying these conditions is declared MTD of the trial arm, in accordance with the rules stated in Section 7. A trial arm was considered to be stopped without declaring an MTD when the number of patients exceeded a pre-specified maximum sample size (40 for monotherapy, 40 for combination) before the conditions for MTD selection were satisfied.

Table 20 Simulated operating characteristics.

	% of trials declaring a MTD with true DLT rate in				# Patients	# DLTs
Scenario	UD	TD	OD	Stopped	Mean (Min-Max)	Mean (Min-Max)
1: Realistic	14.3	50.5	35.2	0.1	16.15 (9 – 33)	3.5 (1 – 11)
2: Low-toxicity	40.8	59.2	0	0	19.83 (12 – 60)	1.74 (1 – 6)
3: High-toxicity	0	10.9	46.6	42.5	11.31 (3 – 33)	3.88 (1 – 12)
4: Too-toxic	0	3.7	36	60.3	10.96 (3 – 30)	4.18 (2 -12)
5: Non-logistic	32.5	56.3	11.2	0	17.2 (12 – 36)	2.85 (1 – 10)

UD =under dose; TD = target dose; OD = overdose

In Scenario 1, which reflects the Realistic case, 50.5% of the simulated trials declared the dose 4 mg/kg as MTD with true DLT rate under the targeted dose range.

Scenario 2 shows that when the true DLT rate is low, 59.2% of the simulated trials declared the dose 16 mg/kg as MTD with true DLT rate under the targeted dose range, and 40.8% of the simulated trials declared a MTD in the underdose interval.

Scenario 3 shows that when the true DLT rate is high, i.e. the majority dose levels with true DLT rate above the target interval, the probability of observing a DLT at 1.3 mg/kg is 0.35 and therefore very close to the upper bound of the target range. About 43% (42.5%) of the trials were stopped without declaring a MTD since all dose levels were too toxic. This is an expected situation for a high-toxicity scenario.

Scenario 4 shows that when the true DLT rate is "too-toxic", 60.3% of simulated trials stopped since none of the doses is considered tolerable anymore. This is an expected situation for a "too-toxic" scenario.

Scenario 5 represents a case where the assumed true dose-toxicity curve does not follow a logistic shape. In this scenario, 56.3% of trials declared MTDs with true DLT rate in the target interval, and this behaviour was similar to scenario 1. This illustrates that the model is not sensitive to model misspecification.

The mean patient numbers range from 10.96 patients (Scenario 4) to 19.83 patients (Scenario 2) and the maximum number of patients was 60. Therefore, the patient numbers are as expected and increase when moving away from the high toxicity scenario.

By reviewing the metrics presented in Table 20 it can be seen that the model is not sensitive to different scenarios of truth. In general, this model is conservative due to the overdose control criteria. In all scenarios (except for high and too toxic scenarios), the probabilities of recommending a dose with true P(DLT) ≥ 33% as MTD are much smaller than probabilities of recommending a dose with true P(DLT) between 16% and 33% as MTD.

On-study recommendations based on the model are consistent with the clinical decision-making process and should be considered in conjunction with other available clinical information by the BI clinical trial team and trial investigators in deciding the dose levels to be tested to determine the MTD estimate.

R version 4.1.3 and JAGS were used for data scenarios and simulations.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

This amendment is considered to be non-substantial based on the criteria set forth in Regulation (EU) No 536 / 2014 of the European Parliament and the Council of the European Union because it does not impact the safety of participants, it does not change the interpretation of the scientific documents in support of the conduct of the trial, and is not otherwise significant.

Overall rationale for the amendment

Revisions to this clinical trial protocol are in response to FDA reviewers' comments. No patients have been enrolled at the time of introduction of this amendment.

A high-level summary of changes and the rationale for the changes, is tabulated below.

Amendment and date of amendment	Amendment 1, 23 Feb 2024	
Global Amendment		X
Global Amendment due to urgent safety reasons		
Section changed	**Description of change**	**Rationale for change**
Title page	Title changed to: A first-in-human open label Phase Ia/Ib, multicenter/multiregional, dose escalation study of BI 765883 administered as monotherapy and in combination with gemcitabine and nab-paclitaxel in unselected patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) or patients with PDAC who have relapsed after post-surgery adjuvant therapy	Title revised to remove mode of administration and to clarify the indication under investigation.
Synopsis, title of trial	Title revised to match title page	To be consistent with title page.
Synopsis, Benefit-risk assessment and ethical considerations	Predicted efficacy of the proposed starting dose was changed to: …at least ~70% tumor growth inhibition relative to vehicle treated control…	Correction of the parameter used for predicting efficacy of BI 765883 from tumor shrinkage to

