Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c17895778-08**
EudraCT No.	2018-003268-29	
BI Trial No.	1412-0001	
BI Investigational Medicinal Product(s)	BI 905711	
Title	A first-in-human phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in patients with advanced gastrointestinal cancers	
Lay Title	A study to find a safe and effective dose of BI 905711 in patients with advanced gastrointestinal cancer	
Clinical Phase	Ia/Ib	
Clinical Trial Leader	[redacted] Tel: [redacted]	
Coordinating Investigator	[redacted] Tel: [redacted]	
Status	Final Protocol (revised protocol [based on global Amendment 6])	
Version and Date	Version: 7.0	**Date: 17Apr2023**

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	20Feb2019
Revision date	17Apr2023
BI trial number	1412-0001
Title of trial	A first in human phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in patients with advanced gastrointestinal cancers
Coordinating Investigator	[redacted] Tel [redacted]
Trial site(s)	Multi-centre
Clinical phase	Ia/Ib
Trial rationale	This is a first in human study to explore BI 905711 safety and efficacy in advanced gastrointestinal cancer patients.
Trial objective(s)	Phase Ia: • Explore safety and establish maximum tolerated dose (MTD) of BI 905711 • Explore pharmacokinetics/pharmacodynamics and efficacy to guide determination of a potentially effective dose range for phase Ib in the absence of MTD Phase Ib: • Evaluate efficacy and safety of BI 905711 at a potentially effective dose range and determine RP2D (recommended dose for Phase 2)
Trial endpoints	Primary endpoints: Phase Ia: • Maximum tolerated dose (MTD) 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. • Number of patients with DLTs in the MTD evaluation period. Phase Ib: • Objective response (OR) based on RECIST 1.1 criteria • Progression-free survival (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.

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	Secondary endpoints: Phase Ia: • The following PK parameters of BI 905711 will be evaluated after the first and after the third administrations of BI 905711: o Cmax: maximum measured concentration of BI 905711 in plasma o AUC0-t2: area under the concentration-time curve of BI 905711 in plasma • Objective response based on RECIST 1.1 criteria Phase Ib: • The following PK parameters of BI 905711 will be evaluated after the first and after the third administrations of BI 905711: o Cmax: maximum measured concentration of BI 905711 in plasma o AUC0-t2: area under the concentration-time curve of BI 905711 in plasma • Number of patients with treatment-emergent AEs • Radiological (CT Scan) tumor shrinkage, defined as the difference between the minimum post-baseline sum of longest diameters of target lesions and the baseline sum of longest diameters of the same set of target lesions according to RECIST 1.1. • The duration of overall response is measured from the time measurement criteria are first met for Complete Response (CR)/ Partial Response (PR) (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study) according to RECIST 1.1. • Disease control, defined as CR, PR, or stable disease according to RECIST 1.1 from the start of treatment until the earliest of progression disease, death or last evaluable tumor assessment and before start of subsequent anti-cancer therapy.
Trial design	Phase Ia is an open-label, dose escalation study of BI 905711 administered intravenously. The eligible patient population will be patients with advanced refractory gastrointestinal cancers. Dose escalation will be guided by a Bayesian logistic regression model with overdose control. Pharmacokinetics and efficacy will be evaluated to guide determination of a potentially effective dose range for phase Ib. Phase Ib is a randomised, open label study to determine safety and efficacy of BI 905711 in the expansion cohorts of colorectal cancer (CRC) patients and pancreatic cancer (PDAC) patients. CRC

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	patients will be randomised into four cohorts (three dose levels in biweekly regimen and one dose level in weekly regimen (3 weeks on, 1 week off). PDAC patients will be enrolled into one cohort (3 weeks on, 1 week off).
Total number of patients	Approximately 140 evaluable patients
Number of patients on each treatment	Phase Ia (dose escalation): approximately 40 evaluable CRC patients and 20 non-CRC GI cancer patients. Phase Ib (dose expansion): approximately 60 evaluable CRC patients in 3 dose levels with 4 cohorts, and approximately 20 evaluable PDAC patients in 1 cohort.
Diagnosis	Patients with advanced, refractory gastrointestinal cancers of following histologies: • Colorectal adenocarcinoma • Gastric adenocarcinoma • Esophageal adenocarcinoma • Pancreatic adenocarcinoma • Cholangiocarcinoma and gallbladder carcinoma • Small intestine adenocarcinoma
In- and exclusion criteria	**Inclusion Criteria** 1. a. Phase Ia (dose escalation only) Histologically or cytologically confirmed, advanced unresectable or metastatic gastrointestinal cancers of following histologies: • Colorectal adenocarcinoma • Gastric adenocarcinoma • Esophageal adenocarcinoma • Pancreatic adenocarcinoma • Cholangiocarcinoma and gallbladder carcinoma • Small intestine adenocarcinoma b. Phase Ib (expansion phase) Histologically or cytologically confirmed, advanced unresectable or metastatic gastrointestinal cancers of following histologies: • Colorectal adenocarcinoma • CDH17 positive pancreatic adenocarcinoma (in tumour tissue as assessed by central testing) 2. Patient who has failed all available conventional therapies known to confer clinical benefit for their disease based on local approved standards. For patients with colorectal cancer, prior treatment with regorafenib or TAS-102 is optional. 3. a. Phase Ia (dose escalation) only: • Patient with either measurable or non-measurable/non-evaluable disease.

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b. Phase Ia (expanded cohort) and Phase Ib (expansion phase) only:
   - At least one target lesion that can be accurately measured per RECIST v.1.1.

4. Availability and willingness to provide archived tumor tissue specimen and to undergo tumor biopsy before treatment. Pre-treatment fresh tumor biopsy collections for biomarker analyses are considered optional in phase Ia and mandatory in phase Ib. Only non-significant risk procedures per the investigator's judgment will be used to obtain any biopsies specified in this study. In case a fresh tumor biopsy cannot be obtained due to before mentioned reasons an archived tumor tissue specimen obtained within ≤6 months of screening must be submitted. In case the patient undergoes baseline tumor biopsy, an archived tumor tissue specimen must be submitted regardless of date of collection.
5. Adequate hepatic, renal and bone marrow functions as defined by all of the below:
   a. Total bilirubin ≤ 1.5x institutional ULN (≤ 3 x ULN for patient with Gilbert's syndrome)
   b. ALT and AST ≤2.5 x institutional ULN (≤ 5x institutional ULN for patients with known liver metastases)
   c. Serum creatinine ≤1.5x institutional ULN. If creatinine is > 1.5 x ULN, patient is eligible if concurrent creatinine clearance ≥ 50 ml/min (≥ 0.05 L/min) (measured or calculated by CKD-EPI formula or Japanese version of CKD-EPI formula for Japanese patients).
   d. ANC ≥ 1.0x 10^9/L (≥ 1.0 x 10^3/µL, ≥ 1,000/mm^3)
   e. Platelets ≥ 100x10^9/ L (≥ 100 x 10^3/µL, ≥ 100 x 10^3/mm^3)
   f. Hemoglobin (Hb) ≥8.5 g/dl, ≥ 85 g/L, or ≥ 5.3 mmol/L (without transfusion within previous week)
   g. Phase Ia, and Phase Ib CRC cohort: Serum lipase ≤ 1.5 institutional ULN
   h. Phase Ib PDAC cohort: Serum lipase >1.5 - 2.0 x ULN or asymptomatic >2.0 - 5.0 x ULN if related to PDAC
6. Recovery from any adverse events according to CTCAE v5.0 of previous anti-cancer therapies to baseline or CTCAE grade 1, except for alopecia CTCAE grade 2, sensory peripheral neuropathy CTCAE grade ≤2 or considered not clinically significant.
7. ECOG performance status ≤ 1
8. Life expectancy ≥ 3 months in the opinion of the investigator
9. Of legal adult age (according to local legislation) at screening.
10. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
11. Male or female patients. Women of childbearing potential (WOCBP) and men able to father a child must be ready and able

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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 is provided in the protocol.

Exclusion criteria:

1. Previous systemic anti-cancer therapy within the specified timeframe from the last dose intake to the first dose of trial treatment as shown below:
    - Any non-investigational drug, including anti-angiogenic antibodies (bevacizumab or ramucirumab) and anti-EGFR antibodies (cetuximab or panitumumab), within 14 days.
    - Any investigational drug or other antibodies including immune checkpoint inhibitors, within 28 days.
2. Radiation therapy within 4 weeks prior to start of treatment. However, palliative radiotherapy for symptomatic metastasis is allowed if completed within 2 weeks prior to start of treatment but must be discussed with the sponsor.
3. 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 or active ulcers (gastro-intestinal tract, skin) or laboratory abnormality that may increase the risk associated with trial participation or trial drug administration, and in the judgment of the Investigator, would make the patient inappropriate for entry into the trial. Any history of stroke or myocardial infarction within 6 months prior to screening.
4. Known pathological condition of GI tract, liver and pancreas, excluding the disease under study, that may interfere with assessment of drug safety or increase the risk of toxicity:
    a. inflammatory bowel disease
    b. chronic pancreatitis
    c. other serious GI pathological conditions by judgment of the investigator e.g. autoimmune disease with GI involvement, unexplained active diarrhea CTCAE grade ≥2 according to CTCAE v5.0.
5. Known history of human immunodeficiency virus infection.
6. Any of the following laboratory evidence of hepatitis virus infection. Test results obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date:
    - Positive results of hepatitis B surface (HBs) antigen
    - Presence of HBc antibody together with HBV-DNA
    - Presence of hepatitis C RNA

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	7. Active concomitant malignancies, other than the one treated in this trial. 8. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes the patient an unreliable trial participant or unlikely to comply with the protocol requirements or not expected to complete the trial as scheduled. 9. Women who are pregnant, nursing, or who plan to become pregnant while in the trial; female patients who do not agree to the interruption of breast-feeding from the start of study treatment to within 30 days after the last study treatment. 10. 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 MRI. 11. Patients who are under judicial protection and patients who are legally institutionalized 12. Major surgery (major according to the investigator's assessment) performed within 3 weeks prior to treatment start or planned within 3 months after screening, e.g. hip replacement. 13. Any of the following cardiac criteria: • Resting corrected QT interval (QTc) >470 msec • Any clinically important abnormalities (as assessed by the Investigator) in rhythm, conduction, or morphology of resting ECGs, e.g., complete left bundle branch block, third degree heart block. • Patients with a known ejection fraction (EF) <50% or the lower limit of normal of the institutional standard will be excluded. Only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the EF, will the EF be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multigated acquisition scan). A historic measurement of EF no older than 6 months prior to first administration of study drug can be accepted provided that there is clinical evidence that the EF value has not worsened since this measurement in the opinion of the Investigator or of the treating physician or both. 14. Known hypersensitivity to the trial medication and/or its components *i.e.* polysorbate 20, sodium citrate, lysine hydrochloride, sucrose, citric acid.
Test product(s)	BI 905711
dose	Phase Ia: starting dose of 0.02 mg/kg

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	Phase Ib: CRC patients - Three dose levels with four cohorts: Biweekly dosing: 0.6mg/kg; 1.2 mg/kg; 2.4mg/kg Weekly dosing: 0.6mg/kg PDAC patients – One dose level with one cohort: Weekly dosing: 0.6mg/kg
method and route of administration	Intravenous
Duration of treatment	BI 905711 will be administered until disease progression, unacceptable toxicity, or other reasons requiring treatment discontinuation.
Safety criteria	Safety and tolerability of BI 905711 by evaluation of the incidence and severity of adverse events according to CTCAE v5.0 and DLTs, safety laboratory parameters, vital signs, and electrocardiograms (ECGs); and the determination of the MTD.
Statistical methods	Phase Ia: Dose escalation is guided by a Bayesian Logistic Regression Model (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. 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. Phase Ib: Primary and secondary endpoints will be analyzed descriptively. Bayesian hierarchical models will be applied to the multiple dose levels..

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FLOW CHART: PHASE IA – No longer applicable per CTP v7.0

		Treatment Period													Post-Treatment			
Visit	**Screen**	**Cycle 1***				**Cycle 2 *β**		**Cycle 3 *β**				**Cycle 4 * β**		**Cycle 5 and beyond *β**	**EOT****	**EOR *****	**FU for PD‡**	**FU for survival status‡**
Day (day range)	**-28 - 1**	**1 (+3)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**2**	**1 (+2)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**2**	**1 (+2)**	**Day 0-7 after last dose**	**30 (+5) days after last dose**		
Informed Consent[1]	x																	
Demographics	x																	
Medical History	x																	
In- /Exclusion Criteria	x	x																
Eligibility for re-treatment[2]						x		x				x		x				
Physical Examination[3]	x	x				x		x				x		x	x	x	x	
Height	x																	
Body weight[4]	x	x				x		x				x		x	x			
ECOG performance score[5]	x	x				x		x				x		x	x		x	
Pregnancy test[6]	x	x						x						x	x			
12-lead-ECG[7]	x	x				x		x				x		x	x			
Echocardiography (or multigated acquisition scan) [17]	x																	
Administration of BI 905711[8]		x				x		x				x		x				
Vital Signs	x	x	x	x	x	x		x				x		x	x			
Safety lab parameters[9]	x	x	x[9]		x	x		x				x		x	x	x	x	
Pharmacokinetics[10]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
ADA sampling[10]		x				x		x						x	x	x		

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FLOW CHART: PHASE IA (CONT.) – No longer applicable per CTP v7.0

		Treatment Period													**Post-Treatment**			
Visit	**Screen**	**Cycle 1***				**Cycle 2 *β**		**Cycle 3 *β**				**Cycle 4 * β**		**Cycle 5 and beyond *β**	**EOT****	**EOR *** **	**FU for PD‡**	**FU for survival status‡**
Day (day range)	**-28 - 1**	**1 (+3)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**2**	**1 (+2)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**2**	**1 (+2)**	**Day 0-7 after last dose**	**30 (+5) days after last dose**		
Fresh tumor biopsy (optional)[11]	x																	
Archival tumor tissue (mandatory)[12]		x																
[redacted]																		
[^{18}F]FDG-PET/CT [13]	x[13]	x[13]																
Adverse Events[14]	x	x	x	x	x	x	x	x	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		
Tumor assessment by CT/MRI RECIST 1.1[15]	x[15]	x[15]																
Termination of study medication															x			
Patient vital status																		x
Brain MRI (in phase Ia only)[16]	x																	

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(*) Each treatment Cycle has a duration of 14 days
(**) Patients who discontinue trial treatment prematurely should undergo the End of Treatment (EOT) visit as soon as possible. If assessments due at EOT are not completed, they may be performed at the 30-Day Safety FUP Visit.
(***) The 30-Day Safety Follow-up visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 (+ 5) days after the last dose of treatment (see Section 6.2.3.2).
ǂAdditional follow-up visits for progression after the 30-Day safety follow-up visit will be performed for patients who discontinue for reasons other than progression or death. Follow-up continues until progression per the imaging schedule (see Section 5.1). The follow-up visits for survival status will be performed every 12 weeks (+/-7 days)(in person or by telephone) until death, lost to follow-up, withdrawal of consent, or end of the whole trial (see Section 6.2.3.3).
ᵝFor every cycle, the interval between two dose administrations must be always at least 14 days.

[1]Written informed consent must be obtained before any protocol specific screening assessments are performed. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the Sponsor's instructions. Separate consent is to be obtained for optional biomarker sampling.
[2]Eligibility for further treatment should be confirmed prior to dosing on Day 1 of each cycle from Cycle 2 onwards by confirming the patient has not met any criteria for protocol discontinuation as described in section 3.3.4.1 and absence of any adverse event requiring treatment discontinuation (section 4.1.2.3).
[3]A full physical exam inclusive of vitals, height (at Screening only) and weight is to be performed at Screening, at Day 1 of each subsequent cycle, at EOT, at EOR, and at Follow-up for PD. Physical exam does not need to be repeated at Cycle 1 Day 1 if completed within 24hrs.
[4]If for logistical purposes patient weight may need to be calculated prior to Cycle 1 Day 1 in order to prepare the pharmacy order, the Cycle 1 Day 1 dose may be calculated based upon a patient weight obtained up to 3 days before administration if the body weight change is by ≤ 10% compared to the reference weight.
[5]ECOG assessment to be performed at Screening, Day 1 of each cycle, at EOT, and at Follow up for PD. ECOG does not need to be repeated at Cycle 1 Day 1 if completed within 24hrs.
[6]A urine pregnancy test is mandatory for female patients of childbearing potential at Screening. If the result is positive, a serum pregnancy test should be performed. A urine pregnancy test must be performed within 72 hours prior to start of study treatment, every 2 cycles (Cycle 3 Day 1, Cycle 5 Day 1, etc.) thereafter, and at EOT.
[7] ECG to be performed at Screening, Day 1 of each cycle, and at EOT.
[8] Dispensing of BI 905711 will be performed via the IRT. Assessment for signs and symptoms of infusion-related reactions and Cytokine Release Syndrome (CRS) is described in Sections 4.1.4.1.1 and 4.1.4.1.2.
[9]Includes Hematology, Biochemistry, Coagulation, and Urine. Refer to protocol Section 5.2.3 for specific laboratory requirements. Safety lab tests performed during screening do not need to be repeated at Cycle 1 Day 1 if performed within 10 days prior to treatment start and there is no clinical reason to repeat lab tests. During Cycle 1, safety labs should be performed at Day 1, and Day 8. On Cycle 1 Day 1, patients also need to have safety labs performed between 4-6 hours post-dose and repeated at 24-hour timepoint. A patient that experiences an elevated ALT and/or AST value after Cycle 1 Day 1 administration needs to have safety labs performed post-dose after the second and third administrations to assess ALT and AST values. During subsequent cycles, safety labs should be performed within 48 hours prior to each treatment administration as well as at EOR, EOT and at Follow up for PD. Safety lab tests are to be repeated as clinically indicated. At Screening visit, patients are to be tested for hepatitis virus infection which includes hepatitis B surface (HBs) antigen, presence of HBc antibody together with HBV-DNA, and presence of hepatitis C RNA. Results for hepatitis virus infection obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date.
[redacted]
[11]Pre-treatment fresh tumor biopsy collections for biomarker analyses are considered optional in phase Ia and mandatory in phase Ib. Only non-significant risk procedures per the investigator's judgment will be used to obtain any biopsies specified in this study. For each biopsy, a minimum of 2 core needle biopsies needs to be freshly taken between screening and before first study treatment (Cycle 1 Day 1) after eligibility has been confirmed. In case a fresh pre-treatment tumor biopsy cannot be obtained due to before mentioned reasons an archived tumor tissue specimen needs to be submitted.

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[12]For phase Ia, an archival tumor tissue is mandatory.
[13]In CRC patients, [^{18}F]FDG-PET/CT should be performed at baseline within 14 days (±7 days) prior to treatment start (Cycle 1 Day 1). A second [^{18}F]FDG-PET/CT will be performed at the 8-week tumor assessment timepoint. It may be performed together with standard CT assessment if feasible.
[14]After the individual patient's end of the trial, the investigator should report only any occurrence of cancer, related SAEs and related AESIs of which the investigator may become aware of and only via the SAE form, see Section 5.2.6.2.1.
[15]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. Tumor assessment does not need to be performed at the Screening visit if there are valid results available from assessments which were performed as part of routine clinical practice within 28 days prior to start of treatment. Repeat tumor assessment will be performed every 8 weeks (± 7 days) until progression or start of further treatment for disease:
Repeat imaging at > 4 weeks to confirm response. In the event of early discontinuation for reasons other than progressive disease or interruption/delay of treatment the tumor assessment schedule should not be changed. If the patient's cancer is being monitored with a specific tumor marker (e.g. CEA, CA19.9, etc.), tumor marker levels should be obtained at baseline, and at every protocol-specified tumor assessment timepoint.
[16]**During phase Ia only**, a brain MRI should be performed at baseline and repeated as clinically indicated. Brain MRI does not need to be performed at screening if there are results available from a brain MRI performed within 12 weeks prior to start of treatment. In case of contraindication for MRI, a brain CT scan can be performed after agreement between the investigator and Sponsor.
[17]To evaluate Exclusion criteria #13, only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the ejection fraction (EF), the EF will be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multigated acquisition scan). A historic measurement of EF no older than 6 months prior to first administration of study drug can be accepted provided that there is clinical evidence that the EF value has not worsened since this measurement in the opinion of the Investigator or of the treating physician or both. Echocardiography (or multigated acquisition scan) may be performed at any time during the study if clinically indicated.