		tumor growth inhibition.
Synopsis, Benefit-risk assessment and ethical considerations	Revised text: The proposed starting dose is expected to provide a meaningful clinical benefit to cancer patients and is supported by multiples of exposure of the no-observed-adverse effect level (NOAEL) from nonclinical toxicology data.	To clarify the nonclinical data referred to in this text.
Synopsis, Trial objectives	Secondary objectives revised: The dose range for further development in Phase II will be determined based on available data, including safety, preliminary efficacy, and PK data from Phase Ia and Phase Ib.	To be consistent with Section 2.1.1.
Synopsis, Trial endpoints	Revised text: Progression-free survival (PFS) PFS is defined as the time from first treatment administration until tumor progression according to RECIST 1.1 or death from any cause, whichever occurs earlier.	The definition of PFS was revised to remove mention of unacceptable toxicity.
Synopsis, Inclusion criteria	Inclusion criteria were revised to describe the patient population more clearly.	To be consistent with revised inclusion criterion no. 10 Section 3.3.1.
Flow chart	Wording of some footnotes revised.	For clarity and to be consistent with changes in the main text of the protocol.
Flow chart	Timing of follow-up changed from every 12 weeks to every 3 months.	Change made in flow chart and updated as needed for consistency within the text of the CTP.

1.4.1 Benefits	Revised text: Eligible patients for combination therapy as second-line (2L) will include resected patients who have relapsed within 6 months after adjuvant therapy as these patients are considered as frontline failed and are now 2L treatment eligible.	Text updated to be consistent with revised inclusion criterion no. 10.
1.4.2 Risks	Revised text: … the proposed starting dose of 0.4 mg/kg in Phase I.	Starting dose added within this sentence. The starting dose is unchanged.
1.4.3 Discussion	Revised text: The proposed starting dose (0.4 mg/kg) is expected to provide a meaningful clinical benefit to cancer patients and is supported by multiples of exposure of the NOAEL from nonclinical toxicology data.	To clarify the nonclinical data referred to in this text.
2.1.1 Main objectives	Secondary objectives wording revised: The dose range for further development in Phase II will be determined based on available data, including safety, preliminary efficacy, and PK data from Phase Ia and Phase Ib.	Wording clarified because a range of doses rather than a single dose of BI 765883 may be identified for further development in Phase II.
2.1.3 Secondary endpoints	Revised text: Progression-free survival (PFS) PFS is defined as the time from first treatment administration until tumor progression according to RECIST 1.1 or death from any cause, whichever occurs earlier.	The definition of PFS was revised to remove mention of unacceptable toxicity.
3.1 Overall trial design	Sentence added: Further dose optimization will be conducted in future Phase II trials or earlier if required.	To make clear that dose optimization is not the purpose of the present trial.

3.1.1 Dose escalation (Phase Ia)	Revised text: During Phase Ia dose escalations, a minimum of 48 h must have elapsed between the first dose of one patient and the first dose of the next subsequent patient within a dose level. Following completion of each dose level (monotherapy or combination therapy), the DEC will assess available study data to ensure the overall safety of the patients treated at each DL, before opening the next monotherapy or combination therapy dose level.	The text was extended to clarify the period that must have elapsed between dosings for patients in different dosing levels (monotherapy or combination therapy).
3.3.2 Inclusion criteria	Inclusion criterion no. 10 was revised to: Patients who have progressive metastatic disease after prior platin and/or irinotecan-based first line therapy (combination therapy). Eligible patients for combination therapy as second-line (2L) include patients who have relapsed within 6 months and present with metastatic disease after resection and neo- and/or adjuvant therapy as these patients are considered as frontline failed and are now 2L treatment eligible.	Inclusion criterion no. 10 was revised to describe the patient population more clearly.
3.3.2 Inclusion criteria	Inclusion criterion no. 11 was updated to reflect EPI-CKD eGFR definitions of renal impairment; units for ANC and platelet counts were also corrected.	Per regulatory request, eligibility criteria were revised to evaluate renal function based on creatinine clearance only.
3.3.3 Exclusion criteria	Exclusion criterion no. 5 changed to the following: 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)	Changed from less than 30 days to less than 28 days to be consistent with timing of administration of relevant treatments.