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FLOW CHART: PHASE IB- BIWEEKLY DOSING – No longer applicable per CTP v7.0

		Treatment Period													Post-Treatment			
Visit	**Screen**	**Cycle 1***				**Cycle 2 *β**		**Cycle 3 *β**				**Cycle 4 * β**		**Cycle 5 and beyond *β**	**EOT****	**EOR *** **	**FU for PD‡**	**FU for survival status‡**
Day (day range)	**-28 - 1**	**1 (+3)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**3**	**1 (+2)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**2**	**1 (+2)**	**Day 0-7 after last dose**	**30 (+5) days after last dose**		
Informed Consent[1]	x																	
Demographics	x																	
Medical History	x																	
In- /Exclusion Criteria	x	x																
Eligibility for re-treatment[2]						x		x				x		x				
Physical Examination[3]	x	x				x		x				x		x	x	x	x	
Height	x																	
Body weight[4]	x	x				x		x				x		x	x			
ECOG performance score[5]	x	x				x		x				x		x	x		x	
Pregnancy test[6]	x	x						x						x	x			
12-lead-ECG[7]	x	x				x		x				x		x	x			
Echocardiography (or multigated acquisition scan)[8]	x																	
Randomization[4]		x																
Administration of BI 905711[9]		x				x		x				x		x				
Vital Signs	x	x	x	x	x	x		x				x		x	x			
Safety lab parameters[10]	x	x	x[9]		x	x		x				x		x	x	x	x	
Pharmacokinetics[11]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
ADA sampling[11]		x				x		x						x	x	x		

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FLOW CHART: PHASE IB- BIWEEKLY DOSING (CONT.) – No longer applicable per CTP v7.0

		Treatment Period													**Post-Treatment**			
Visit	**Screen**	**Cycle 1***				**Cycle 2 *β**		**Cycle 3 *β**				**Cycle 4 * β**		**Cycle 5 and beyond *β**	**EOT****	**EOR *****	**FU for PD‡**	**FU for survival status‡**
Day (day range)	**-28 - 1**	**1 (+3)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**3**	**1 (+2)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**2**	**1 (+2)**	**Day 0-7 after last dose**	**30 (+5) days after last dose**		
Fresh tumor biopsy[12]	x[12]						x[12]								x[12]			
Archival tumor tissue [12]	x[12]																	
[redacted]																		
[^{18}F]FDG-PET/CT [13]	x[13]	x[13]																
Adverse Events[14]	x	x	x	x	x	x	x	x	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		
Tumor assessment by CT/MRI RECIST 1.1[15]	x[15]	x[15]																
Tumor marker[16]	x[16]	x[16]																
Termination of study medication															x			
Patient vital status																		x

(*) Each treatment Cycle has a duration of 14 days
(**) Patients who discontinue trial treatment prematurely should undergo the End of Treatment (EOT) visit as soon as possible. If assessments due at EOT are not completed, they may be performed at the 30-Day Safety FUP Visit.

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(***) The 30-Day Safety Follow-up visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 (+ 5) days after the last dose of treatment (see Section 6.2.3.2).
ǂAdditional follow-up visits for progression after the 30-Day safety follow-up visit will be performed for patients who discontinue for reasons other than progression or death. Follow-up continues until progression per the imaging schedule (see Section 5.1). The follow-up visits for survival status will be performed every 12 weeks (+/-7 days)(in person or by telephone) until death, lost to follow-up, withdrawal of consent, or end of the whole trial (see Section 6.2.3.3).
ᵝFor every cycle, the interval between two dose administrations must be always at least 14 days.

[1]Written informed consent must be obtained before any protocol specific screening assessments are performed. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the Sponsor's instructions. Separate consent is to be obtained for optional biomarker sampling.
[2]Eligibility for further treatment should be confirmed prior to dosing on Day 1 of each cycle from Cycle 2 onwards by confirming the patient has not met any criteria for protocol discontinuation as described in section 3.3.4.1 and absence of any adverse event requiring treatment discontinuation (section 4.1.2.3).
[3]A full physical exam inclusive of vitals, height (at Screening only) and weight is to be performed at Screening, at Day 1 of each subsequent cycle, at EOT, at EOR, and at Follow-up for PD. Physical exam does not need to be repeated at Cycle 1 Day 1 if completed within 24hrs.
[4]If for logistical purposes patient weight may need to be calculated prior to Cycle 1 Day 1 in order to prepare the pharmacy order, the Cycle 1 Day 1 dose may be calculated based upon a patient weight obtained up to 3 days before administration if the body weight change is by ≤ 10% compared to the reference weight. In phase Ib, randomization will be performed in the IRT after eligibility has been confirmed.
[5]ECOG assessment to be performed at Screening, Day 1 of each cycle, at EOT, and at Follow up for PD. ECOG does not need to be repeated at Cycle 1 Day 1 if completed within 24hrs.
[6]A urine pregnancy test is mandatory for female patients of childbearing potential at Screening. If the result is positive, a serum pregnancy test should be performed. A urine pregnancy test must be performed within 72 hours prior to start of study treatment, every 2 cycles (Cycle 3 Day 1, Cycle 5 Day 1, etc.) thereafter, and at EOT.
[7]ECG to be performed at Screening, Day 1 of each cycle, and at EOT.
[8]To evaluate Exclusion criteria #13, only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the ejection fraction (EF), the EF will be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multigated acquisition scan). A historic measurement of EF no older than 6 months prior to first administration of study drug can be accepted provided that there is clinical evidence that the EF value has not worsened since this measurement in the opinion of the Investigator or of the treating physician or both. Echocardiography (or multigated acquisition scan) may be performed at any time during the study if clinically indicated.
[9]Dispensing of BI 905711 will be performed via the IRT. Assessment for signs and symptoms of infusion-related reactions and Cytokine Release Syndrome (CRS) is described in Sections 4.1.4.1.1 and 4.1.4.1.2.
[10]Includes Hematology, Biochemistry, Coagulation, and Urine. Refer to protocol Section 5.2.3 for specific laboratory requirements. Safety lab tests performed during screening do not need to be repeated at Cycle 1 Day 1 if performed within 10 days prior to treatment start and there is no clinical reason to repeat lab tests. During Cycle 1, safety labs should be performed at Day 1, and Day 8. On Cycle 1 Day 1, patients also need to have safety labs performed between 4-6 hours post-dose and repeated at 24 hour timepoint. A patient that experiences an elevated ALT and/or AST value after Cycle 1 Day 1 administration needs to have safety labs performed post-dose after the second and third administrations to assess ALT and AST values. During subsequent cycles, safety labs should be performed within 48 hours prior to each treatment administration as well as at EOT, EOR and at Follow up for PD. Safety lab tests are to be repeated as clinically indicated. At Screening visit, patients are to be tested for hepatitis virus infection which includes hepatitis B surface (HBs) antigen, presence of HBc antibody together with HBV-DNA, and presence of hepatitis C RNA. Results for hepatitis virus infection obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date.

[redacted]

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[12]Pre-treatment fresh tumor biopsy collections for biomarker analyses are considered mandatory in phase Ib. Only non-significant risk procedures per the investigator's judgment will be used to obtain any biopsies specified in this study. For each biopsy, a minimum of 2 core needle biopsies needs to be freshly taken between screening and before first study treatment (Cycle 1 Day 1) after eligibility has been confirmed. In case a fresh pre-treatment tumor biopsy cannot be obtained due to before mentioned reasons an archived tumor tissue specimen obtained within ≤6 months of screening must be submitted. In case the patient undergoes baseline tumor biopsy, an archival tumor tissue must also be submitted (mandatory) regardless of the date of collection. An additional fresh tumor biopsy should be taken on Cycle 2 Day 3 (optional) and/or at disease progression (optional) for a patient in which a fresh biopsy has been successfully obtained before first study treatment (refer to Section 5.4.1).[13][^{18}F]FDG-PET/CT should be performed at baseline within 14 days (±7 days) prior to treatment start (Cycle 1 Day 1). A second [^{18}F]FDG-PET/CT will be performed at the 8 week tumor assessment timepoint. It may be performed together with standard CT assessment if feasible.
[14]After the individual patient's end of the trial, the investigator should report only any occurrence of cancer, related SAEs and related AESIs of which the investigator may become aware of and only via the SAE form, see Section 5.2.6.2.1.
[15]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. At least one prior pre-study digital scan of the target lesion should be sent to the central imaging facility of an independent vendor if available. Tumor assessment does not need to be performed at the Screening visit if there are valid results available from assessments which were performed as part of routine clinical practice within 28 days prior to start of treatment. Repeat tumor assessment will be performed every 8 weeks (± 7 days) until progression or start of further treatment for disease:
Repeat imaging at > 4 weeks to confirm response. In the event of early discontinuation for reasons other than progressive disease or interruption/delay of treatment the tumor assessment schedule should not be changed.
[16]Patient's cancer will be monitored with a specific tumor marker (e.g. CEA, CA19.9, etc.). Tumor marker levels should be obtained at baseline, and at every protocol-specified tumor assessment timepoint.

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FLOW CHART: PHASE IB- WEEKLY DOSING – No longer applicable per CTP v7.0

			Treatment Period															Post-Treatment			
Visit	**SV1**[18]	**SV2**[18] **/ Screen**	**Cycle 1***				**Cycle 2 *β**		**Cycle 3 *β**				**Cycle 4 *β**		**Odd cycles (e.g. 5, 7, 9, etc) *β**		**Even cycles (e.g. 6, 8, 10, etc) *β**	**EOT****	**EOR *****	**FU for PD‡**	**FU for survival status‡**
Day (day range)	**Any time before SV2**	**-28 - 1**	**1 (+3)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**3**	**1 (+2)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**2**	**1 (+2)**	**8 (± 3)**	**1 (+2)**	**Day 0-7 after last dose**	**30 (+5) days after last dose**		
Tissue analysis consent	x[18]																				
CDH17 status analysis	x[18]																				
Informed Consent[1]		x																			
Demographics		x																			
Medical History		x																			
In- /Exclusion Criteria		x	x																		
Eligibility for re-treatment[2]							x		x				x		x		x				
Physical Examination[3]		x	x				x		x				x		x		x	x	x	x	
Height		x																			
Body weight[4]		x	x				x		x				x		x		x	x			
ECOG performance score[5]		x	x				x		x				x		x		x	x		x	
Pregnancy test[6]		x	x						x						x		x	x			
12-lead-ECG[7]		x	x				x		x				x		x		x	x			
Echocardiography (or multigated acquisition scan)[8]		x																			

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FLOW CHART: PHASE IB- WEEKLY DOSING (CONT.) – No longer applicable per CTP v7.0

			Treatment Period															**Post-Treatment**			
Visit	**SV1**[18]	**SV2**[18] **/ Screen**	**Cycle 1***				**Cycle 2 *β**		**Cycle 3 *β**				**Cycle 4 *β**		**Odd cycles (e.g. 5, 7, 9, etc) *β**		**Even cycles (e.g. 6, 8, 10, etc) *β**	**EOT****	**EOR *****	**FU for PD‡**	**FU for survival status‡**
Day (day range)	**Any time before SV2**	**-28 - 1**	**1 (+3)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**3**	**1 (+2)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**2**	**1 (+2)**	**8 (± 3)**	**1 (+2)**	**Day 0-7 after last dose**	**30 (+5) days after last dose**		
Randomisation[4]			x																		
Administration of BI 905711[9,17]			x[17]			x[17]	x[17]		x[17]			x[17]	x[17]		x[17]	x[17]	x[17]				
Vital Signs		x	x	x	x	x	x		x			x	x		x	x	x	x			
Safety lab parameters[10]		x	x	x[10]		x	x		x			x	x		x	x	x	x	x	x	
Pharmacokinetics[11]			x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x		
ADA sampling[11]			x				x		x						x		x	x	x		
Fresh tumor biopsy[12]	x[12,18]	x[12]						x[12]										x[12]			
Archival tumor tissue[12]	x[12,18]	x[12]																			
[redacted]																					
[^{18}F]FDG-PET/CT [13]		x[13]	x[13]																		
Adverse Events[14]		x	x	x	X	x	x	x	x	x	x	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	x		

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FLOW CHART: PHASE IB- WEEKLY DOSING (CONT.) – No longer applicable per CTP v7.0

			Treatment Period															Post-Treatment			
Visit	**SV1[18]**	**SV2[18] / Screen**	**Cycle 1***				**Cycle 2 *β**		**Cycle 3 *β**				**Cycle 4 *β**		**Odd cycles (e.g. 5, 7, 9, etc) *β**		**Even cycles (e.g. 6, 8, 10, etc) *β**	**EOT**	**EOR**	**FU for PD‡**	**FU for survival status‡**
Day (day range)	**Any time before SV2**	**-28 - 1**	**1 (+3)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**3**	**1 (+2)**	**2**	**3**	**8 (± 3)**	**1 (+2)**	**2**	**1 (+2)**	**8 (± 3)**	**1 (+2)**	**Day 0-7 after last dose**	**30 (+5) days after last dose**		
Tumor assessment by CT/MRI RECIST 1.1[15]		x[15]	x[15]																		
Tumor marker[16]		x[16]	x[16]																		
Termination of study medication																		x			
Patient vital status																					x

(*) Each treatment Cycle has a duration of 14 days
(**) Patients who discontinue trial treatment prematurely should undergo the End of Treatment (EOT) visit as soon as possible. If assessments due at EOT are not completed, they may be performed at the 30-Day Safety FUP Visit.
(***) The 30-Day Safety Followup visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 (+ 5) days after the last dose of treatment (see Section 6.2.3.2).
‡Additional follow-up visits for progression after the 30-Day safety follow-up visit will be performed for patients who discontinue for reasons other than progression or death. Follow-up continues until progression per the imaging schedule (see Section 5.1). The follow-up visits for survival status will be performed every 12 weeks (+/-7 days)(in person or by telephone) until death, lost to follow-up, withdrawal of consent, or end of the whole trial (see Section 6.2.3.3).
βThe interval between two dose administrations must be always at least 7 days with the exception of the interval between dose administration on Day 1 of an even-numbered cycle and Day 1 of the subsequent odd-number cycle which must always be at least 14 days (e.g. Cycle 2 Day 1 and Cycle 3 Day 1, Cycle 4 Day 1 and Cycle 5 Day 1, etc.).

[1]Written informed consent must be obtained before any protocol specific screening assessments are performed. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the Sponsor's instructions. Separate consent is to be obtained for optional biomarker sampling.

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[2]Eligibility for further treatment should be confirmed prior to dosing on Day 1 of each cycle from Cycle 2 onwards by confirming the patient has not met any criteria for protocol discontinuation as described in section 3.3.4.1 and absence of any adverse event requiring treatment discontinuation (section 4.1.2.3).

[3]A full physical exam inclusive of vitals, height (at Screening only) and weight is to be performed at Screening, at Day 1 of each subsequent cycle, at EOT, at EOR, and at Follow-up for PD. Physical exam does not need to be repeated at Cycle 1 Day 1 if completed within 24hrs.

[4]If for logistical purposes patient weight may need to be calculated prior to Cycle 1 Day 1 in order to prepare the pharmacy order, the Cycle 1 Day 1 dose may be calculated based upon a patient weight obtained up to 3 days before administration if the body weight change is by ≤ 10% compared to the reference weight. In phase Ib, randomization will be performed in the IRT after eligibility has been confirmed.

[5]ECOG assessment to be performed at Screening, Day 1 of each cycle, at EOT, and at Follow up for PD. ECOG does not need to be repeated at Cycle 1 Day 1 if completed within 24hrs.

[6]A urine pregnancy test is mandatory for female patients of childbearing potential at Screening. If the result is positive, a serum pregnancy test should be performed. A urine pregnancy test must be performed within 72 hours prior to start of study treatment, every 2 cycles (Cycle 3 Day 1, Cycle 5 Day 1, etc.) thereafter, and at EOT.

[7] ECG to be performed at Screening, Day 1 of each cycle, and at EOT.

[8]To evaluate Exclusion criteria #13, only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the ejection fraction (EF), the EF will be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multigated acquisition scan). A historic measurement of EF no older than 6 months prior to first administration of study drug can be accepted provided that there is clinical evidence that the EF value has not worsened since this measurement in the opinion of the Investigator or of the treating physician or both. Echocardiography (or multigated acquisition scan) may be performed at any time during the study if clinically indicated.

[9] Dispensing of BI 905711 will be performed via the IRT. Assessment for signs and symptoms of infusion-related reactions and Cytokine Release Syndrome (CRS) is described in Sections 4.1.4.1.1 and 4.1.4.1.2.

[10]Includes Hematology, Biochemistry, Coagulation, and Urine. Refer to protocol Section 5.2.3 for specific laboratory requirements. Safety lab tests performed during screening do not need to be repeated at Cycle 1 Day 1 if performed within 10 days prior to treatment start and there is no clinical reason to repeat lab tests. During Cycle 1, safety labs should be performed at Day 1, and Day 8. On Cycle 1 Day 1, patients also need to have safety labs performed between 4-6 hours post-dose and repeated at 24 hour timepoint. A patient that experiences an elevated ALT and/or AST value after Cycle 1 Day 1 administration needs to have safety labs performed post-dose after the second and third administrations to assess ALT and AST values. During subsequent cycles, safety labs should be performed within 48 hours prior to each treatment administration as well as at EOT, EOR and at Follow up for PD. Safety lab tests are to be repeated as clinically indicated. At Screening visit, patients are to be tested for hepatitis virus infection which includes hepatitis B surface (HBs) antigen, presence of HBc antibody together with HBV-DNA, and presence of hepatitis C RNA. Results for hepatitis virus infection obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date.

[redacted]

[12]Pre-treatment fresh tumor biopsy collections for biomarker analyses are considered mandatory in phase Ib. Only non-significant risk procedures per the investigator's judgment will be used to obtain any biopsies specified in this study. For each biopsy, a minimum of 2 core needle biopsies needs to be freshly taken between screening and before first study treatment (Cycle 1 Day 1) after eligibility has been confirmed. In case a fresh pre-treatment tumor biopsy cannot be obtained due to before mentioned reasons an archived tumor tissue obtained within ≤6 months of screening specimen must be submitted. In case the patient undergoes baseline tumor biopsy, an archival tumor tissue must also be submitted (mandatory) regardless of the date of collection. An additional fresh tumor biopsy should be taken on Cycle 2 Day 3 (optional) and /or at disease progression (optional) for a patient in which a fresh biopsy has been successfully obtained before first study treatment (refer to Section 5.4.1).
For the PDAC cohort, a pre-treatment biopsy will be used to measure CDH17 positivity and direct patient enrolment. Therefore, biopsies must be immediately sent to the designated vendor (see lab manual for shipment instructions).

[13][^{18}F]FDG-PET/CT should be performed at baseline within 14 days (±7 days) prior to treatment start (Cycle 1 Day 1). A second [^{18}F]FDG-PET/CT will be performed at the 8 week tumor assessment timepoint. It may be performed together with standard CT assessment if feasible.

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[14]After the individual patient's end of the trial, the investigator should report only any occurrence of cancer, related SAEs and related AESIs of which the investigator may become aware of and only via the SAE form, see Section 5.2.6.2.1.
[15]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. At least one prior pre-study digital scan of the target lesion should be sent to the central imaging facility of an independent vendor if available. Tumor assessment does not need to be performed at the Screening visit if there are valid results available from assessments which were performed as part of routine clinical practice within 28 days prior to start of treatment. Repeat tumor assessment will be performed every 8 weeks (± 7 days) until progression or start of further treatment for disease:
Repeat imaging at > 4 weeks to confirm response. In the event of early discontinuation for reasons other than progressive disease or interruption/delay of treatment the tumor assessment schedule should not be changed.
[16]Patient's cancer will be monitored with a specific tumor marker (e.g. CEA, CA19.9, etc.). Tumor marker levels should be obtained at baseline, and at every protocol-specified tumor assessment timepoint.
[17]A patient will receive BI 905711 as a single administration every week for 3 weeks on, 1 week off (refer to Section 4.1.2.2).
[18]Required only for phase Ib PDAC cohort. SV1 and SV2 can occur in parallel.

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FLOW CHART: PHASE 1B – BIWEEKLY - REDUCED SCHEDULE PER CTP V7.0 – ONGOING PATIENTS

	Treatment Cycle 6and subsequent cycles*	**Post-Treatment**	
Visit	**CxD1[a]**	**EOT****	**EOR / EOS*****
Day (day range)	**1 (+2)**	**Day 0-7 after last dose**	**30 (+5) days after last dose**
Physical Examination and Vital Signs	Per institutional practice[6]		
Safety lab parameters	Per institutional practice[6]		
Tumor assessment by CT/MRI RECIST 1.1[1]	Per institutional practice		
Pregnancy test[2]	Per institutional practice[6]		
12-lead-ECG	Per institutional practice[6]		
Body weight	x		
Administration of BI 905711[3]	x		
Adverse Events[4]	x	x	x
Concomitant therapy[5]	x	x	x
Termination of study medication		x	

(*) Each treatment Cycle has a duration of 14 days(**) Patients who discontinue trial treatment prematurely should undergo the End of Treatment (EOT) visit as soon as possible. If assessments due at EOT are not completed, they may be performed at the 30-Day Safety FUP (i.e. EOR) Visit.
(***) This combined visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 (+ 5) days after the last dose of treatment (see Section 6.2.3.2).

[a]x is the number of the treatment cycle

[1]Tumor assessment will be performed according to institutional practices. Images no longer need to be sent to imaging vendor. Only overall response and disease progression will be collected in the electronic CRF.
[2]Serum and/or urine pregnancy testing to be performed for female patients of childbearing potential as per institutional practice.
[3] Dispensing of BI 905711 will be performed via the IRT. Assessment for signs and symptoms of infusion-related reactions and Cytokine Release Syndrome (CRS) is described in Sections 4.1.4.1.1 and 4.1.4.1.2.

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[4] After the individual patient's end of trial: the investigator does not need to actively monitor for new AEs but should only report any occurrence of cancer of new histology, trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of and only via the SAE form, see Section 5.2.6.2.1.
[5]Concomitant medications that are used to treat adverse events.
[6] The results of these assessments will be documented in the source data, but will not be collected in the eCRF. Findings which qualify as an (S)AE will be reported in the eCRF, and in case of an SAE, on the SAE form.

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FLOW CHART: PHASE 1B – WEEKLY - REDUCED SCHEDULE PER CTP V7.0 – ONGOING PATIENTS

	Treatment Cycle 6 and subsequent cycles*			**Post-Treatment**	
Visit	**Even cycles (e.g. 6, 8, 10)**	**Odd cycles (e.g. 7, 9, 11)**		**EOT****	**EOR / EOS*****
Day (day range)	**1 (+2)**	**1 (+2)**	**8 (± 3)**	**Day 0-7 after last dose**	**30 (+5) days after last dose**
Physical Examination and Vital Signs	Per institutional practice[6]				
Safety lab parameters	Per institutional practice[6]				
Tumor assessment by CT/MRI RECIST 1.1[1]	Per institutional practice				
Pregnancy test[2]	Per institutional practice[6]				
12-lead-ECG	Per institutional practice[6]				
Body weight	x	x			
Administration of BI 905711[3]	x	x	x		
Adverse Events[4]	x	x	x	x	x
Concomitant therapy[5]	x	x	x	x	x
Termination of study medication				x	

(*) Each treatment Cycle has a duration of 14 days
(**) Patients who discontinue trial treatment prematurely should undergo the End of Treatment (EOT) visit as soon as possible. If assessments due at EOT are not completed, they may be performed at the 30-Day Safety FUP Visit.
(***) This combined visit is the End of Residual Effect Period visit (EOR) which must happen at the earliest 30 (+ 5) days after the last dose of treatment (see Section 6.2.3.2).

[1]Tumor assessment will be performed according to institutional practices. Images no longer need to be sent to imaging vendor. Only overall response and disease progression will be collected in the electronic CRF.
[2]Serum and/or urine pregnancy testing to be performed for female patients of childbearing potential as per institutional practice.
[3] Dispensing of BI 905711 will be performed via the IRT. Assessment for signs and symptoms of infusion-related reactions and Cytokine Release Syndrome (CRS) is described in Sections 4.1.4.1.1 and 4.1.4.1.2.
[4] After the individual patient's end of trial: the investigator does not need to actively monitor for new AEs but should only report any occurrence of cancer of new histology, trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of and only via the SAE form, see Section 5.2.6.2.1.

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[5]Concomitant medications that are used to treat adverse events.
[6] The results of these assessments will be documented in the source data, but will not be collected in the eCRF. Findings which qualify as an (S)AE will be reported in the eCRF, and in case of an SAE, on the SAE form.

Applicable to all patients ongoing patients:

After implementation of CTP v7.0, the patient will have assessments as medically indicated to monitor the safety at the discretion of the investigator. These assessments may include: physical examination, vital sign, safety lab and ECG at a frequency decided by the investigator. The study treatment is administered and the administration information will be documented in the eCRF. Tumour assessment will be performed according to standard of care based on medical opinion of the investigator.

The results of any assessments will be documented in the source data, but will not be collected in the eCRF, except tumor assement (overall response and progression date).

Findings which qualify as an (S)AE will be reported in the eCRF and in case of an SAE, on the SAE form (timelines and distribution requirements for SAEs apply).

The data collection is required only for the following items:

- Adverse events
- Concomitant medications that are used to treat adverse events
- Drug admistration information
- Dose changes
- Tumor assessment (overall response and progression date).
- At EOT visit: visit date, end of treatment – BI 905711, and subject retention
- At safety follow-up visit: visit date and end of study page
- Death details (if applicable)

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ABBREVIATIONS

AE	Adverse Event
ADA	Anti-drug Antibodies
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
AUC	Area under the Curve
BHM	Bayesian Hierarchical Model
b.i.d.	bis in die (twice daily dosing)
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
CA	Competent Authority
cfDNA	Circulating free DNA
CI	Confidence Interval
C_{max}	Maximum Concentration
C_{min}	Minimum Plasma Concentration
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organization
CRS	Cytokine release syndrome
ctDNA	Circulating tumor DNA
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

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eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EoT	End of Treatment
EudraCT	European Clinical Trials Database
EWOC	Escalation with Overdose Control
[^{18}F]FDG-PET	[^{18}F]Fluorodeoxyglucose-Positron Emission Tomography
FIH	First in Human
FUP	Follow Up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HA	Health Authority
HED	Human equivalent dose
HNSTD	Highest Non-Severely Toxic Dose
i.v.	Intravenous
IB	Investigator's Brochure
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemical
INN	International Non-Proprietary Name
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LMWH	Low Molecular Weight Heparin
LPLT	Last Patient Last Treatment
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Activities
MTD	Maximum Tolerated Dose
NGS	Next Generation Sequencing
NOAEL	No Observed Adverse Effect Level
OPU	Operative Unit
OR	Objective Response

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ORR	Objective Response Rate
PD	Progressive disease
PDAC	Pancreatic Ductal Adenocarcinoma
PFS	Progression-free survival
p.o.	per os (oral)
PK	Pharmacokinetics
PR	Partial Response
q.d.	quaque die (once a day)
Q1W	Once per week
Q2W	Once every 2 weeks
RA	Regulatory Authority
REP	Residual Effect Period
RP2D	Recommended Phase 2 Dose
s.c.	subcutaneous
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOI	Start of infusion
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Half Life Time
t_{max}	Timepoint of Maximum Plasma Concentration
TMF	Trial Master File
ULN	Upper Level of Normal
WHO	World Health Organization
WOCBP	Woman of childbearing potential

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1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Tumor cell death and apoptosis can be induced by activation of the extrinsic pathway via targeting TRAIL receptors (R16-1878). TRAILR2 pathway represents a valid opportunity for cancer treatment, but it has not been successful in the clinic so far. Multiple clinical trials with conventional antibodies against TRAILR2 indicated minimal clinical activity with no toxicity, and these compounds have been discontinued (P16-04691).

Targeting TRAILR2 requires agonistic properties of a potential drug candidate, and this is difficult to achieve with conventional antibodies (R17-2985). Available data suggest that activation of TRAIL receptor depends not only on binding of the ligand to the receptor but require formation of complex higher level receptor-ligand multimeric structures. Such receptor clustering is critical for generation of an adequate signal capable of down-stream propagation and apoptosis induction (R17-2986). Agonistic properties of conventional TRAILR2 targeting antibodies can be highly enhanced by antibody immobilisation via binding of their Fc part on the solid surface *in-vitro* or FcR cross-linking on membrane of the tumor infiltrating immune cells *in-vivo* (R17-2987). It is likely that first generation conventional TRAILR2 antibodies had very weak and inconsistent agonistic potential for TRAILR2 in human clinical trials related to the above mentioned reasons e.g. high level of endogenous immunoglobulins that were effectively competing for Fc gamma receptors on immune cells in-vivo and/or low and a variable number of immune cells in the tumor microenvironment (P16-04691).

New pharmacological approaches are needed that would overcome above mentioned limitation of conventional antibodies and capable to activate TRAIL receptors independently of Fc interactions. BI 905711 is a tetravalent bispecific molecule targeting both TRAILR2 and CDH17, and it is designed to selectively induce apoptosis in CDH17 expressing tumor cells via the CDH17-dependent clustering of TRAILR2. CDH17 is a cell surface molecule expressed in adenocarcinomas of gastrointestinal origin (R18-1615). Via the CDH17-dependent clustering of TRAILR2, BI 905711 induces the pro-apoptotic activity independently of additional cross-linking (R17-4112) and selectively in CDH17 expressing tumor cells. The L234A/L235A mutation was incorporated to specifically avoid CDH17-independent crosslinking by ablating binding to FcγR and complements.
BI 905711 has the potential to provide a therapeutic window and avoid hepatotoxicity associated with clustering of TRAILR2 and apoptosis in the liver (R16-1795) due to the lack of detectable CDH17 protein in non-neoplastic liver tissue (R17-2598). The limited set of non-neoplastic tissues with CDH17 expression (small intestine, colon, gastric mucosa, gall bladder and pancreas ducts) should be spared from apoptosis and tissue damage due to their insensitivity to TRAILR2 activation (R17-4113, R16-4563).

Potential indications for BI 905711 include gastrointestinal cancers expressing CDH17: colorectal cancer, gastric cancer, oesophageal adenocarcinoma, pancreatic cancer and biliary tract cancers as indicated in Table 1.1: 1

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Table 1.1: 1 Gastrointestinal cancers expressing CDH17. Percentage indicate relative number of positive tumors for CDH17 by IHC/IF* according to tumor origin and histology type.

	Altree-Tacha et al, 2017 (R18-2263)	Panarelli et al, 2012 R18-1615	BI's Prevalence study (data on file)
Colon adenocarcinoma	97%	100%	100%[#]
Esophageal adenocarcinoma	39%	82%	48%
Gastric adenocarcinoma	64%	90%	84%
Pancreatic ductal adenocarcinoma	39%	50%	70%
Cholangiocarcinoma	33%	53%	

* Method and threshold for CDH17-positivity by IHC vary between reports. For BI's prevalence study, positive tumors have ≥5% CDH17 positive cells.
[#]only metastatic samples

Colorectal cancer (CRC) consistently expresses CDH17 at a high or intermediate level by immunohistochemistry in primary tumors and metastatic sites (R17-2598, R18-1615). High CDH17 expression in CRC was confirmed in a BI prevalence study where metastatic CRC samples showed CDH17 expression in 100 % of the samples analyzed (n=39), and 97% of the samples showed CDH17 expression on over 50% of the tumor cells (77% of samples with >90% positive cells). Expression of CDH17 in gastric cancer, oesophageal adenocarcinoma, pancreatic cancer and biliary tract cancers is more variable.

The rate of positive CRC tumors with ≥5% CDH17 positive cells in 1412-0001 phase 1a was 95%, with 78.5% being double-positive for CDH17/TRAILR2 (data on file).

It is important to recognize that BI 905711 can potentially activate TRAILR2 on both CDH17 positive tumor cells and adjacent tumor cells (cis- and trans-activation). BI 905711 can therefore induce TRAILR2 activation in the CDH17 negative cells if surrounded by CDH17 positive cells. Nevertheless, possible correlation between quantitative CDH17 expression and efficacy will be explored in this study.

For a more detailed description of the BI 905711 profile, refer to the current Investigator's Brochure (IB).

1.2 DRUG PROFILE

Mode of action

BI 905711 is tetravalent bispecific antibody specifically designed to have potent agonistic activity via the CDH17-dependent clustering of TRAILR2 and therefore induces apoptosis in CDH17 expressing tumor cells. Refer also to the IB for additional details (c16856466).

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CDH17 is a cell surface molecule expressed in different gastrointestinal adenocarcinomas (R17-4114). In humans, CDH17 is also present in normal cells of stomach, intestine, pancreas and gall bladder, but it is not expressed in liver tissue. Normal GI tissues were shown to be resistant to TRAILR2 induced apoptosis (R16-4563) while the liver may be sensitive to TRAILR2 activation (R16-1795). BI 905711 should achieve a therapeutic window by avoiding liver toxicity due to lack of CDH17 on hepatocytes (R17-2598), avoiding GI toxicity due to high threshold for TRAILR2 mediated apoptosis in normal cells of the GI tract (R16-4563). These expectations are supported by extensive pre-clinical data as described in the IB (c16856466) and summarized in the following sections.

Absorption, bioavailability, distribution, metabolism, and excretion

No human data are available. The information below is based on preclinical considerations.

Distribution
No dedicated distribution studies have been performed. In the cynomolgus monkey, Cmax and AUC0-168 increased approximately dose-proportionally upon dosing for all dosing groups (1, 10, 30, and 100mg/kg), and it is expected that distribution of BI 905711 will be mostly distributed to the blood after IV administration in a manner typical of IgG molecules (c16856466). Once distributed from intravascular space into the tissues, BI 905711 is expected to bind CDH17 and TRAILR2. CDH17 in expressed in pancreas, small and large intestine, gall bladder, and target tumor tissue. TRAILR2 is broadly expressed in tumors and to some extent in normal tissues particularly liver (R18-2045, R17-4113).

Metabolism
BI 905711 is a protein and is expected to undergo protein catabolism in animals and humans to peptides and amino acids. Dedicated metabolism studies were not conducted for BI 905711.

Excretion
The molecular weight of BI 905711 is approximately 201 kDa, which is above the renal filtration cut-off threshold (approximately 60 kDa). Dedicated excretion studies were not conducted.

Pharmacokinetic drug interactions
BI 905711 is a therapeutic protein, and its clearance is through protein catabolism. BI 905711 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, pharmacokinetic drug interaction between BI 905711 and co-administered small molecule drugs is not expected.

Residual Effect Period
The expected Residual Effect Period (REP) of BI 905711 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.

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Non-clinical studies

BI 905711 demonstrated high preclinical activity in-vitro and in-vivo for CDH17 positive tumor cell lines in extensive batteries of pre-clinical experiments fully described in the IB. A short summary is given below.

The sensitivity of a panel of 24 CDH17-positive colorectal cancer cell lines to BI 905711 treatment was evaluated and is shown in Figure1.2: 1. A V-shaped dose-response is predicted for this bi-specific MoA where concentrations above the optimum will favor individual target recruitment, thus preventing TRAILR2 cross-linking and therefore reducing efficacy. Within the range of concentrations tested, different cell lines showed a reduced efficacy when using higher than optimal doses. Importantly, despite differences in CDH17 and TRAILR2 protein expression levels and the intrinsic sensitivity to TRAILR2 agonists among these cells, there was a common concentration range inducing the maximal effect for all of them (Figure 1.2: 1)

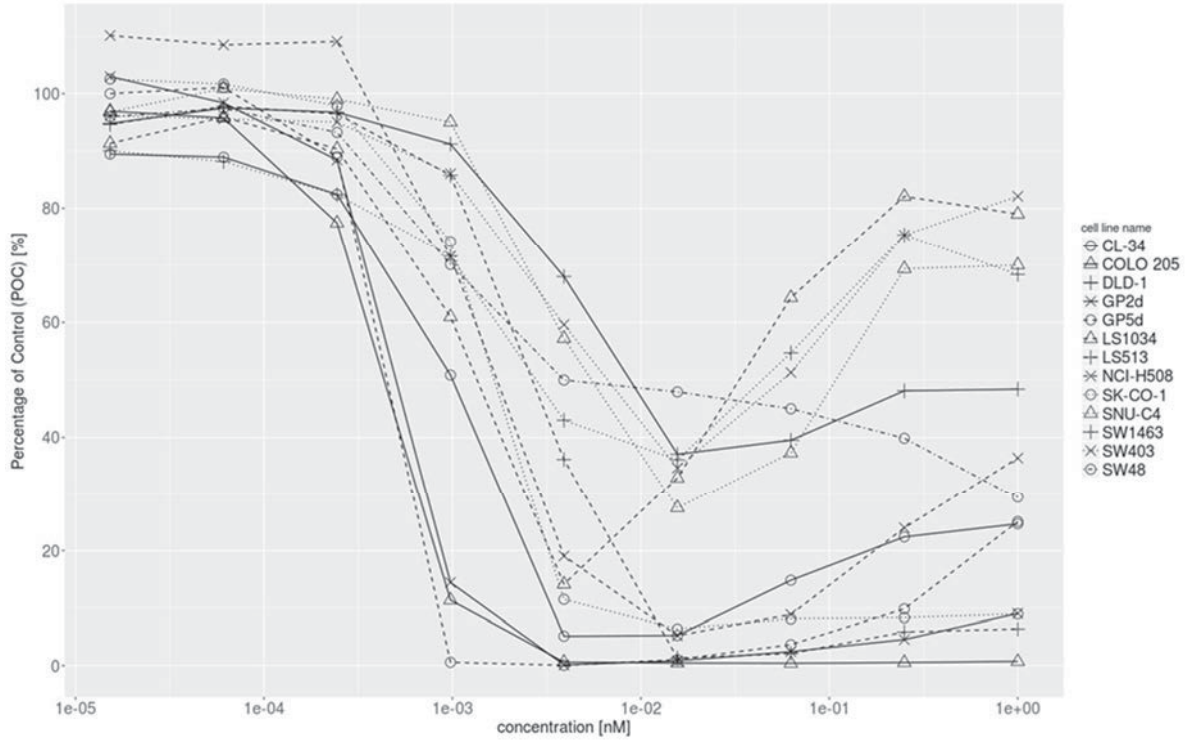

Figure 1.2: 1 Dose response graph of CRC cell lines classified as sensitive to BI 905711 as determined in the Cell Titer-Glo assay. Within the range of concentrations tested, different cell lines showed a V-shaped dose-response curve, and reduced efficacy was detected when using higher than optimal doses (c16856466).

BI 905711 was also tested in CDH17 negative liver-derived cells, and Hep G2 was used as a surrogate for TRAIL sensitive hepatocytes. In Hep G2 cells, no significant effect of BI 905711 decreasing cell viability was observed. The potent tetrameric nanobody agonist targeting TRAILR2 (EX 77749) was used as a reference of sensitivity to TRAILR2 agonists. As expected for a CDH17-independent molecule, a significant effect of EX 77749 decreasing

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cell viability was observed independently of the absence of CDH17 membrane expression (Figure 1.2: 2).