3.3.4.2 Withdrawal of consent to trial participation	Revised text: Any blood, serum, plasma, blood cells, urine, or tumor samples collected prior to withdrawal of consent to trial participation (WoC) has been confirmed will still be used in the analysis of study results, unless patients inform their doctor that it is preferred these samples be destroyed.	Text revised to clarify that samples collected before WoC may still be analyzed unless consent for this is also withdrawn.
4.1.2.1 Dose escalation	The text was revised to: Based on nonclinical efficacy data from PDAC/ PDX animal models, a starting dose of 0.4 mg/kg q2w with a predicted activity of 70% TGI is proposed for this Phase I clinical trial	Correction of the parameter used for predicting efficacy of BI 765883. The text was revised because predicted activity of BI 765883 is evaluated based on tumor growth inhibition rather than tumor shrinkage.
4.1.2.1 Dose escalation	Revised text: The proposed starting dose is expected to provide a meaningful clinical benefit to cancer patients and is supported by multiples of exposure of the NOAEL from nonclinical toxicology data.	This sentence was updated to clarify the nonclinical data referred to in this text.
4.1.2.1 Dose escalation	Added text: During Phase Ia dose escalations, a minimum of 48 h must have elapsed between the first dose of one patient and the first dose of the next subsequent patient within a dose level. Following completion of each dose level (monotherapy or combination therapy), the DEC will assess available study data to ensure the overall safety of the patients and before opening the next monotherapy or combination therapy dose level.	The text was added to clarify the period that must have elapsed between dosing for patients in different dosing levels (monotherapy or combination therapy).

4.1.4.1	Text deleted: If a patient's weight is ≤50 kg, the infusion duration may be less than 30 minutes depending upon the infusion rate and the patient's condition.	The infusion timing is not anticipated to be reduced if a patient's weight is ≤50 kg.
4.1.4.3 Criteria for receiving further treatment	Revised text: Serum creatinine ≤1.5 x institutional ULN. If creatinine is >1.5 x ULN, patient is eligible if concurrent eGFR is ≥45 mL/min (≥0.045 L/min) (measured or calculated by applicable CKD-EPI formula) [R12-1392, R22-1535, R22-1536]	Consistent with the change in Section 3.3.1, per regulatory request, criteria for further treatment were revised to evaluate renal function based on creatinine clearance.
4.2.2.3 Contraception requirements	Text updated to specify that WOCBP included trial patients or female partners of trial patients, and men able to father a child were defined as non-vasectomized men.	Contraception requirements were clarified to ensure they clearly were consistent with the requirements of the regulatory authorities.
5.2.2 Vital signs	Text added: Patients will remain under surveillance to monitor potential occurrences of IRRs or CRS for at least 6 h after the end of infusion for the administration of BI 765883. Vital signs should be evaluated pre-dose, post-dose, and then every 2 h during the BI 765883 post-infusion observation period. In the absence of IRR/CRS this can be reduced in subsequent administrations (see Section 4.2.3.1).	Text added to clarify monitoring period for vital signs before and after dosing with BI 765883.
5.2.3 Safety laboratory parameters	Safety laboratory parameters (Table 9) were updated.	The text was updated to specify the calculations required for evaluation of

		eGFR, and to note that urea could be tested in place of BUN, and an HCG blood test could be done in place of a urine pregnancy test.
5.2.4 Electrocardiogram	Text added: At the screening visit only, LVEF (left ventricular ejection fraction), measured by MUGA (multigated acquisition scan) or echocardiography (Echo-CG) can be used to access eligibility instead of a 12-lead ECG.	Text added to clarify procedures permitted for determining eligibility at screening.
5.2.7 Dose-limiting toxicity (DLT)	Definitions of non-hematologic laboratory DLTs and non-laboratory DLTs were updated in Table 10.	Definitions were updated to comply with regulatory requests.
5.3.4 Pharmacokinetic - pharmacodynamic relationship	Revised text: If the data allow, the relationship between drug exposure (e.g. AUC or C_{avg}) and clinical anti-tumor activity or efficacy data, as well as safety and tolerability endpoints, are planned to be investigated. Population pharmacokinetics (PopPK) analyses, graphical explorations on exposure-response relationships, as well as exposure-response modeling, as applicable, are planned to be performed based on preliminary data from the ongoing study and updated as new data become available. If limited dose-response relationships are detected, further PK-PD evaluations or modeling activities might be omitted. Modeling activities will be planned and documented separately according to internal and external guidelines and SOPs.	The text was revised to provide more information on the types of analyses that may be performed if the available data are appropriate for such analyses.