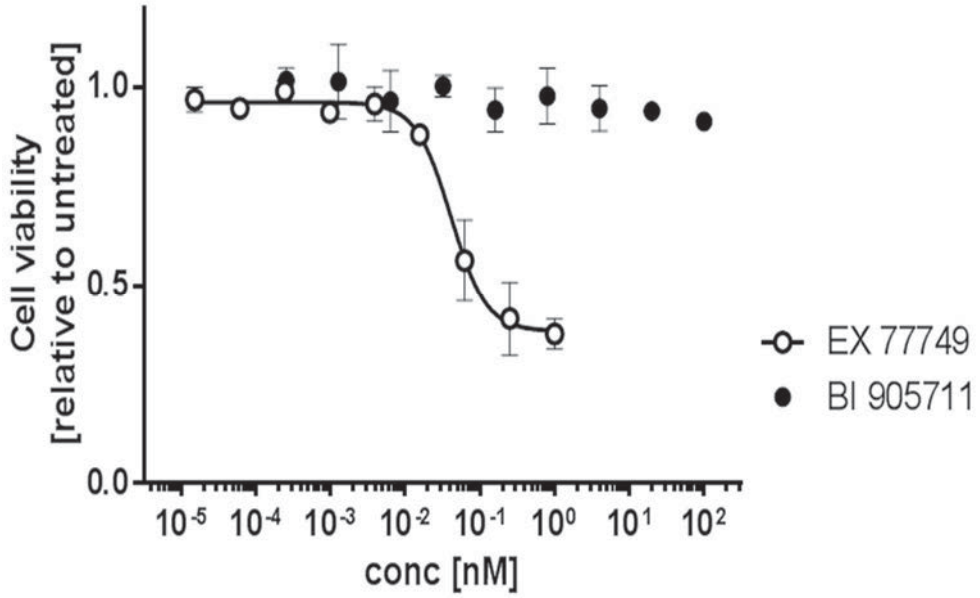

Figure 1.2: 2 Representative graph of concentration response curves as determined in the 72h Hep G2 Cell Titer-Glo assay (c16856466).

BI 905711 *in vivo* efficacy was demonstrated in the COLO 205 xenograft tumor model, where a single dose administration (0.3, 1, 5 and 15 mg/Kg) led to significant growth inhibition for all treatment groups. The GP2d cell line was selected as a second CRC xenograft tumor model for *in vivo* profiling of BI 905711. Compared to COLO 205 derived tumor samples, CDH17 distribution in GP2d derived tumor samples was more similar to those of metastatic CRC patients. BI 905711 was initially administered at doses of 1.67, 5 and 15 mg/kg. After a single dose, BI 905711 administered at 1.67 mg/kg led to sustained tumor regressions for most of the tumors from day 6 until day 36 (end of the experiment). In a follow up study, BI 905711 was administered at lower doses (0.05, 0.2, 0.8, and 1.67 mg/kg). Similar to the 1.67mg/kg group, BI 905711 administered at 0.8 mg/kg as a single dose led to sustained tumor regressions for most of the tumors from day 3 until day 29. The minimal efficacious dose was defined as 0.2 mg/kg with only a few regressions as compared to the 1.67 and 0.8 mg/kg groups, but still demonstrating a statistical significant tumor growth inhibition at the end of the experiment.

Similar to the *in vitro* setting, reduced efficacy was observed in the GP2d xenograft model at both lower and higher than optimum doses, resulting in a V-shaped (evaluating *in vitro* treatment-induced cell death) or a bell-shaped (evaluating *in vivo* treatment induced-tumor growth inhibition relative to control) dose-response relationship (Figure 1.2:1, Figure 4.1.2.1: 1).

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Anticancer activity of BI 905711 in PDAC was tested in vivo using 11 patient-derived PDAC xenograft models (PDX) characterized by target expression of TRAILR2 and CDH17 in the range of 45 to 174 TPM (transcripts per million) and 26 to 604 TPM, respectively. Upon treatment with BI 905711, 4/11 PDX models showed tumor growth inhibition [TGI] ranging from 107 to 126% and 2/11 models showed moderate response (TGI 61% and 76%).
First in vivo experiments (two PDAC PDX models) to study synergistic anticancer effect of BI 905711 in combination with chemotherapy (irinotecan) showed deepened response.

The pharmacokinetics (PK) and immunogenicity for BI 905711 was investigated in the cynomolgus monkey following a single intravenous (i.v.) dose at 8 mg/kg, or 100 mg/kg by bolus injection, demonstrating dose-proportional PK. The well-characterized cynomolgus PK was subsequently used to predict the human pharmacokinetics and inform the phase Ia dose selection, as described in Section 4.1.2 and in full detail in the IB (c16856466).

Preclinical toxicology
Preclinical toxicology is fully described in the IB (c16856466). BI 905711 intravenously administered once per week (Q1W) to cynomolgus monkeys for 6 weeks up to dose levels of 100 mg/kg produced no overt adverse effects. No changes in clinical pathology (hematology, clinical chemistry, urinalysis), ophthalmology, or immunophenotyping were observed, nor were any alterations to body weight or food consumption apparent. The majority of treated monkeys displayed ADAs to BI 905711 at the end of the 6-week drug phase, which slightly reduced total exposure (AUC0-168) when compared to the first administration.

BI 905711-related effects in the 6-week monkey study were limited to microscopic findings in the brain (choroid plexus, meninges, and cerebrum) at ≥ 30 mg/kg, and in the spinal cord (meninges, gray matter) and kidney (glomerulus) at 100 mg/kg. Changes in the brain and spinal cord were characterized by minimal to mild perivascular mononuclear cell infiltrates that contained admixed eosinophils. In animals allowed a 4-week recovery phase, changes in the choroid plexus and meninges of the brain remained apparent, but no findings were noted in the spinal cord. The perivascular accumulation of mononuclear cell infiltrates may represent immune responses originating within the Virchow-Robin space, continuous with the subarachnoid space and outside of the blood-brain barrier. In the kidney, glomerulopathy was observed in monkeys at the end of treatment and recovery phases and was considered related to BI 905711 administration, although no alterations to serum blood urea nitrogen and creatinine or urinary protein were observed. Immunohistochemical (IHC) investigation (Monkey IgM, IgG, C3) did not reveal evidence of immune complex deposition, suggesting an absence of immune complex formation or immune complex levels below the IHC detection limit.

The Highest Non-Severely Toxic Dose (HNSTD) in the 6-week monkey toxicity study was judged to be 100 mg/kg Q1W, and the No Observed Adverse Effect Level (NOAEL) was considered to be 30 mg/kg Q1W.

No hemolytic or local effects due to BI 905711 intravenous injection were noted. BI 905711 did not cause *in vitro* cytokine release (c16856466).

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Data from clinical studies

This open-label, dose-escalation study represents the first protocol for BI 905711 treatment in humans. Safety, pharmacokinetic, and pharmacodynamic profiles, as well as preliminary antitumor activity assessments, will be assessed.

In Phase Ia, 48 patients (26 with CRC, 22 with non-CRC GI cancers) have received BI 905711 (dose range 0.02–4.8 mg/kg). Patients had received a median of 3 (range 1–11) prior lines of treatment. No patients experienced a DLT and the MTD was not reached.

Forty-eight patients (26 with CRC, 22 with non-CRC GI cancers) were included in the analysis with the data cut-off date August 11, 2022. 41 patients (85.4%) experienced treatment-emergent AE. 14 patients (29.2%) had CTCAE grade ≥3 AEs. 2 patients experienced Gr 5 events (Intestinal obstruction in 0.6 mg/kg cohort, Ischaemic stroke 0.2 mg/kg cohort) while 1 patient experienced 2 Gr 4 events (Small intestinal obstruction and intestinal perforation in 2.4 mg/kg cohort). 11 patients experienced Gr 3 events; most common events were AST increased, abdominal pain, anaemia, ALT increased, acute kidney injury and neoplasm progression. 17 patients (35.4%) had drug-related AEs. None of these were grade ≥4 AEs. 3 patients had 4 drug-related grade 3 AEs, 2 in the 1.2 mg/kg dose group (1 case of fatigue and 1 case of transient aspartate aminotransferase increase in a patient with cholangiocarcinoma and liver metastasis) and 2 in 3.6 mg/kg (transient aspartate aminotransferase and alanine aminotransferase increase, 1 case of each). 13 patients (27.1%) had serious AEs, out of which only 1 patient (2.1%) had 2 serious adverse events (Fatigue and Decreased appetite). Three patients had grade 1 or 2 infusion-related reactions that resolved with supportive measures and did not preclude retreatment. Adverse events led to discontinuation of study treatment in 5 (10.4%) patients.

Cmax and $AUC_{0–336}$ of BI 905711 increased proportionally with dose; terminal geometric mean $T_{1/2}$ was ~2–3 days (0.6–4.8 mg/kg dose groups). No accumulation was seen after repeated doses. Systemic exposure was comparable for CRC and non-CRC GI cancers patients in all cohorts evaluated to date.

[redacted]

Median duration of treatment was 30.5 days (range, 15–246) overall and 71 days (range, 15–211) in the 0.6 mg/kg group. In the CRC group, 6/26 (23%) had a best overall response of stable disease and 3 (11.5%) were progression-free for ≥4 months. In non-CRC GI cancers group 7/22 (31.8%) evaluable patients achieved best overall response of stable disease with some tumor shrinkage and 5 (22.7%) were progression-free for ≥4 months. Three of 8 patients in the 0.6 mg/kg dose group (predicted therapeutic dose), 1/8 patients in the 1.2 mg/kg and 1/8 in the 2.4 mg/kg dose groups remained progression-free at ≥4 months. Additionally, 1 CRC patients in 2.4 mg/kg dose group achieved 21.2% tumor shrinkage accompanied by a 50% decrease in tumor marker (i.e. CEA) and 2 non-CRC GI cancer patients in 0.6 mg/kg and 4.8 mg/kg dose groups achieved >10% tumor shrinkage, [redacted] in a patient from 4.8mg/kg dose group.

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Median duration of treatment in non-CRC GI cancers patients was 35.5 days (range, 15–246) overall and 116.5 days (range, 15–211) in the 0.6 mg/kg group. Thirteen (13) of 22 non-CRC GI cancer patients had PDAC. Six (6/13) PDAC patients achieved best overall response of stable disease including 4 patients that remained progression-free at ≥4 months.

Safety, pharmacokinetic, and pharmacodynamic profiles, as well as preliminary antitumor activity of BI 905711 given biweekly at three dose levels (0.6 mg/kg, 1.2 mg/kg and 2.4 mg/kg) or weekly at one dose level (0.6 mg/kg), will be assessed during 1412-0001 expansion phase 1b.

For a more detailed description of the BI 905711 profile, refer to the current Investigator's Brochure (IB).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Efficacy of current standard therapies for gastrointestinal cancers at advanced or metastatic stage is limited. The majority of these patients die due to primary or secondary resistance to therapy, and there is a significant need to develop new approaches for their treatment. BI 905711 represents a novel class of bispecific antibody that may be developed as a new treatment option for these patients. BI 905711 showed efficacy in relevant preclinical models, and its development is supported by extensive pharmacology and toxicology preclinical data (Section 1.2).

This open-label, dose-escalation study represents the first protocol for BI 905711 treatment in humans. Safety, pharmacokinetic, and pharmacodynamic profiles, as well as preliminary antitumor activity assessments, acquired in this trial will provide the basis for further development of BI 905711.

Based on available preliminary data from phase I clinical studies (1412.1 and 1412.3), the decision was made to terminate BI 905711 (TRAILR2/CDH17) development program. This decision is not related to any safety concerns or unfavorable benefit/risk balance, but to the lack of predictive biomarkers and the limited efficacy particularly in the context of the evolving treatment landscape for advanced CRC and other GI cancers.

The purpose of CTP v7.0 is to reduce the study related activities to the minimum required to monitor patient safety and to avoid undue burden on patients.

1.4 BENEFIT - RISK ASSESSMENT

Most patients with advanced or metastatic gastrointestinal cancers have limited treatment options, develop resistance to currently available therapies, and succumb to their disease. BI 905711 can potentially provide a new therapeutic option for these patients as suggested by its efficacy in relevant preclinical models and further supported by extensive pharmacology and toxicology preclinical data (Section 1.2).

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Only a minimum number of patients should be exposed to doses of BI 905711 with low likelihood of activity. Therefore, a Bayesian Logistic Regression Model (BLRM) design will be used in order to escalate the dose into a dose range where optimal efficacy may be seen while still minimizing the risk of undue toxicity.

Conventional anti-TRAILR2 antibodies have been extensively tested and well tolerated in clinic with a well-defined safety profile. The majority of these compounds did not induce DLTs in phase 1 trials with no established MTD. Treatment-related adverse events with such compounds mostly included mild elevation of AST, ALT and/or pancreatic amylase with no reported severe events (R16-1793, R16-1794, R17-2590, R17-2600, R17-2601, R16-4524, R17-2606). There is limited clinical experience with the second generation of compounds inducing TRAILR2 clustering independently of FcR interactions. Recently, phase I data of the TRAILR2 binding tetramer (TAS 266) was reported indicating reversible liver toxicity at the first administered dose level leading to TAS 266 discontinuation from further development (R16-1795). Detailed review of published pre-clinical and clinical data suggest that a relatively high exposure at the starting dose in phase 1 trial may have contributed to the observed toxicity of this drug (R16-1800). A similar compound (ABBV-621) is currently investigated in an ongoing phase 1 study (NCT03082209) (R18-2222). A bi-specific compound targeting TRAILR2 and FAP (RG 7386) has completed phase 1 (NCT02991196) with no reported DLTs and MTD (R18-1695).

The summary of observed adverse events during phase Ia is provided in previous section 1.2. The anticipated adverse events based on the BI 905711 mode of action, pharmacological data and results of preclinical toxicology studies are described below:

- Injury of GI tissues expressing CDH17

CDH17 is expressed in the small intestine, colon, gastric mucosa, gall bladder and pancreatic ducts. BI 905711 may potentially cross-link TRAILR2 to CDH17 in these tissues and induce apoptosis and injury (Section 1.2). No signs of GI injury were observed in preclinical toxicology studies in cynomolgus monkeys up to the highest administered dose (c16856466). There are preclinical in-vitro data suggesting that normal human colon epithelial cells are insensitive to TRAILR2 induced apoptosis, but their sensitivity can be increased during inflammation and viral infection (R16-4563, R17-2592). Patients with inflammatory bowel disease and bowel infection should not participate in clinical trials with BI 905711. Based on above considerations, possible anticipated Adverse Events of BI 905711 may include nausea, anorexia, diarrhea, vomiting, pancreatitis, increase in pancreatic lipase/amylase, abdominal pain and/or other GI tract related signs/symptoms. Guidelines for management of nausea, diarrhea and vomiting are provided in Section 4.1.4.1.2.

- Liver injury

Liver tissue is reported as the most sensitive non-cancerous tissue to TRAILR2 mediated apoptosis (R16-1795, R16-1793). Human hepatocytes do not express CDH17 and in Hep G2 cells used as a surrogate for TRAIL sensitive hepatocytes, no significant effect of BI 905711 on cell viability was observed. Still, liver damage induced by BI 905711 cannot be excluded particularly in patients with liver metastases. Patients should be followed closely for potential elevation of AST, ALT, and bilirubin, and for clinical signs/symptoms of liver injury as described in Section 5.2.6.1.4.

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- Renal injury

A 6-week GLP toxicology study in monkeys showed glomerulopathy at the highest tested dose of 100 mg/kg (c16856466). These finding were not accompanied by clinical or biochemical changes in renal functions with no increase in serum creatinine or BUN and no proteinuria. CDH17 has not been detected in the kidneys of monkeys or humans (c16856466). Granular deposits containing human IgG and/or monkey IgG were identified in the kidneys of animals displaying glomerulopathy. The presence of these granular deposits is consistent with processes of immune complex formation, deposition, and clearance in response to the test article. Formation of immune complexes followed by deposition in the kidneys with resultant glomerulopathy has been described when monkeys form ADA in response to heterologous protein administration and is generally not considered predictive of similar findings in humans. The relevance of these observed renal findings for humans is 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 Section 5.2.3.

- Tumor lysis

BI 905711 induces apoptosis within a short time frame in-vitro and leads to tumor regression in-vivo in preclinical models. Theoretically, tumor lysis syndrome can occur. Patients should be monitored for occurrence of tumor lysis syndrome particularly after the first administration of BI 905711 with guidelines provided in Section 4.1.4.1.4.

- Infusion-related reaction

BI 905711 is a humanized bi-specific antibody with atypical format, and it may induce infusion-related reactions due to multiple mechanisms. Recent data from a similar bi-specific antibody targeting TRAILR2 and FAP reported an incidence of 9% of grade 1-2 infusion reactions with no grade ≥3 (R18-1695). Management guidelines for infusion-related reactions are provided in Section 4.1.4.1.1.

- Cytokine release syndrome (CRS) and immune-mediated reactions

The TRAIL pathway has been implicated in inflammation in some preclinical experiments, but the clinical relevance of these findings are unknown (R18-2770). BI 905711 did not induce any cytokine release using a standard in vitro assay (c16856466). There was no CRS reported in historical studies with conventional TRAILR2 antibodies and TRAILR2 clustering agents (R16-1793, R16-1794, R17-2590, R17-2600, R17-2601, R16-4524, R17-2606). The risk of CRS cannot be excluded, and patients should be followed for possible occurrence of CRS with guidelines provided in Section 4.1.4.1.2.

- Neurological adverse events

A six week GLP toxicology study in monkeys showed minimal to mild perivascular eosinophilic/monocyte cell infiltrations in brain and spine at doses of 30mg/kg and 100mg/kg with no apparent clinical neurological finding in affected animals. More details are described in the IB and in Section 5.3. Cytoplasmic CDH17 staining was occasionally present in cerebral neurons of both humans and monkeys. Since CDH17 is membrane bound, the cytoplasmic staining is non specific and pathological findings in monkey brains are not considered related to BI 905711 mediated cross-linking of TRAILR2 and CDH17. TRAILR2 have been described in human brain particularly in certain pathological conditions (R18-

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2769). There were no neurological findings described in studies with other conventional TRAILR2 agonists up to the highest tested dose levels (R16-1793; R16-1794), R17-2590, R17-2600, R17-2601, R16-4524, R17-2606). In summary, dose dependent, minimal to mild eosinophilic/monocyte cells infiltrations in perivascular region of the brain and spine observed in toxicology studies in monkeys are of unknown significance and were considered to be possibly secondary effects related to the immunogenicity of BI 905711 or test article platform. Relevance of these findings for humans is unknown. The risk of possible neurological adverse reactions will be closely monitored in human studies. Thus, a baseline brain MRI will be performed in all patients enrolled in the phase Ia part. Patients who develop new neurological symptoms or deficits need to undergo neurological investigations including a brain MRI, and treatment with BI 905711 must be interrupted or discontinued. Guidelines for management of possible neurological toxicities are provided in Section 4.1.4.1.5. The possibility of their relationship to ADA will be assessed.

- ADA (anti-drug antibodies) related adverse reaction

BI 905711 may lead to development of ADA, and its occurrence will be explored in this study (refer to Section 5.3.2). The consequence of ADA occurrence for safety is currently unknown. There is a single preclinical report indicating the possibility of ADA mediated clustering of TRAILR2 and its potential contribution to liver injury (R17-2603). Patients will be closely followed for development of liver injury for the whole duration of BI 905711 treatment, and possible contribution of ADA to liver injury will be assessed.

- Tumor biopsy

As part of the screening, patients are required to have a tumor tissue biopsy. Pre-treatment fresh tumor biopsy collections for biomarker analyses are considered optional in phase Ia and mandatory in phase Ib. There is an added risk for pain, swelling, bleeding for those patients who will undergo tumor biopsies. For this reason, biopsies will only be performed when deemed safe by the investigator and if the platelet count is sufficient to allow for haemostasis. As the results from the biopsy will provide more information which will assist clinical decisions for future patients, the benefit is assumed to outweigh the risks associated with the biopsy.

During 1412-0001 phase 1a dose escalation the Safety Monitoring Committee (SMC) assessed trial data to ensure the overall safety of the patients treated. Based on the accumulated data, the SMC reached joint recommendations on the next dose level of BI 905711 to be investigated and the sample size for the next dose-escalation cohort. They also provided the Investigators and the Sponsor with advice about the overall conduct of the trial (refer to Section 8.7).

The Safety Monitoring Committee reviewed the safety data of BI 905711 up to 3.6 mg/kg in CRC and non-CRC GI cancer patients and concluded that no DLT was observed, no MTD was achieved, and there was no evidence of any dose/adverse effect relationship. In addition, there was no evidence for drug-induced liver injury and no pattern of anticipated AEs (see section 7 of current IB) has been observed except infusion-related reactions (see previous section 1.2 for details).

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A Benefit-Risk assessment in the context of the COVID-19 pandemic for patients treated with BI 905711 has been performed. Based on the mode of action, BI 905711 is not expected to have a relevant impact on the susceptibility to or the course of a SARS-CoV-2 infection.

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

Patients in this trial may be immuno-compromised and at higher risk for severe illness from COVID-19. In case of an increased risk of SARS-CoV-2 infection due to the physical visits to the sites, the visits should be avoided where the investigator judges that this is the safest course of action. These measures ensure the safety of the patients throughout the trial, maintain the integrity of the trial and will not affect the benefit-risk balance of BI 905711.

In summary, the present trial has implemented a number of safety measures to mitigate possible risks for patients. It is concluded that participation in this study and treatment with BI 905711 may provide patients with potential clinical benefit at an acceptable risk.

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2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

Phase Ia:

- Explore safety and establish the maximum tolerated dose (MTD)/recommended dose levels for phase Ib expansion phase of BI 905711 based on the frequency of patients experiencing dose limiting toxicities (DLTs) during the MTD evaluation period. The MTD evaluation period is defined as the first two treatment cycles (from first dose administration until the day preceding the third dose administration or end of REP in case of discontinuation before start of Cycle 3).
- Explore pharmacokinetics/pharmacodynamics and efficacy to guide the determination of a potentially effective dose range for phase Ib in the absence of MTD.

Phase Ib:

- Evaluate efficacy and safety of BI 905711 at a potentially effective dose range and determine the Recommended Phase 2 Dose (RP2D)

2.1.2 Primary endpoint(s)

Phase Ia:

- Maximum tolerated dose (MTD) 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 the definition of DLTs, refer to Section 5.2.6.1.5.
- Number of patients with DLTs in the MTD evaluation period.

A BLRM employing the escalation with overdose control (EWOC) principle will be used during the escalation phase for the selection of the dose levels and, if applicable, the estimation of the MTD. Cohorts of patients will receive escalating doses of BI 905711 until the MTD is reached. Each cohort will consist of newly enrolled patients. Estimation of the MTD during the escalation phase of the trial will be based upon the estimation of the probability of a DLT in the MTD evaluation period in the set of evaluable patients for MTD. The corresponding methodology is described in Section 7 and Appendix 10.3. The MTD estimate established during the dose escalation phase will be re-investigated after the expansion phase by re-running the BLRM including all data from escalation and expansion phases, including DLTs observed at all treatment cycles.

Phase Ib:

- Objective response based on RECIST 1.1 criteria. Objective response is defined as best overall response of complete response or partial response, where best overall response is the best response 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.

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- Progression-free survival (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.

2.1.3 Secondary endpoint(s)

Phase Ia:

- The following PK parameters of BI 905711 will be evaluated after the first and after the third administrations of BI 905711:
  - Cmax: maximum measured concentration of BI 905711 in plasma
  - AUC0-t2: area under the concentration-time curve of BI 905711 in plasma
- Objective response based on RECIST 1.1 criteria in patients with measurable disease.

Phase Ib:

- The following PK parameters of BI 905711 will be evaluated after the first and after the third administrations of BI 905711:
  - Cmax: maximum measured concentration of BI 905711 in plasma
  - AUC0-t2: area under the concentration-time curve of BI 905711 in plasma
- Number of patients with treatment-emergent AEs
- Radiological (CT Scan) tumor shrinkage, defined as the difference between the minimum post-baseline sum of longest diameters of target lesions and the baseline sum of longest diameters of the same set of target lesions according to RECIST 1.1.
- The duration of overall response is measured from the time measurement criteria are first met for Complete Response (CR)/ Partial Response (PR) (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study) according to RECIST 1.1.
- Disease control, defined as CR, PR, or stable disease according to RECIST 1.1 from the start of treatment until the earliest of progression disease, death or last evaluable tumor assessment and before start of subsequent anti-cancer therapy.

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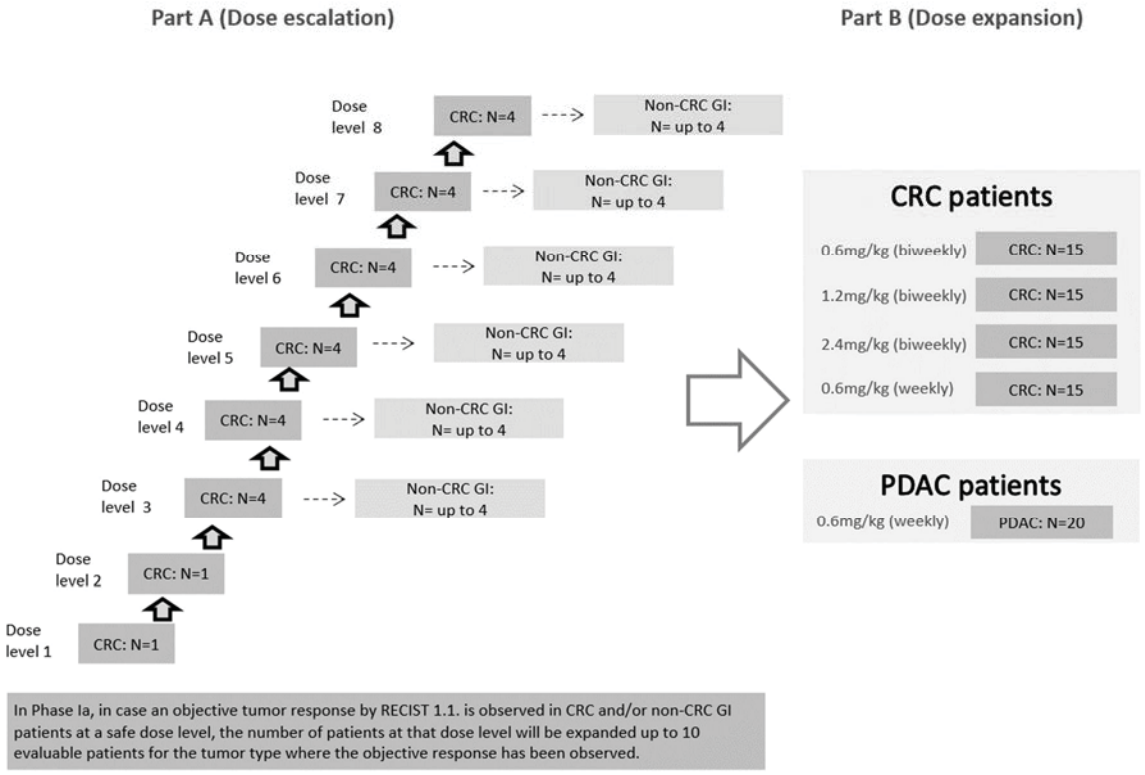
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will consist of two parts: phase Ia (escalation part) and phase Ib (expansion part) as displayed in Figure 3.1: 1 and described in Sections 3.1.1 and 3.1.2.



Note: Displayed dose levels are for illustration only. The number of patients in the dose escalation cohorts may be increased in case of DLT observation. Non-CRC includes any other non-colorectal GI cancers.

Figure 3.1: 1 Overall study design

3.1.1 Phase Ia: dose escalation (Part A)

Phase Ia is an open-label, dose escalation study of BI 905711 administered intravenously. Provisional dose escalation levels are described in Table 4.1.2.1: 1.

Recruitment in Phase Ia is complete.

3.1.1.1 Recruitment in CRC escalation cohorts

CRC patients represent a homogenous population regarding CDH17 expression. CRC preclinical models were used for prediction of dose levels to be tested in phase Ia and BI 905711 pharmacological activity. Thus, CRC patients will be recruited as mandatory cohorts at all dose levels. Gastrointestinal cancers in patients of various ethnicity, including Japanese patients, express CDH17 to a similar extent (R18-3554), and ethnicity based differences for BI 905711 tolerability and PK are not expected (R18-3553). Patients of any ethnicity can be

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enrolled into the first two dose levels. Starting from dose level 3 onwards, at least one Japanese patient should be included into each dose level to establish the safety for Japanese patients. The possible cohort size is described in Table 4.1.2.1: 1.

3.1.1.2 Recruitment in non-CRC GI cancer cohorts

Non-CRC GI cancer patients were recruited as "back-filled" cohorts at one level below the current dose being investigated in the CRC cohort to confirm safety also for this population. The decision to open enrollment of non-CRC GI cancer cohorts and the selection of the starting dose were taken by the SMC. Recruitment at a specified dose level occurred once it was determined to be safe in CRC cohorts per SMC decision.

Once the first site in China was initiated while the phase Ia was ongoing, the first Chinese patient was enrolled into the non-CRC dose level that was open at the time of site initiation. Thereafter, at least one Chinese patient was enrolled in China at each subsequent dose level in phase Ia.

3.1.1.3 MTD determination/recommended dose range for expansion

The data obtained from the trial was to determine the MTD estimate based on a BLRM with overdose control (R13-4803). The BLRM estimates the MTD by updating estimates of the probability of observing a DLT in the MTD evaluation period for each dose level in the trial as patient information becomes available. At any time in the trial, it was not permitted to escalate to a dose which does not fulfil the escalation with overdose control (EWOC) principle (refer to Section 7).

Recruitment at every dose level started with CRC patients. As soon as all CRC patients enrolled for safety evaluation on a dose level completed the MTD evaluation period, a BLRM with overdose control was be applied by using all available data from all dose levels assessed (from both CRC and non-CRC GI cancer patients) to determine the next dose levels in CRC and non-CRC cohorts and evaluate MTD. The overdose risk was then calculated for each preliminary dose level from Table 4.1.2.1: 1 and escalation was permitted to a dose level which fulfilled the EWOC criterion. Intermediate or higher dose levels could be used as long as it fulfilled the EWOC criterion. Specifications and details of the BLRM are indicated in Section 7.1 and Appendix 10.3.

The safety data from non-CRC GI cancer patients as well as data from the Japanese patients was evaluated additionally in a descriptive manner and provided to SMC at every dose escalation step. If DLTs in non-CRC GI cancer patients were observed in a lower dose level as compared to CRC patients, some sensitivity analysis was run based on BLRM by adding CRC/non-CRC as a covariate to evaluate whether to reduce the dose level or recruit more patients at the same dose level for non-CRC GI cancer patients. The SMC made a decision about continuation of dose escalation for non-CRC GI cancer patients based on these data. The SMC also discussed whether the dose level for CRC patients should be adjusted or not.

Decision on further recruitment, dose escalation, de-escalation or cohort expansion was made by the SMC.

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At each dose level, the first patient was treated and was observed for at least 1 week before allowing the second patient to receive BI 905711 infusion.

- For the initial two dose levels (dose levels of 0.02 mg/kg and 0.06 mg/kg), at least one CRC patient was required. In case patients have not experienced a DLT within the first two cycles, enrollment into a higher dose level occured. In case a DLT occured, the number of patients was increased to four patients per dose level, and BLRM was performed to determine the next escalation steps. At least one Japanese patient should be included in the additional three patients that are enrolled. Then, all subsequent dose levels consisted of at least four patients. For further dose-escalation steps (dose level of 0.2 mg/kg and above), four CRC patients were required. However, in the case that only three patients were evaluable (including one Japanese patient) and none experienced a DLT as defined in Section 5.2.6.1.5 within the MTD evaluation period, then dose escalation occured based on these three evaluable patients.

If DLTs were observed in the first two consecutive patients of a previously untested dose level, subsequent enrollment to this dose cohort was stopped. The BLRM was to be re-run to confirm whether the dose level still fulfils the EWOC criterion. Based on this information, the SMC evaluated whether the next patients will be enrolled at the same dose level, or at a lower dose level.

The SMC may have recommended stopping the dose escalation phase after the criterion for MTD (Section 7.1) is fulfilled. Further patients may have been included to confirm this MTD estimate, i.e. to confirm that the EWOC criterion is still fulfilled.

The planned highest dose to be tested in the dose escalation was 4.8mg/kg based upon the pharmacodynamic modeling (refer to Figure 4.1.2.1: 1). Based on the available safety data and the BLRM, exploration of doses higher than 4.8 mg/kg was considered.

3.1.2 Phase Ib: expansion cohorts (Part B)

Phase Ib is a randomised open label study to determine safety and efficacy of BI 905711 in the 4 expansion cohorts of patients with colorectal cancer and the 1 expansion cohort of patients with pancreatic cancer.

The selection of the dose levels for phase Ib was made by the SMC with the aim to select a safe and potentially effective dose range of BI 905711 based on all data collected in phase Ia. Selected dose(s) for phase Ib expansion cohorts cannot be higher than the MTD. The overall framework for dose selection for phase Ib is described in Section 4.1.2.2.

If any DLTs are observed during cohort expansion, the BLRM will be run to confirm if that dose level still fulfils the overdose risk control. Further expansion to 15 patients for the CRC cohorts or 20 patients for the PDAC cohorts may be stopped due to over toxicity.

The SMC can declare any dose fulfilling the EWOC criterion as RP2D by considering all available efficacy (OR), PK/PD, biomarker and safety data, independent of the MTD estimate.

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To determine the RP2D, the MTD estimate established during the dose escalation phase will be re-investigated after the expansion phase by re-running the BLRM including all data from escalation and expansion phases.

Furthermore, continuation of the trial using the optimal dose and selected patient population will be considered and further specified in a protocol amendment if appropriate.

Recruitment in this trial was discontinued during Phase I expansion, and no PDAC patients were enrolled in this expansion cohort.

3.1.2.1 Randomized CRC expansion cohort

Approximately 60 evaluable CRC patients can be enrolled into phase Ib into 3 dose levels with 4 cohorts of 15 evaluable CRC patients. Statistical justification for the number of patients per dose level is indicated in Section 7.7.

Patients will be randomised into three dose levels in four cohorts (three dose levels in biweekly regimen and one dose level in weekly regimen (3 weeks on, 1 week off)) of BI 905711 for a total of approximately 60 evaluable patients.

3.1.2.2 Single Arm PDAC expansion cohort

Approximately 20 evaluable patients with CDH17-positive PDAC will be enrolled into phase Ib. Patients will be enrolled on one dose level in weekly regimen (3 weeks on, 1 week off) of BI 905711.

CDH17 analysis must be performed by a designated vendor and results reviewed prior to patient enrollment.

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

The primary objective of this trial is to determine the MTD and the RP2D. The secondary objective is to explore efficacy and safety at a potentially effective dose range of BI 905711 monotherapy.

The phase Ia dose escalation and cohort size was determined based upon the recommendation of the SMC, guided by a BLRM with overdose control. An escalation with overdose control design would increase the chance of treating patients at efficacious doses while reducing the risk of overdosing. This design was based on practical experience and was a preferable algorithmic method due to its superior ability to identify the dose with the desired toxicity rate and its allocation of a greater proportion of patients to doses at, or close to, that dose (R13-4802, R13-4804, R13-4805). The use of BLRM for phase I studies has also been advocated by the EMA guideline on small populations (R07-4856) and by the FDA (R13-4881).
The phase Ib expansion part will serve for early evaluation of anti-tumor effect of BI 905711 at a potentially effective dose range (0.6mg/kg, 1.2mg/kg, 2.4mg/kg) and to explore anti-cancer effect of BI 905711 at 0.6mg/kg dose given weekly (3 weeks on, 1 week off) and at 0.6mg/kg,

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1.2mg/kg, and 2.4mg/kg given biweekly. Selection of the weekly dosing regimen is based upon the following data:

- [redacted]
- PK assessment in 1412-0001 phase 1a showed that the terminal half-life estimates approach 3 days in the higher dose groups (2.4 mg/kg and 3.6 mg/kg). Peak and total exposure within the same dose group were comparable between Cycle 1 and 3, i.e. no accumulation was observed up to 3.6 mg/kg dose level.

Evaluation of the safety data of 48 CRC and non-CRC GI cancer patients in phase Ia revealed good tolerance of BI 905711 up to 4.8 mg/kg. The primary endpoints of Phase 1b will include ORR and PFS which are considered appropriate efficacy endpoints in patients with advanced unresectable or metastatic colorectal adenocarcinoma. Currently available targeted treatment options show very little tumor regression in clinical trials, as evidenced by a very low ORR (R22-1028) and a short median PFS. The ultimate goal is to enhance progression-free survival (PFS) and prolong overall survival while maintaining QOL (P22-01934).

3.3 SELECTION OF TRIAL POPULATION

Approximately 40-60 patients were planned to be entered in the phase Ia (dose escalation) part of this international, multi-center trial, which will be conducted at about 8 sites in Europe, Japan, China, and the United States. For the expansion phase Ib, approximately 80 evaluable patients are planned to be entered in total (i.e. across all cohorts) at sites that participate in the phase Ia part of the study plus additional sites in Europe and South Korea to fulfill the planned enrollment. Each site is expected to enroll on average 3-5 patients. If site(s) are unable to recruit patients, additional sites may be opened, and under-performing sites may be closed.

All PDAC patients in phase Ib will be required to undergo central testing of tumour tissue for CDH17 status at screening visit 1 (SV1) before proceeding to full screening assessments at screening visit 2 (SV2). There are no inclusion/exclusion criteria at screening visit 1 except that the patient must have tissue available for analysis and must be expected, as far as is possible to determine, to meet all inclusion and exclusion criteria at the time of screening visit 2.

3.3.1 Main diagnosis for trial entry

The patient population for this trial includes patients with advanced refractory gastrointestinal cancers of the following histologies: colorectal adenocarcinoma, gastric adenocarcinoma, oesophageal adenocarcinoma, pancreatic ductal adenocarcinoma, cholangiocarcinoma and gallbladder carcinoma, and small intestine adenocarcinoma in phase 1a, and histologically or cytologically confirmed, advanced unresectable or metastatic colorectal adenocarcinoma and CDH17 positive pancreatic ductal adenocarcinoma in Phase Ib (expansion phase).

Inclusion/exclusion are criteria specified in Section 3.3.2 and 3.3.3.

Screening of patients for this trial is competitive, however recruitment slots will be assigned by the Sponsor. Screening for the trial will stop at all sites at the same time once a sufficient

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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.

Should the patient not sign consent or be determined to be a screen failure, the site needs to notify the BI team as soon as possible so the slot may be re-opened to other potential patients.

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

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrollment), the Sponsor should be contacted immediately. Refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

A patient who has been declared as a "screening failure" may be re-screened once, after Sponsor agreement. A new informed consent must be signed by the patient, and all eligibility criteria must be re-assessed, including all safety laboratory parameters within the screening time period specified in the Flow Chart, to confirm the patient's eligibility.

3.3.2 Inclusion criteria

1. a. Phase Ia (dose escalation only)
   - Histologically or cytologically confirmed, advanced unresectable or metastatic gastrointestinal cancers of following histologies:
     - Colorectal adenocarcinoma
     - Gastric adenocarcinoma
     - Esophageal adenocarcinoma
     - Pancreatic adenocarcinoma
     - Cholangiocarcinoma and gallbladder carcinoma
     - Small intestine adenocarcinoma

   b. Phase Ib (expansion phase)
   - Histologically or cytologically confirmed, advanced unresectable or metastatic gastrointestinal cancers of following histologies:
     - Colorectal adenocarcinoma.
     - CDH17 positive pancreatic adenocarcinoma (in tumour tissue as assessed by central testing)
2. Patient who has failed all available conventional therapies known to confer clinical benefit for their disease based on local approved standards. For patients with colorectal cancer, prior treatment with regorafenib or TAS-102 is optional.
3. a. Phase Ia (dose escalation) only:
   - Patient with either measurable or non-measurable/non-evaluable disease.

   b. Phase Ia (expanded cohort) and Phase Ib (expansion phase) only:
   - At least one target lesion that can be accurately measured per RECIST v.1.1
4. Availability and willingness to provide an archived tumor tissue specimen and undergo tumor biopsy before treatment. Pre-treatment fresh tumor biopsy collections for biomarker analyses are considered optional in phase Ia and mandatory in phase Ib. Only non-

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significant risk procedures per the investigator's judgment will be used to obtain any biopsies specified in this study. In case a fresh tumor biopsy cannot be obtained due to before mentioned reasons an archived tumor tissue specimen obtained within ≤6 months of screening must be submitted. In case the patient undergoes baseline tumor biopsy, an archived tumor tissue specimen must be submitted regardless of the date of collection.