6.2.1 Screening period	Revised text: Staging and grading information at diagnosis and at screening	Timing added for collection of staging and grading information.
6.2.3.3 Follow-up	Text added: In addition to follow-up for survival status, follow-up for disease progression via tumor assessments will continue for patients that discontinue early from the study for reasons other than progressive disease. This follow-up will continue until disease progression or the start of subsequent anti-cancer treatment.	Text revised to indicate that patients who discontinue will continue to be followed for disease progression in addition to being followed for survival status.
7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE	The text from the start of Section 7 to the start of Section 7.1 was replaced and updated to comply with changes in the planned analyses requested by regulatory authorities.	As suggested by the FDA, BLRM models for monotherapy and combination therapy were conducted independently. The text used for a joint BLRM model was replaced with the 2-parameter BLRM model applied independently for monotherapy and combination therapy.
7.2.3.1 Main analyses	Revised text: In the case of concurrent monotherapy and combination therapy dose escalations, the dose escalations will be guided by a BLRM with overdose control modelling approach to independently model the escalations in both groups.	Text revised because 2-parameter BLRM model is now applied independently for monotherapy and

		combination therapy.
7.2.3.2 Sensitivity analyses	Revised text: There is no pre-defined sensitivity analysis.	This text was revised since the separate BLRM models now described in Sections 7 and 10.2 were previously added as a sensitivity analysis, which is no longer required.
7.5 Determination of sample size	Revised text: Assuming a true OR rate of 30% at a DL, a sample size of 28 patients (10 patients from previous dose escalation and backfill, 18 patients from expansion part) leads to a probability of 71% of observing an OR rate of ≥25% and a probability of 16% to stop for futility at inflection point 1 (IP1).	This text discusses the scenario from Table 17; the value was originally entered as 9% (from the 35% scenario) rather than 16% (from the 30% scenario).
9 References	Additional references added.	Five additional published references on measurement of eGFR and statistical methods were added within the text and included in the list of references, as well as one additional nonclinical study unpublished reference.
10.2 STATISTICAL APPENDIX INCLUDING	All text and tables in Appendix 10.2 were replaced.	The hypothetical scenarios for joint BLRM modeling described in the

MODEL PERFORMANCE AND DATA SCENARIOS		previous text were replaced with separate hypothetical scenarios independently for monotherapy and combination therapy BLRM models. The operating characteristics for the models were also updated using the 2-parameter BLRM model rather than the joint BLRM model.
Throughout	Updated the protocol version number and date.	To align with the amendment number.
Throughout	Minor editorial (grammar, style, spelling) and document formatting revisions.	For clarity and/or internal consistency.

11.2 GLOBAL AMENDMENT 2

This amendment is considered to be non-substantial based on the criteria set forth in Regulation (EU) No 536 / 2014 of the European Parliament and the Council of the European Union because it does not impact the safety of participants, it does not change the interpretation of the scientific documents in support of the conduct of the trial, and is not otherwise significant.

Overall rationale for the amendment

Revisions to this clinical trial protocol are in response to EMA reviewer comments.

A high-level summary of changes and the rationale for the changes, is tabulated below.

Amendment and date of amendment	Amendment 2, 19 Jul 2024

Global Amendment		X
Global Amendment due to urgent safety reasons		
Section changed	**Description of change**	**Rationale for change**
Clinical Trial Protocol Synopsis	Revised the description of the total number of patients	To describe patient numbers based on evaluable patients.
Section 1.3	Added a statement to confirm safety results from dose escalation and RDE recommendations of the DEC will be provided to the regulatory authority prior to initiation of dose expansion	Requested by the EMA.
Section 3.1.3	Additional enrollment stopping criteria added	To clarify events leading to a temporary stop of enrollment.
Section 3.3	Revised description of the total number of patients	To describe patient numbers based on evaluable patients.
Section 3.3.3	Revised Exclusion Criterion #20, changing exclusionary viral load >400 copies/µL to 400 copies/mL.	To correct a typographical error in the previous protocol version.
Section 3.3.3	Added a statement to Exclusion Criterion #20, clarify that for patients with known, results from CD4+ count and viral load testing within a year of screening can be used to determine eligibility	To clarify CD4+ count and viral load testing must be performed within a year of screening to determine eligibility.
Section 3.3.4.1	Added a statement that if BI 765883 is discontinued, the patient can continue on gemcitabine and nab-paclitaxel	Requested by EMA.
Section 4.1.2.1	Added statement to clarify that no combination cohort will be tested without prior determination of safety of corresponding monotherapy cohort	Requested by EMA.