5. Adequate hepatic, renal and bone marrow functions as defined by all of the below:
    a. Total bilirubin (≤ 1.5 x institutional ULN (≤ 3 x institutional ULN for patient with Gilbert's syndrome)
    b. ALT and AST ≤2.5 x institutional ULN (≤5 x institutional ULN for patients with known liver metastases)
    c. Serum creatinine ≤1.5x institutional ULN. If creatinine is > 1.5 x ULN, patient is eligible if concurrent creatinine clearance ≥ 50 ml/min (≥ 0.05 L/min) (measured or calculated by CKD-EPI formula or Japanese version of CKD-EPI formula for Japanese patients).
    d. ANC ≥ 1.0x 10^9/L (≥ 1.0 x 10^3/µL, ≥ 1,000/mm^3)
    e. Platelets ≥ 100x10^9/ L (≥ 100 x 10^3/µL, ≥ 100 x 10^3/mm^3)
    f. Hemoglobin (Hb) ≥8.5 g/dl, ≥ 85 g/L, or ≥ 5.3 mmol/L (without transfusion within previous week)
    g. Phase Ia, and Phase 1b CRC cohort: Serum lipase ≤ 1.5 institutional ULN
    h. Phase Ib PDAC cohort: Serum lipase >1.5 - 2.0 x ULN or asymptomatic >2.0 - 5.0 x ULN if related to PDAC
6. Recovery from any adverse events according to CTCAE v5.0 of previous anti-cancer therapies to baseline or CTCAE grade 1, except for alopecia CTCAE grade 2, sensory peripheral neuropathy CTCAE grade ≤ 2 or considered not clinically significant.
7. ECOG performance status ≤ 1
8. Life expectancy ≥ 3 months in the opinion of the investigator
9. Of legal adult age (according to local legislation) at screening.
10. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
11. Male or female patients. Women of childbearing potential (WOCBP)[1] and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in Section 4.2.2.3.

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

3.3.3 Exclusion criteria

1. Previous systemic anti-cancer therapy within the specified timeframe from the last dose intake to the first dose of trial treatment as shown below:
    - Any non-investigational drug, including anti-angiogenic antibodies (bevacizumab or ramucirumab) and anti-EGFR antibodies (cetuximab or

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panitumumab), within 14 days.
- Any investigational drug or other antibodies including immune checkpoint inhibitors, within 28 days.

2. Radiation therapy within 4 weeks prior to start of treatment. However, palliative radiotherapy for symptomatic metastasis is allowed if completed within 2 weeks prior to start of treatment but must be discussed with the sponsor.
3. 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 or active ulcers (gastro-intestinal tract, skin) or laboratory abnormality that may increase the risk associated with trial participation or trial drug administration, and in the judgment of the Investigator, would make the patient inappropriate for entry into the trial. Any history of stroke or myocardial infarction within 6 months prior to screening.
4. Known pathological condition of GI tract, liver and pancreas, excluding the disease under study, that may interfere with assessment of drug safety or may increase the risk of toxicity:
   a. inflammatory bowel disease
   b. chronic pancreatitis
   c. other serious GI pathological conditions by judgment of the investigator e.g. autoimmune disease with GI involvement, unexplained active diarrhea CTCAE grade ≥2 according to CTCAE v5.0.
5. Known history of human immunodeficiency virus infection.
6. Any of the following laboratory evidence of hepatitis virus infection. Test results obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date:
   - Positive results of hepatitis B surface (HBs) antigen
   - Presence of HBc antibody together with HBV-DNA
   - Presence of hepatitis C RNA
7. Active concomitant malignancies, other than the one treated in this trial.
8. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes the patient an unreliable trial participant or unlikely to comply with the protocol requirements or not expected to complete the trial as scheduled.
9. Women who are pregnant, nursing, or who plan to become pregnant while in the trial; female patients who do not agree to the interruption of breast feeding from the start of study treatment to within 30 days after the last study treatment.
10. 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 MRI.
11. Patients who are under judicial protection and patients who are legally institutionalized
12. Major surgery (major according to the investigator's assessment) performed within 3 weeks prior to treatment start or planned within 3 months after screening, e.g. hip replacement.
13. Any of the following cardiac criteria:
    a. resting corrected QT interval (QTc) >470 msec

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b. Any clinically important abnormalities (as assessed by the Investigator) in rhythm, conduction, or morphology of resting ECGs, e.g., complete left bundle branch block, third degree heart block.
c. Patients with an ejection fraction (EF) <50% or the lower limit of normal of the institutional standard will be excluded. Only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the EF, will the EF be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multigated acquisition scan). A historic measurement of EF no older than 6 months prior to first administration of study drug can be accepted provided that there is clinical evidence that the EF value has not worsened since this measurement in the opinion of the Investigator or of the treating physician or both.

14. Known hypersensitivity to the trial medication and/or its components i.e. polysorbate 20, sodium citrate, lysine hydrochloride, sucrose, citric acid.

3.3.4 Withdrawal of patients from treatment or assessments

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

Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrollment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If the reason for treatment discontinuation is death, this should be reported on the SAE form as well, regardless of causal relationship.

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and Sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the investigational drug.
- The patient can no longer receive trial treatment for medical reasons (such as cancer progression, surgery, adverse events, other intercurrent diseases, or pregnancy, or nursing).
- The patient experiences an infection with SARS-CoV-2. The patient may resume trial treatment following recovery from SARS-CoV-2 infection if the patient is expected to derive clinical benefit, as agreed between the investigator and sponsor.

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Additional patients may be recruited to replace patients who discontinued their participation early for non-safety related reasons (e.g. unable to attend the protocol defined visits for to personal reason), or trial disruption e.g. measures to control the spreading of COVID-19. Patients may only be replaced after an agreement with the sponsor.

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 Medical Monitor of the Sponsor,
- The patient has signed an informed consent describing this circumstance.

Criteria required to continue treatment through 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

Even if the trial treatment is discontinued, the patient remains in the trial and, given his/her agreement, will undergo the procedures for treatment discontinuation and follow up as outlined in the Flowchart and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

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

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

3.3.4.3 Discontinuation of the trial by the Sponsor

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

1. Failure to meet expected enrollment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information that could significantly affect the continuation of the trial.
3. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

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

3.3.4.4 Replacement of patients for MTD determination and PK evaluation in phase Ia

Patients who experience a DLT during the MTD evaluation period were not replaced.
The following patients without DLT during the MTD evaluation period were considered non-evaluable for MTD determination and were not included in the BLRM analysis:

- Patients who withdrew consent or who were lost from follow-up before completing first two cycles of study treatment.
- Patients who have received less than 70% of the planned BI 905711 doses during first two cycles of study treatment
- Patients who missed 2 or more partial or complete visits during the first two cycles of study treatment.
- Patients with missing PK and evaluation of safety parameters.

These patients were replaced for DLT evaluation during the MTD evaluation period if not decided otherwise by the SMC (e.g. if the number of evaluable patients for the current dose cohort is considered sufficient for a dose escalation decision or MTD determination).

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

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4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product 1

Substance:	BI 905711
Pharmaceutical formulation:	Powder for Solution for Infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	100 mg/vial (10 mg/mL)
Posology:	Single administration every two weeks for a patient enrolled in a biweekly regimen. Single administration every week for 3 weeks on, 1 week off for a patient enrolled in a weekly regimen.
Method and route of administration:	intravenous

4.1.2 Selection of doses in the trial and dose modifications

4.1.2.1 Dose(s) selection for Phase Ia

A detailed description of the methods and considerations to determine a safe starting dose and the phase Ia dose levels, taking into account the available nonclinical information, including PK/PD and toxicity data, is described in the current IB (c16856466).

In summary, human pharmacokinetics of BI 905711 upon intravenous administration were predicted based on cynomolgus monkey PK data. Dose-normalized, concentration-time data were scaled to human by means of elementary Dedrick scaling (scaling factors d=1 and b=0.85) with mean body weights of 2.9 and 70 kg for monkeys and humans, respectively.

PK and tumor growth inhibition data from both the COLO205 and GP2d xenograft models were incorporated into dose–response models and used, by means of plasma exposure matching over the proposed 2 week dosing interval (AUC0-336h), to predict the efficacious human dose and relevant dose-range to be investigated in phase Ia. (Figure 4.1.2.1: 1).

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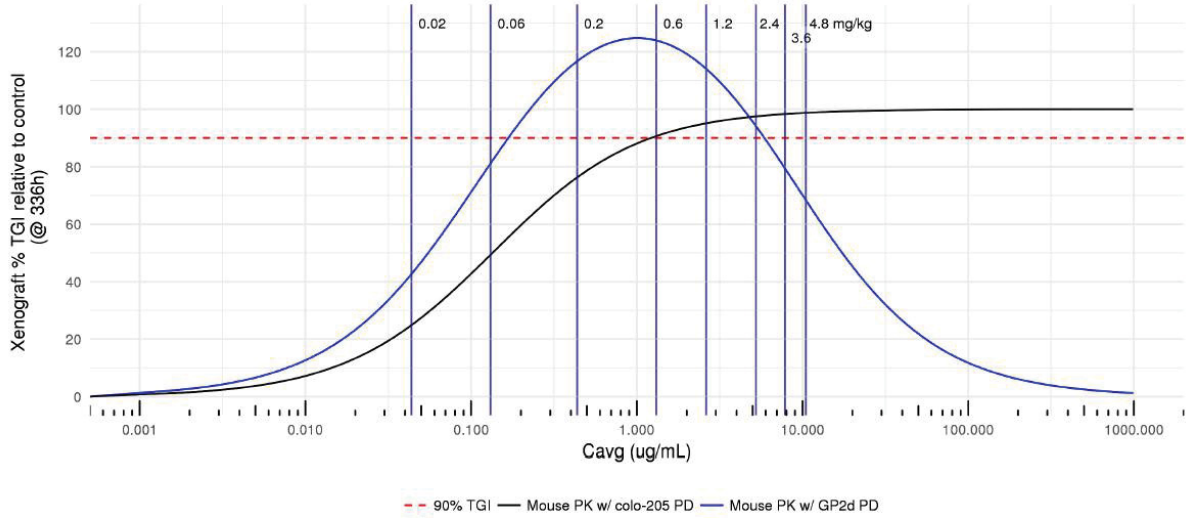

Figure 4.1.2.1: 1 Simulated BI 905711 exposure vs. response at 14 days after a single i.v. administration. Cavg (AUC0-336h divided by 336h) vs % Tumor Growth Inhibition relative to untreated control-curves for GP2d (blue) and Colo-205 (black) xenograft PK/PD models. Predicted Cavg (µg/mL) values at the projected human doses levels (mg/kg) are shown as overlay

The recommended starting dose for phase Ia is based on an integrated evaluation of the predicted exposure-response relationship, the HNSTD exposure in the 6-week toxicology study in cynomolgus monkeys, literature review of other TRAILR2 agonists and the proposed patient population (c16856466).

A starting dose of 0.02 mg/kg of BI 905711 with following characteristics has been selected:

- The starting dose is a human equivalent dose (HED) based on matching 14 day predicted plasma exposure with the simulated PK/PD relationship in two xenograft models. This exposure level corresponds to an activity of ~ 30% tumor growth inhibition as compared to maximally active dose in those two models (25% for COLO 205 and 34% for GP2d) as shown in Figure 4.1.2.1: 1.
- The starting dose is 30-fold lower as compared to the modelled maximally active human equivalent dose in the studied xenografts models (0.6 mg/kg).
- The predicted exposure in humans at the starting dose is 1045- and 650-fold below the Cmax and AUC0-336, respectively, at the NOAEL, and >3600-fold below both parameters at the HNSTD in monkeys. Therefore, this starting dose is supported by the 6-week repeat-dose toxicity study in cynomolgus monkeys.

For further starting dose details, refer to the Investigator's Brochure (c16856466).

The dose is planned to be escalated in cohorts at the pre-defined dose levels in Table 4.1.2.1:1. In-between or higher dose levels may be investigated as long as they fulfill the EWOC criterion. Rationale for the provisionally selected dose levels in phase Ia is based on the predicted human pharmacologically active dose and ensures a complete coverage and investigation of the projected BI 905711 dose-response relationship as shown in Figure 4.1.2.1: 1. At any time during the trial, it will not be permitted to escalate to a dose

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which does not fulfill the EWOC criterion (refer to Section 7.1). Dose escalation rules are described in protocol Section 3.1.1 and Section 7.1.

Table 4.1.2.1: 1 Provisional dose levels for dose escalation of BI 905711 in phase Ia

Dose level	Dose (mg/kg)	Increment from previous dose	Minimum number of CRC patients[ǂ]	Number of Non – CRC GI cancer patients[##]
1	0.02		1 (any)	1
2	0.06	200%	1 (any)	1
3	0.2	230%	4 (include at least 1 Japanese patient)	Up to 4
4	0.6*	200%	4 (include at least 1 Japanese patient)	Up to 4
5	1.2	100%	4 (include at least 1 Japanese patient)	Up to 4
6	2.4	100%	4 (include at least 1 Japanese patient)	Up to 4
7	3.6	50%	4 (include at least 1 Japanese patient)	Up to 4
8	4.8	33%	4 (include at least 1 Japanese patient)	Up to 4

*Predicted optimal biological dose.
ǂThe number of patients in the dose escalation cohorts may be increased in case of DLT observation.
If the first site in China is initiated while the phase Ia is ongoing, it is planned the first Chinese patient will be enrolled into the non-CRC dose level that is open at the time of site initiation. Thereafter, at least one Chinese patient will be enrolled in China at each subsequent dose level in phase Ia.

At the end of the MTD evaluation period for each treatment cohort, BI convened a meeting with the SMC. At the SMC meeting, the safety data including DLTs during and beyond the MTD evaluation period and PK/PD data as available for each patient in the current dose cohort was presented. Based on that, a decision on the next dose level to be tested was made. Dose escalation continued until identification of the MTD, safety concerns arose, or the trial was terminated for other reasons. Further escalation steps above 4.8 mg/kg could occur if deemed appropriate by the SMC.

4.1.2.2 Dose(s) selection for phase Ib

Dose(s) selection for phase Ib was made by the SMC with the aim to select a safe and potentially effective dose range of BI 905711 and is based on integrated analysis of all data collected in phase Ia (including safety, PK, biomarker, tumor response)

Selected dose(s) cannot be higher than the MTD observed in phase Ia, if the MTD was determined.

A patient will receive BI 905711 either as a single administration every two weeks or as a single administration every week for 3 weeks on, 1 week off depending on which dose

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level and regimen the patient is randomised to. Each treatment Cycle has a duration of 14 days.

Table 4.1.2.2: 1 Dose levels of BI 905711 in phase Ib

Dose (mg/kg)	Dose regimen	Treatment Cycle	Treatment Day
0.6	Biweekly (Q2W)	Cycle 1 Every Cycle thereafter	Day 1
1.2			
2.4			
0.6	Weekly (Q1W)	Cycle 1 Every odd-numbered Cycle thereafter	Day 1, Day 8
		Cycle 2 Every even-numbered Cycle thereafter	Day 1

4.1.2.3 Dose modification

Patients who experience DLT (Section 5.2.6.1.5) or any grade 3-4 AE possibly related to BI 905711 should interrupt or delay treatment until recovery to CTCAE grade 1 or baseline condition. Restart of BI 905711 treatment can be considered at reduced dose if toxicity is adequately managed and there is approval from the medical representative of Sponsor.

For phase Ia, the subsequent dose level was reduced to the next lower dose level as specified in Table 4.1.2.1: 1 after approval by the Sponsor and provided SMC has agreed the lower dose level is considered safe.

Patients on the first 3 dose levels who continued treatment after completion of Cycle 4, were considered for intra-patient dose escalation to a higher dose level that was determined as being safe and appropriate by the SMC. More than one dose-escalation was considered if deemed appropriate by the Investigator.

For phase Ib, restart of BI 905711 treatment can be considered at a reduced dose by 25% to 50%, if there is approval from the medical representative of the Sponsor.

No more than 2 dose reductions will be allowed. After a dose reduction, no dose re-escalation will be permitted.

At the time the recommended doses for expansion are determined by SMC, patients that are on any other dose levels may be adapted to the recommended dose at investigator's discretion.

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The dose cannot be escalated if the dose has been previously reduced for toxicity reason.

4.1.3 Method of assigning patients to treatment groups

For phase Ia, treatment slots were assigned to recruiting sites that have identified a potentially eligible patient in consultation with the Clinical Trial Leader (CT Leader) to the current enrolling dose level cohort. Slots were assigned on a competitive basis based upon availability.

Patients enrolled for safety evaluation were assigned to their dose levels by the SMC based on available data on toxicity, PK, PD, and anti-tumor activity, refer to Section 4.1.2.1.

Patients enrolled for efficacy evaluation were assigned to safe dose levels at which objective responses were observed.

Enrollment into the current dose level cohort for dose escalation should have been always prioritized.

If more than one dose cohort for efficacy evaluation was enrolling patients at the same time, the patient should have been enrolled into the dose level which had the lowest patient number (if ties happened, the patient should have been enrolled into the lower dose level first).

For phase Ib, each eligible patient will be assigned to an appropriate expansion cohort, and the appropriate medication number will be assigned via Interactive Response Technology (IRT). Patients will be randomised via IRT into five cohorts (three dose levels in biweekly regimen and one dose level in weekly regimen (3 weeks on, 1 week off)) of BI 905711.

4.1.4 Drug assignment and administration of doses for each patient

The study drug will be prepared and handled according to the ‘Preparation and Handling of BI 905711 for 1412-0001 instructions which will be filed in the ISF. Upon notification that a patient will be treated in the study, the pharmacy will prepare the study drug at the assigned dosage for administration to the patient.

The Cycle 1 Day 1 dose will be calculated using the Cycle 1 Day 1 weight or 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.

BI 905711 will be given as an intra-venous infusion by authorised site staff in a specialised unit where emergency care can be provided (e.g. intensive care unit available, medical personnel trained in advanced life support). Appropriate drugs and medical equipment to treat anaphylactic reactions must be immediately available, and study personnel must be trained to recognise and treat anaphylaxis. No routine premedication will be required for BI 905711 i.v. infusions.

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The 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). 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.

Priming and flushing should not be included in the administration duration. Total storage time for ready-to-use solution at room temperature should not exceed 150 minutes between preparation and end of infusion time.

Post-infusion observation period for phase Ia and phase Ib:

- Patients will remain under surveillance for at least 8 hours after first, second and third administrations of BI 905711. 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, eg. 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 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).

- On the first day of treatment, although patients will not be required to stay overnight at the hospital, they should be advised to remain close to the study site where medical coverage will be ready to support them, if required. Thereafter, patients will be assessed at regular safety visits.

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

4.1.4.1 Management of toxicities

4.1.4.1.1 Management of infusion-related reactions

Infusion-related reactions 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 nonallergic, clinical symptoms are difficult to distinguish and require rapid assessment and immediate management to avoid severe adverse events, including fatality.

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If an infusion-related reaction of ≥ CTCAE Grade 3 occurs, study treatment must be permanently discontinued. If symptoms of an infusion-related reaction of CTCAE Grade 2 occur, which do not qualify as DLT according to Section 5.2.6.1.5, the infusion should be temporarily stopped. Upon recovery, the following guidance should be followed:

- If at least 50% of the planned dose of BI 905711 was administered, no further BI 905711 will be administered until the next scheduled dose.
- If less than 50% of the planned dose of BI 905711 was administered due to an infusion-related reaction, a further dose of 50% of the intended total dose may be administered on the following day and after recovery to baseline for at least 24 hours. Administration may occur within up to 3 days after the original planned dose. Refer to Section 10.2 for details regarding PK and biomarker sample collection. 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.
- During the first re-exposure, patients must remain under observation for at least 8 hours post start of infusion. If required, patients may be hospitalised 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 p.o., or equivalent
    - Antihistamine p.o. or i.v., equivalent to Diphenhydramine 50 mg i.v.
    - Glucocorticoid i.v., equivalent to prednisolone 50-100 mg
- The infusion rate for further treatment cycles may be adapted according to Investigator's decision, but any adaption of the infusion rate must be agreed with the Sponsor. It must not exceed 150 minutes in total as outlined in Section 4.1.4.

If infusion reactions and/or hypersensitivity reactions occur in a substantial proportion of treated patients without premedication, the SMC may decide that all future patients treated in the study must receive premedication (as described above) prior to BI 905711 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.

4.1.4.1.2 Management of Cytokine Release Syndrome (CRS)

CRS is a disorder characterised by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. As outlined above in Section 4.1.4.1.1, clinical manifestations of CRS and other forms of infusion-related reactions are difficult to distinguish (especially at first occurrence) and require rapid diagnosis and immediate management to avoid severe adverse events, including fatality.

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 8 hours following the end of infusion of BI 905711. 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

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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 4.1.4.

In case of suspected or confirmed CRS, patients will be appropriately treated according to institutional standards and/or medical publications (e.g. R16-2323). 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 infusion-related reaction must be followed (Section 4.1.4.1.1).

4.1.4.1.3 Management of diarrhea, nausea and vomiting

The occurrence, severity and duration of diarrhea, vomiting and nausea, and the outcomes of these events will 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 905711. If severe injury to GI tissues is excluded, these events could be managed symptomatically according to Tables 4.1.4.1.3: 1 and 4.1.4.1.3: 2.

Table 4.1.4.1.3: 1 Management of diarrhea

CTCAE Grade	Action for anti-diarrheal treatment	Action for BI 905711
Grade 1	Anti-diarrheal treatment according to the local standard e.g. loperamide p.r.n. and hydration	Continue BI 905711 treatment
Grade 2 > 7 days despite optimal medical management	Anti-diarrheal treatment according to the local standard e.g. loperamide p.r.n, and hydration	Delay BI 905711 treatment until recovery. Consider a colonoscopy. Consider BI 905711 treatment at the reduced dose after recovery to Grade ≤ 1 based on clinical findings
Grade ≥3	Anti-diarrheal treatment according to the local standard e.g. loperamide p.r.n, and hydration	Delay BI 905711 treatment until recovery. Perform colonoscopy. Consider BI 905711 treatment at the reduced dose after recovery based on colonoscopy and other clinical findings.

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Table 4.1.4.1.3: 2 Management of nausea and vomiting

CTCAE Grade	Anti-emetic treatment	Action for BI 905711
Nausea Grade 1	Anti-emetic treatment may be considered according to the local standard e.g. metoclopramide p.r.n.	continue BI 905711 treatment
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.	continue BI 905711 treatment
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	Delay BI 905711 until recovery. Consider a gastrofibroscopy, biochemistry tests (lipase, liver function tests, abdominal imaging (X Ray, ultrasound, CT scan). Consider BI 905711 treatment at the reduced dose only after recovery to Grade ≤ 1 according to clinical findings

4.1.4.1.4 Tumor lysis syndrome

All patients have to be assessed for clinical or laboratory suspicion of tumor lysis syndrome. To prevent tumor lysis syndrome, patients should remain appropriately hydrated throughout the administration period. For details of laboratory assessment, refer to Section 5.2.3. In case tumor lysis syndrome (TLS) is observed, patients should be managed according to local or available guidelines (R10-4517).

4.1.4.1.5 Neurological adverse events

Toxicology studies in cynomolgus monkeys showed that BI 905711 at high doses induced minimal to mild monocytic/eosinophilic cells infiltrates in CNS (c16856466). Clinical significance of these findings for humans is currently unknown. Patients should be monitored for possible neurological toxicity. During dose escalation phase (phase Ia), patients will undergo baseline brain MRI and should be followed for possible new neurological signs and symptoms at each visits of the study drug administration and at end of treatment. Patients who develop worsening or new neurological signs/symptoms CTCAE grade ≥ 2 should undergo full neurological investigation including a brain MRI. Treatment with BI 905711 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.

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4.1.4.1.6 Renal adverse events

Toxicology studies in cynomolgus monkeys showed that BI 905711 at high doses induced minimal to mild glomerulopathy with no proteinuria or increase of serum creatinine and urea (c16856466). Clinical significance of these findings for humans is currently unknown. Patients will be followed periodically for kidney function by measurement of serum creatinine and protein in urine followed by 24 hours quantitative proteinuria in patients with protein + in urine. Patients with proteinuria ≥ CTCAE grade 3 should interrupt BI 905711. Continuation of treatment with BI 905711 at a reduced dose may be considered if proteinuria recovers to ≤ grade 1 within 3 weeks.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

In this open-label trial, treatment allocation will not be concealed throughout the trial. The CRF will contain information on randomised treatment.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

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

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

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

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

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the Sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,

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- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572 (if applicable).

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

Rescue medications to reverse the actions of BI 905711 are not available. Potential adverse events should be treated symptomatically with concomitant medications to provide adequate supportive care as clinically necessary. Section 4.1.4.1 provides guidance for management of toxicities.

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

No experimental or approved anti-cancer treatment including chemotherapy, targeted therapy, immunotherapy, hormone therapy (except hormone replacement), or radiotherapy (other than described in Section 4.2.1) is allowed throughout the study treatment period.

Gonadotropin-releasing hormone or luteinizing hormone releasing hormone analogs for patients with prostate cancer or breast cancer can be continued but should not be initiated during trial.

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

Heparin is incompatible with many injectable preparations e.g. some antibiotics, opioid analgesics, antihistamines and cytotoxics (R20-1190, R20-1191).It has been reported in the literature that many incompatibilities are concentration-dependent (R20-1196, R20-1190). At high concentrations, BI 905711 showed in-vitro incompatibility with heparin but not at clinically relevant concentrations (See IB section 4 for more details). Thus, the use of heparin (including flushing and locking of intravenous catheters) or LMWH is permitted during study treatment. However, the following restrictions must be applied:

- BI 905711 and heparin should not be mixed or infused through the same IV line
- If the same IV line has to be used, flush thoroughly with 0.9% saline prior to and following BI 905711 infusion.
- If a catheter will be locked with heparin, this must be flushed thoroughly with 0.9% saline prior to and following BI 905711 infusion.

In phase Ia, hematopoietic growth factor agents were not allowed for use as primary prevention during the first 2 cycles. Thereafter hematopoietic growth factor agents may have been 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 National Comprehensive Cancer Network guidelines. In Japan, erythropoietic therapy is not approved for anemia caused by cancer chemotherapies.

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 905711 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.

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4.2.2.3 Contraception requirements

WOCBP (for the definition refer to Section 3.3.3) and men able to father a child must use two medically approved methods of birth control throughout the trial, and for a period of at least 3 months after last trial drug intake, one barrier method, and one highly effective non-barrier method.

Men (trial participant or partner of a trial participant) must be vasectomised with documented absence of sperm or use a condom if their sexual partner is a WOCBP.

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

- 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

Or

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

4.3 TREATMENT COMPLIANCE

BI 905711 will be administered as an i.v. infusion under the supervision of the investigator or designated personnel at the investigative site. Dosing will be recorded in the eCRF. Missed or interrupted doses will be recorded in the eCRF with the associated reasons. Compliance may also be verified by pharmacokinetic assessment.

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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 Tumours (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.

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 5.2.6.1.5.

5.2.1 Physical examination

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 and body weight will be performed at the time points specified in the Flowchart. The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated as per institutional practice, 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 5 minutes of rest. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3:1. For the sampling time points, these are performed as per institutional practice.

All analyses will be performed at local laboratory, and the respective reference ranges will be provided in the ISF. Patients do not have to be fasted for the blood sampling for the safety laboratory.

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 (refer to Section 5.2.6).

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In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (refer to Section 5.2.6.1 and the DILI Checklist provided in the EDC system). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

Table 5.2.3: 1 Safety laboratory tests

Category	Parameters
Haematology	Haemoglobin, red blood cell count (RBC), white blood cell count (WBC) with differential, platelets (PLT) count.
Biochemistry	Glucose, sodium, potassium, total calcium, inorganic phosphate, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (AP), amylase[1], lactate dehydrogenase (LDH), total bilirubin (direct and indirect bilirubin in case of elevated total bilirubin values or if required per local guidelines), urea or blood urea nitrogen (BUN), total protein, albumin, uric acid, lipase. 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).
Coagulation	Activated partial thromboplastin time (aPTT), prothrombin time (PT) or, if applicable, international normalised ratio (INR)
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.
Infectious disease	Hepatitis B surface (HBs) antigen, presence of HBc antibody together with HBV-DNA, and presence of hepatitis C RNA. Results for hepatitis virus infection obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date.
Pregnancy	A urine pregnancy test needs to be obtained at the time points indicated in the Flowchart in patients of childbearing potential. A serum pregnancy test should be performed at screening if urine test is positive.

[1]Applicable only to Phase Ib patients

In case a treatment course is delayed due to an adverse event, 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.

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5.2.4 Electrocardiogram

The 12-lead ECGswill be performed per institutional practice . ECGs may be repeated for quality reasons and the repeated recording used for analysis. ECGs will be performed locally.

If necessary, additional ECGs may be recorded for safety reasons.

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

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation,
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,

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- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

For Japan only: the following events will be handled as "deemed serious for any other reason". AEs which possibly lead to disability will be reported as SAEs.

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 further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.

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

Every new occurrence of cancer of new histology must be classified as a serious event regardless of the time since the discontinuation of the trial medication and must be reported as described in Section 5.2.6.2, subsections "AE Collection" and "**AE reporting to Sponsor and timelines**".

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:
Potential Severe DILI

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

For patients with normal hepatic function at baseline:

- an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or

ALT and / or AST elevations ≥10 fold ULN

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- For patients with abnormal aminotransaminase levels; ALT and AST are both between >1 and <3 x ULN at baseline:
    - An elevation of AST and/or ALT ≥3 fold the baseline value combined with an elevation of bilirubin ≥2 fold ULN (if bilirubin is normal at baseline) or ≥2 fold the baseline value (if bilirubin is elevated at baseline), measured in the same blood sample, or in samples drawn within 30 days of each other

    or

    - Aminotransferase elevations (ALT and/or AST ≥5 fold the baseline value).

- For patients with abnormal aminotransaminase levels; ALT and/or AST between ≥3 and <5 x ULN at baseline:
    - An elevation of AST and/or ALT ≥2 fold the baseline value combined with an elevation of bilirubin ≥2 fold ULN (if bilirubin is normal at baseline) and/or ≥2 fold the baseline value (if bilirubin is elevated at baseline) measured in the same blood sample or in samples drawn within 30 days of each other

    or

    - Aminotransferase elevations (ALT and/or AST ≥3 fold the baseline value).

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the “DILI checklist” provided in the eDC system. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are 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 5.2.6.1.4: 1 below.

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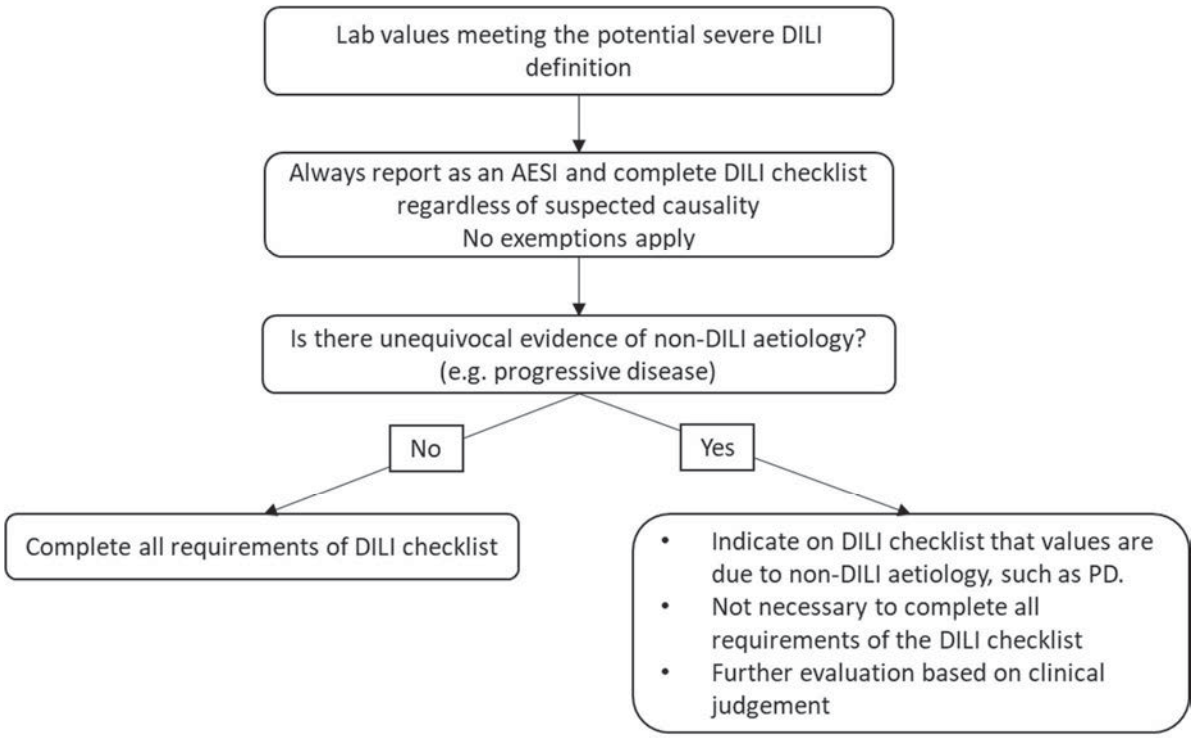

Figure 5.2.6.1.4: 1 Potential severe DILI reporting

Dose Limiting Toxicity
Any medical event fulfilling the criteria of DLT (see Section 5.2.6.1.5) should be reported as an AESI.

Infusion-related reactions and cytokine release syndrome (CRS)
The following terms describe those events that are to be considered infusion-related reactions or CRS. Regardless of grade, these events, when occurring within 72 hours of study drug administration, are considered AESIs and must be reported as such:

- Allergic reaction
- Anaphylaxis
- Cytokine-release syndrome (see description below)
- Serum sickness (may include skin rashes, joint stiffness, and fever).
- Infusion reactions
- Infusion-like reactions
- Any other event which the investigator determines may be a potential infusion-related AE

Treatment of infusion-related reactions and the handling of subsequent trial dosing are described in Section 4.1.4.1.1.

The initial clinical sign of a CRS is fever that can rise to high temperatures and is often associated with flu-like symptoms (e.g. nausea, fatigue, headache, myalgias, malaise, chills, rigor, tremor, hypoxia, tachypnea, rash, vomiting, diarrhea, abdominal pain, muscle and joint

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pain, and generalised weakness). CRS may occur quickly during or after administration, or after several hours or days.

Management guidelines and treatment of CRS are described in Section 4.1.4.1.2.

AESIs are to be reported in an expedited manner similar to SAEs, even if they do not meet any of the seriousness criteria − for details please see Section 5.2.6.1.4.

5.2.6.1.5 Dose limiting toxicities

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

Table 5.2.6.1.5: 1 Dose limiting toxicities

Category	Criteria and CTC AE Grade defining a DLT
Hematologic laboratory	• Grade 4 neutropenia lasting >7 days. • Grade ≥ 3 neutropenia with documented infection. • Grade ≥ 3 febrile neutropenia defined as ANC <1000/mm^3 (< 1.0 x 10^9/L, < 1.0 x 10^3/µL) and a single temperature of ≥ 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour; or where there are life-threatening consequences or urgent intervention indicated. • Grade 3 thrombocytopenia (platelet count ≥ 25,000/m^3 (≥ 25 x 10^9/L, ≥ 25 x 10^3/µL) and <50,000/m^3(< 50 x 10^9/L, < 50 x 10^3/µL) associated with bleeding excluding grade 1 epistaxis. • Grade 4 thrombocytopenia (platelet count <25,000/m^3) (< 25 x 10^9/L, < 25 x 10^3/µL). • Thrombocytopenia or anemia requiring transfusion per local or international guidelines. • Neutropenia that requires administration of hematopoietic growth factor agents per local or international guidelines.

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Table 5.2.6.1.5: 1 Dose limiting toxicities (cont.)

Category	Criteria and CTC AE Grade defining a DLT
Non-hematologic laboratory	• Any Grade 3 or Grade 4 non-hematologic laboratory value if: - Medical intervention is required to treat the patient, or - The abnormality is a serious adverse event, or - The abnormality persists >1 week, and considered significant enough to be qualified as DLT in the investigator's opinion, and confirmed by the SMC. • An elevated AST or ALT value ≥ 3 x the upper limit of normal (ULN) and an elevated total bilirubin value ≥ 2 x ULN measured in the same blood draw sample and, at the same time, an alkaline phosphatase value < 2 x ULN, as determined by way of protocol-specified lab testing or unscheduled lab testing. • An elevated AST or ALT value ≥ 5 x ULN and an elevated total bilirubin value ≥ 2 x ULN measured in the same blood draw sample, with the exclusion of causes due to underlying diseases (for patients with elevated liver enzymes at baseline).
Non laboratory	• Any Grade 4 non laboratory toxicity possibly related to study therapy, irrespective of whether patient received maximal supportive therapy. • Any Grade 3 non laboratory toxicities despite the use of adequate/maximal medical interventions and/or prophylaxis as dictated by local institutional clinical practices or the judgment of the investigator, except for: - Fatigue/ asthenia present at baseline that worsens on study and lasts less than 7 days. - New onset of Grade 3 nausea or Grade 3 vomiting lasting ≤ 48 hours, and which resolved to ≤ Grade 1 either spontaneously or with conventional medical intervention. - Nausea or vomiting present at baseline that worsens on-study, and resolves with treatment within 24 hours. - Grade 3 diarrhea not requiring hospitalization, lasting ≤ 48 hours, and which resolved to ≤ Grade 1 either spontaneously or with conventional medical intervention. • Any other toxicity considered significant enough to be qualified as DLT in the opinion of the investigator, and confirmed by the SMC, will be reported as a DLT. • Any toxicity Grade ≥ 2 leading to dose reduction will be considered as a DLT. • Any death not clearly due to the underlying disease or extraneous causes.
Treatment delay	• Any toxicity that result in a treatment delay >14 days

Dose-limiting toxicities (DLTs) will be recorded throughout the trial. Any DLT must be reported 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. All DLTs will be agreed upon by the SMC after review of the data from each cohort. Only DLTs occurring in the first two cycles are necessary for dose-escalation decisions made by the SMC. 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 RP2D.

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Replacement of patients for DLT evaluation during MTD evaluation period

For the definition of DLT, it is essential that patients were sufficiently treated according to supportive care standards described in Section 4.1.4.1. Patients with treatable AEs (nausea, vomiting, and diarrhea) that were not sufficiently treated did not qualify for DLT and needed to be replaced, if this occurred in Cycle 1 or 2. Dose escalation was determined based on all the safety information of all treated patients including those who do not complete the first 2 cycles for reasons other than a DLT. Criteria for replacement of patients during the MTD evaluation period is described in Section 3.3.4.4.

5.2.6.1.6 Intensity (severity) of AEs

The intensity (severity) of adverse events should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) (R18-1357).

5.2.6.1.7 Causal relationship of AEs

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

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.

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- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 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 on the appropriate CRF(s) by the investigator:

From signing the informed consent onwards until the follow-up visit 1 (including the Residual Effect Period, REP):
- all AEs (non-serious and serious) and all AESIs.
- After Follow Up visit 1 until the individual patient's end of trial:
  cancers of new histology and exacerbations of existing cancer, all related SAEs and all related AESIs.
- After the individual patient's end of the trial:
  the investigator does not need to actively monitor the patient for new AEs but should report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see section 5.2.6.2.2), but not on the CRF.

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

Vital Status Data Collection

Patients who discontinue trial medication prematurely, who agree to be contacted further but do not agree to physical visits, should be followed as described in Section 3.3.4.1, withdrawal from trial treatment. From then on until the individual patient's end of the trial the investigator must report all deaths/fatal AEs regardless of relationship, and trial treatment related SAEs and trial treatment related AESIs the investigator becomes aware of.

For description of trial completion for an individual patient, refer to Section 6.2.3.4.

5.2.6.2.2 AE reporting to the Sponsor and timelines

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

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

5.2.6.2.3 Pregnancy

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

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

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

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

5.2.6.2.4 Exemption to (S)AE reporting

Collection and reporting of PD
The outcome progressive disease (PD) is used to assess trial endpoints for the analysis of efficacy. It will be recorded on the appropriate page of the eCRF. Only if it meets standard seriousness criteria (see 'Serious adverse event' definition) it will also be recorded on the AE page in the eCRF and on the BI SAE form and SAE reporting process will be followed.