Section 4.1.4.1	Removed statement on flushing	To align with the Pharmacy Manual (IPAP).
Section 4.1.4.3	Added a statement that if BI 765883 is discontinued, the patient can continue on gemcitabine and nab-paclitaxel	Requested by EMA.
Section 4.1.4.4	Added a statement that if BI 765883 is discontinued, the patient can continue on gemcitabine and nab-paclitaxel	Requested by EMA.
Section 4.2.2.1	Removed statements concerning infusing heparin and BI 765883 through the same line	Heparin and BI 765883 should not be infused through the same line.
Section 4.2.3.7	Added new section, Pancreatic adverse events	To require imaging be performed if an elevation of amylase or lipase grade ≥ 3 is observed.
Section 5.2.3, Table 9	Clarified the type of testing required(quantitative or qualitative) for HBV, HCV, and HIV; added a statement that HIV testing is only necessary at screening for patients with unknown HIV status	To clarify lab HBV, HCV, and HIV testing.
Section 5.2.6.1.2	Added the definition of SUSAR	Definition omitted from prior protocol version.
Section 7.2.3.1	Revised the maximum allowable dose increment for each escalation step from 100% to 225%	To correct a typographical error in the previous protocol version.
Section 7.5	Revised the description of the total number of patients enrolled in the study	To describe patient numbers based on evaluable patients.
Section 8	Added statement on data protection	Required by EU CTR.

Section 8.4	Added the process for SAEs/AESIs and SUSARs reporting; Added definition of SUSAR	To provide clarity surrounding the safety reporting process and define SUSARs.
Section 8.5	Added statement on Data Protection Impact Assessment	Required by the EU CTR.
Throughout	Updated the protocol version number and date.	To align with the amendment number.
Throughout	Minor editorial (grammar, style, spelling) and document formatting revisions.	For clarity and/or internal consistency.

11.3 GLOBAL AMENDMENT 3

This amendment is considered to be non-substantial based on the criteria set forth in Regulation (EU) No 536 / 2014 of the European Parliament and the Council of the European Union because it does not impact the safety of participants, it does not change the interpretation of the scientific documents in support of the conduct of the trial, and is not otherwise significant.

Overall rationale for the amendment

Revisions to this clinical trial protocol are in response to EMA reviewer comments.

A high-level summary of changes and the rationale for the changes, is tabulated below.

Amendment and date of amendment	Amendment 3, 24 Feb 2025	
Global Amendment		X
Global Amendment due to urgent safety reasons		
Section changed	**Description of change**	**Rationale for change**
Synopsis, Inclusion Criteria	Inclusion criteria were revised to clarify the patient population.	To be consistent with revised inclusion criteria

		no. 9 and 10 in Section 3.3.1.
Section 3.1.1	Clarify backfill patient dosing timing	To clarify the requirement of a minimum of 48 h between patient dosing is not applicable for backfill patients.
Section 3.1.3	Additional enrollment stopping criteria added	To clarify events leading to a temporary stop of enrollment.
Section 3.3.2, Inclusion Criteria	Inclusion criteria 9 and 10 were revised to describe the patient population more clearly.	To clarify that Inclusion criterion 9 is for monotherapy cohorts only and Inclusion criterion 10 is for combination cohorts only.
Section 3.3.4.1	Changed the sentence, “The patient can no longer receive BI 765883 or gemcitabine for medical reasons such as surgery, AEs, other diseases, or pregnancy.” to “The patient can no longer receive BI 765883 and gemcitabine for medical reasons such as surgery, AEs, other diseases, or pregnancy.”	To clarify that if both gemcitabine and BI 765883 need to be discontinued, the patient must discontinue from the study.
Section 4.1.2.1	Clarify backfill patient dosing timing	To clarify the requirement of a minimum of 48 h between patient dosing is not applicable for backfill patients.
Section 4.1.4.1	Updated the title of the pharmacy manual	To reflect new terminology.

Section 4.2.2.3	Updated the acceptable methods of contraception to include condoms combined with a highly effective female method of contraception (hormonal birth control, IUD, IUS)	Required by the EU CTR.
Section 5.2.6.1.3	Removed statement regarding location of the list of “Always serious AEs”	To reflect change in template and transition of EDC from BRAVE to Veeva CDMS.
Section 10.2, Table 17	Revised the probabilities for Scenario 1	To correct a typographical error.
Throughout	Updated the protocol version number and date.	To align with the amendment number.
Throughout	Minor editorial (grammar, style, spelling) and document formatting revisions.	For clarity and/or internal consistency.

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