Clinical symptoms and/or signs of PD will be recorded on the AE page in the eCRF. If signs and symptoms of progressive disease (PD) of the patient's underlying malignancy meet standard seriousness criteria, they will additionally be reported on the BI SAE form and SAE reporting procedures will be followed.

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5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

BI 905711 PK parameters will be calculated according to the relevant BI internal procedures.

Pharmacokinetic (PK) profiles of BI 905711 will be investigated after the first and after repeated doses. Standard PK parameters as listed in Appendix 10.1 will be calculated, if data allows and if scientifically reasonable. Noncompartmental PK parameters will be calculated based on actual sampling times using a validated PK software Phoenix WinNonlinTM (version 8.1.1 or higher, [redacted]) or SAS Version 9.4 (or later version).

. Statistical analyses will be performed as described in Section 7.3. A patient's PK data will be flagged and excluded from the statistical analyses in case of protocol violations relevant to the evaluation of PK (to be decided no later than in the Blinded Report Planning Meeting or in case of PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Reasons for exclusion of a patient's data will be documented in the Clinical Trial Report (CTR).

PK data may additionally be analyzed using population PK approach. If required, modelling activities will be planned and documented separately according to internal and external guidelines and SOP.

Preliminary PK analyses can be performed as necessary, e.g. for SMC decisions. In contrast to the final PK analysis, the preliminary analyses will be based on planned sampling times rather than on actual times; no supplementary patient information, e.g. on AEs or concomitant medication, will be used in these analyses, and the outputs will not be validated. Minor discrepancies between preliminary and final results may therefore occur.

5.3.2 Methods of sample collection

Effective from CTP v7.0, PK and ADA samples are no longer collected for ongoing patients.

The timepoints for collection of PK and ADA samples are given in Appendix 10.2. Details of the sample collection, preparation, storage and shipment are described in the ISF/laboratory manual.

Date and clock time of drug administration(s) and PK sampling will be recorded in the CRFs. Exact time points of plasma sampling will be documented in the CRFs by the medical personnel or sent as electronic files to the Trial Data Manager.

The samples may be used for further methodological investigations, e.g. for further investigations to characterise ADA response or to address Health authority questions regarding the results/methodology, stability testing, however, only data related to the analyte and anti-drug antibodies will be generated by these additional investigations.

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[redacted] It is not intended to include the results from such analysis in the clinical trial report. The results may be provided in a stand-alone report.

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

[redacted]

5.3.4 Pharmacokinetic – pharmacodynamic relationship

No formal analysis of a pharmacokinetic/pharmacodynamic relationship is planned. Correlation between drug concentration and response may be made if adequate data are available. In addition, exploratory correlation may also be made between drug concentration and AEs. If required, modeling activities will be planned and documented separately according to internal and external guidelines and SOP.

5.4 [redacted]

[redacted]

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[redacted]

5.4.1 Methods of sample collection

Effective from CTP v7.0, biomarker samples, and optional tumor biopsies at C2D3 and disease progression are no longer collected for ongoing patients.

5.4.1.1 Tumor tissue

Tumor tissue collection in Phase Ia

- Pre-treatment and on-treatment fresh tumor biopsy collections for biomarker analyses were considered optional in phase Ia.
- In phase Ia, an archived tumor tissue specimen must be submitted (mandatory).

Tumor tissue collection in Phase Ib

- Pre-treatment fresh tumor biopsy collections for biomarker analyses are considered mandatory in phase Ib. For PDAC patients, CDH17 expression measured in archival tumor tissue within $\leq$ 6 months or a fresh biopsy sample must be completed as part of screening visit 1 for PDAC cohort. If archival tumor tissue is submitted for screening visit 1, then a fresh biopsy must be provided prior to treatment start on Day 1.
- An additional on treatment fresh tumor biopsy should be taken on Cycle 2 Day 3 (optional) and/or at disease progression (optional) for a patient in which a fresh biopsy has been successfully obtained before first study treatment.
- In case a fresh pre-treatment tumor biopsy cannot be obtained due to the below-mentioned reasons, an archived tumor tissue specimen obtained within $\leq$6 months of screening must be submitted (mandatory).
- In case the patient undergoes baseline tumor biopsy, an archival tumor tissue must also be submitted (mandatory) regardless of the date of collection.

- Only non-significant risk procedures per the investigator's judgment will be used to obtain any biopsies specified in this study.

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- For fresh biopsies always use the equivalent of at least two core needle biopsies (18 gauge or greater).

- Tissue needs to be provided as formalin-fixed and paraffin-embedded tissue block. In case a tissue block cannot be collected as indicated, the site needs to contact the Sponsor for agreement regarding fresh biopsy collection. Potential prioritization of the biomarker analyses might be made according to the available tissue amount.

- Archival tumor tissue sample should be provided as FFPE-preserved tissue, preferably as an embedded block and less preferably as mounted tissue sections prepared under RNase free conditions. In case tissue cannot be collected as indicated, the site needs to contact the Sponsor for agreement regarding tissue collection.

- Timepoints for fresh tumor biopsy collection are detailed in the Flowchart.

5.4.1.2 Plasma samples

[redacted]

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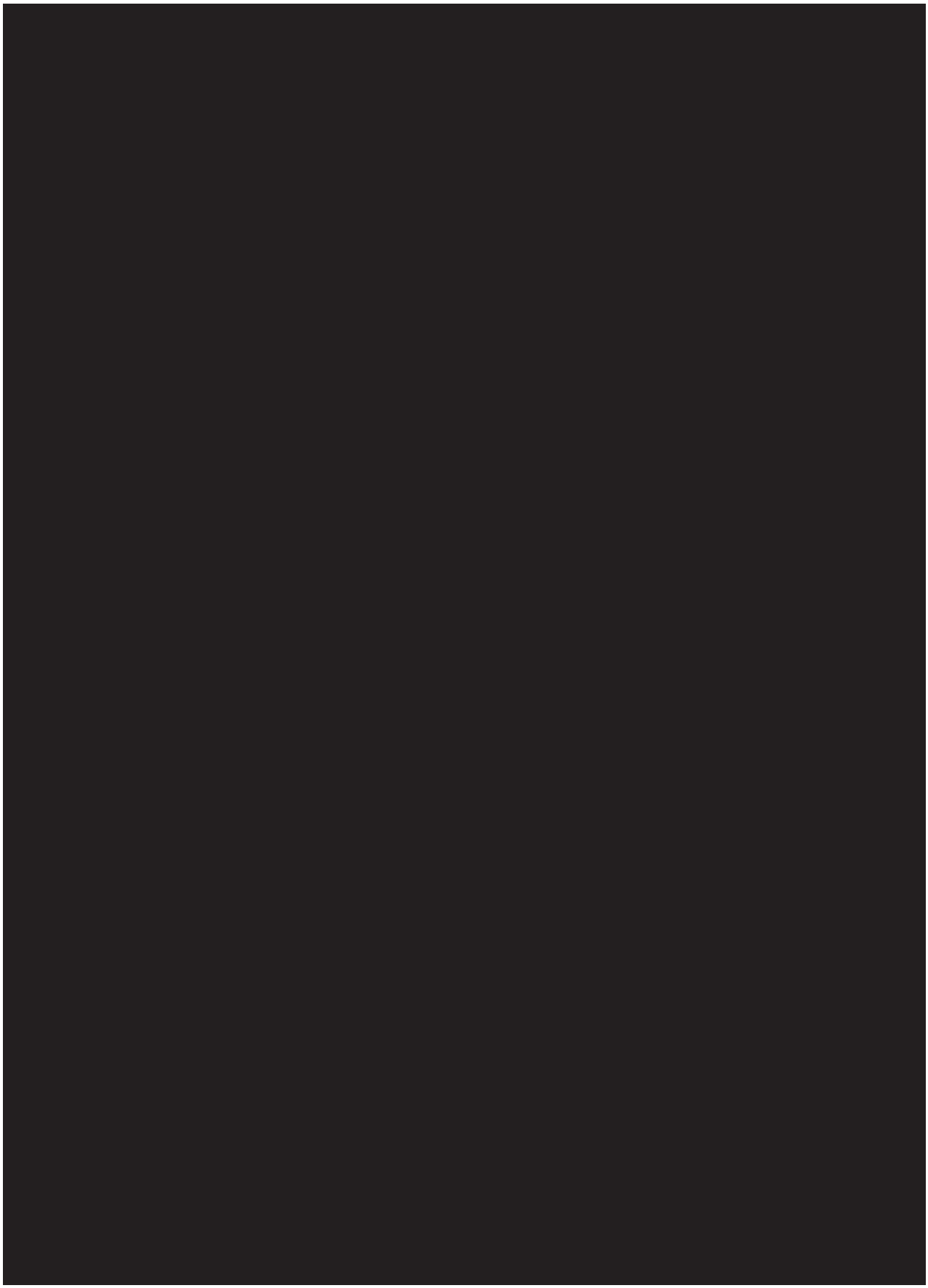

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[redacted]

5.5 BIOBANKING (OPTIONAL)

The therapeutic benefit or occurrence of specific adverse events in patients cannot always be anticipated during the trial setup. Later on there may be new scientific knowledge about biomarkers and other factors contributing to diseases or the action of a drug. In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking. If the patient agrees, banked samples may be used for future drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event, and thereby better match patients with therapies or to gain mechanistic understanding of drug effects and/or to identify genetic or other factors associated with response to therapy or the risk of adverse drug reactions. Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking samples will only be banked after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, see Section 8.5.1.

The leftovers of the following biomarker samples as specified in Section 5.4 might be banked:

- Leftover tumor tissue or derivatives (e.g., RNA, DNA)
- Leftover from patient's plasma

5.5.1 Methods and timing of sample collection

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

All leftover biomarker samples (except for sample for genomic DNA), as specified in Section 5.4, may be banked if the biobanking consent has been signed by the patient. Samples will be stored at an external biobanking facility contracted by the Sponsor. If the patient has not consented to optional biobanking (see Section 5.5) trial samples left over after primary analysis will be discarded after completion of these additional investigations but not later than 5 years after the final trial report has been signed.

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5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

Measurements performed during this trial are in accordance with measurements in phase I oncology trials in order to monitor safety and determine efficacy and PK parameters. Toxicities will be graded according to CTCAE V5.0 (R18-1357), and tumor response will be evaluated according to RECIST 1.1 (R09-0262).

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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 enrollment log (see ISF) and documented in the eCRF. All patients are to adhere to the visit schedule as specified in the Flowchart.

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.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Screening for Phase Ia, and Phase Ib CRC patients
The examinations required for the screening visit may be conducted within a time interval of 28 days prior to the first study drug administration. Tumor assessments performed prior to informed consent as part of routine clinical practice will be accepted if they meet the requirements of the protocol and are performed within 28 days prior to treatment start.

Screening for Phase Ib PDAC patients
There are two screening visits for PDAC patients in Phase Ib: screening Visit 1 (SV1) for CDH17 status, and screening Visit 2 (SV2) for entry into the treatment period and treatment.

Screening visit 1 (SV1) for CDH17 status
The purpose of SV1 for CDH17 status is to offer testing for CHD17 status in archival tumour tissue or in fresh biopsy before proceeding into SV2 for entry into the treatment period.
This procedure will require a separate informed consent (Tissue Analysis Consent) for assessment of CHD17 expression via a central laboratory designated by the sponsor.

No maximum time between SV1 for CDH17 status and SV2 for entry into the treatment period is defined, and the two screening visits can occur in parallel.

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Therefore, patients can be enrolled in the SV1 for CDH17 status at any time, even while ongoing on other treatments and/or clinical trials.

Screening visit 2 (SV2) for entry into the treatment period
The purpose of SV2 is to check full patient eligibility according to in/exclusion criteria. Following informed consent for main study, patients will undergo screening assessment as indicated in the Flowchart.

The SV2 assessments should be performed after CDH17 status is known within 28 days prior to start of treatment (screening visit window) but do not need to be performed on the same day.

For patients whose eligibility was based on archival tissue that is more than 6 months old during SV1, a confirmatory test will be performed on a fresh biopsy that should be collected during SV2. SV2 fresh biopsy analysis will not prevent patient enrolment, should SV1 analysis show CDH17 positivity. SV2 analysis will be only used as a retrospective confirmation of CDH17 positivity.

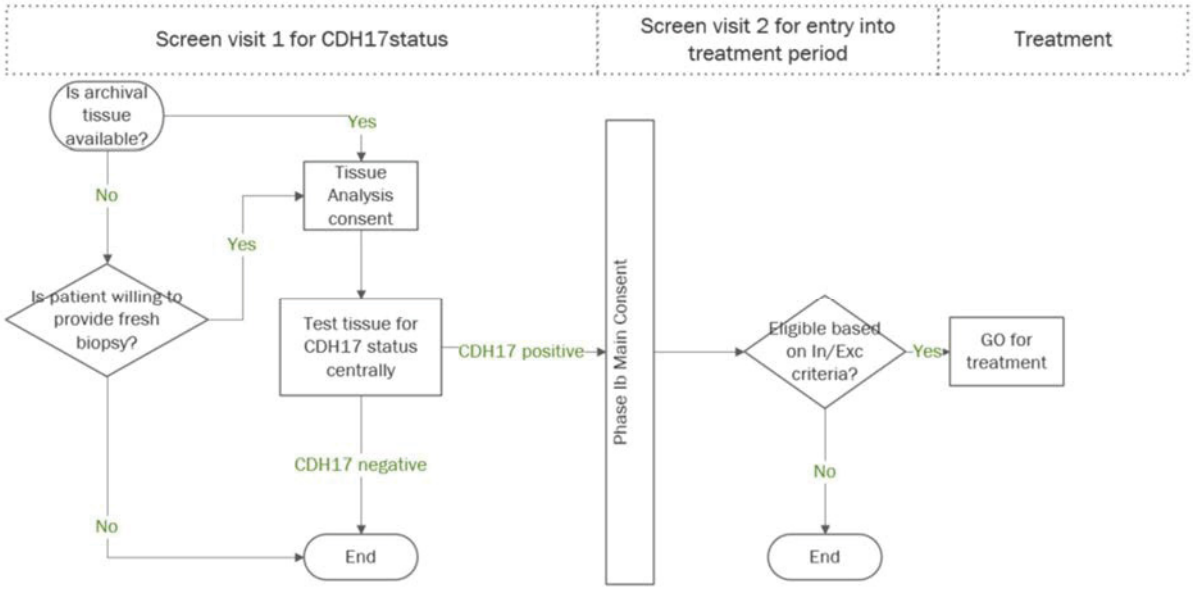

Figure 6.2.1:1 Selection of PDAC patients for study treatment based on SV1 for CDH17 status and on SV2 for entry into the treatment period.

Baseline Conditions
Any new clinically relevant findings assessed during the screening visit should be included in the eCRF. Baseline conditions including demographics, sex, birth date, race, and ethnicity (in accordance with local laws and regulations), and concomitant diagnoses and/or therapies present during screening, will be recorded in the eCRF.

Medical History

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Oncological and relevant non-oncological baseline conditions should be recorded in the eCRF.

For oncological history, the following parameters will be reported on the eCRF:

- The type of tumor, the date of the first histological diagnosis (month and year may be sufficient), and the primary tumor site.
- Any known genomic alterations such as BRAF, KRAS, HER2, BRCA...etc, and the immune markers status such as microsatellite instability and/or DNA mismatch repair deficiency...etc.
- The differentiation grade (not specified, undifferentiated, poorly differentiated, moderately differentiated, well differentiated) obtained at the time of diagnosis and the location of metastatic sites will be provided as obtained at diagnosis and at study screening.
- Previous treatment for the cancer, including any surgery, radiotherapy, and or systemic therapy will be reported.
- Previous tumor response data (i.e. from prior treatment) if available. At least one prior pre-study digital scan of the target lesion should be sent to the central imaging facility of an independent vendor if available.

Date of tumor progression after previous lines of treatment will be recorded, if known, including start and end dates and the outcome.

6.2.2 Treatment period(s)

If a patient is eligible for trial participation, the Cycle 1 Day 1 assessments may be performed as listed in the Flowchart.

Subsequent visits during the treatment period are performed as described in the Flowchart. Patients may continue on treatment for unlimited cycles, until criteria for stopping treatment are met (see Section 3.3.4).

6.2.3 Follow up period and trial completion

6.2.3.1 End of treatment (EOT) visit

The EOT visit will be performed as soon as possible but not later than 7 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 assessments of the EOT visit will then be performed instead of at the next planned visit.

6.2.3.2 Follow-up visits

The REP is defined in Section 1.2. The first follow-up visit corresponds to the End of REP (EOR) visit and may not be performed earlier than 30 days (+ ≤ 5 days) after permanent discontinuation of the trial medication. The information collected at this visit must include all new AEs that occurred after EOT and a follow-up of AEs ongoing at EOT.

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6.2.3.3 Extended follow-up period

The end of study is defined as EOR. No further follow-up visits after EOR are required, unless follow-up is for S(AE) that occurred before EOR period.

If death date is known, this should be reported in the CRF.

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

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

The trial will be performed as an open-label trial. There will be 2 parts phase Ia and Ib, which have different objectives and designs.

Phase Ia:
The primary objective of phase Ia is to determine the MTD of BI 905711 defined as the highest dose with less than 25% risk of the true DLT rate being equal or above 0.33 (EWOC criterion). Dose-escalation will be guided by a two-parameter Bayesian Logistic Regression Model (BLRM), escalating with overdose control (EWOC) (R13-4803; R13-4806).

The Bayesian logistic regression model (BLRM) is formulated 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* = 3.6 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 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. However, according to the dose selection scheme in Table 4.1.2.1:1, the maximum allowable dose increment for each escalation step shall not be more than 230%.

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 15 patients have been treated in phase Ia, of which at least 6 at the MTD.

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

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

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

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

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

Prior derivation:
For the current trial, no relevant information in the form of human data was available, since no trial has been conducted before. Therefore, the three mixture components are established as follows:

1. A weakly informative prior was derived to reflect a priori assumption that the median DLT rate at the starting dose of 0.02 mg/kg would equal 1%, and the median DLT rate at 4.8mg/kg would equal 15%. This yields $\mu_1 = (-1.885, -0.650)$. The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11} = 2$, $\sigma_{1,22} = 1$ and $\rho_1 = 0$, respectively. The prior weight a_1 for the first component was chosen as 0.9.
2. A high-toxicity weakly informative prior was derived to reflect 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 0.02mg/kg would equal 20%, and the median DLT rate at 4.8mg/kg would equal 60%. These assumptions yield $\mu_2 = (0.311, -1.118)$. 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 to reflect 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 0.02mg/kg would equal 0.1%, and the median DLT rate 4.8mg/kg would equal 2%. These assumptions yield $\mu_3 = (-4.050, -0.598)$. The standard deviations and correlations were set to $\sigma_{3,11} = 5$, $\sigma_{3,22} = 0.01$, therefore almost fixing the slope parameter to its mean. The correlation was set to 0, i.e. $\rho_3 = 0$. The prior weight a_3 for the third component was chosen as 0.05.

A summary of the prior distribution is provided in Table 7.1: 1. Additionally, the prior probabilities of DLTs at different doses, as well as the corresponding probability of under-, targeted and overtoxicity, are shown in Table 7.1: 2. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 7.1: 1. As can be seen from both,

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the table and the figure, the prior medians of the DLT probabilities are in-line with the prior medians derived from the weakly informative prior, and the uncertainty around the medians is large, showing the low amount of information this prior provides. This is also supported by the prior sample size, i.e. the information contained in the prior. This is approximately equal to 1.5 patients. A detailed evaluation of the model using hypothetical data scenarios and operating characteristics is provided in the statistical Appendix 10.3.

Table 7.1: 1 Prior distribution

Prior Component	Mixture Weight	Mean vector	SD vector	Correlation
1: Weakly inf.	0.900	-1.885 -0.650	2.000, 1.000	0.000
2: High Tox	0.050	0.311 -1.118	2.000, 1.000	0.000
3: Low Tox	0.050	-4.050 -0.598	5.000, 0.010	0.000

Table 7.1: 2 Prior probabilities of DLT at selected doses

Dose	Probability of true DLT rate in					Quantiles		
	[0–0.16)	[0.16–0.33)	[0.33–1]	Mean	SD	2.5%	50%	97.5%
0.02	0.862	0.063	0.075	0.076	0.165	0.000	0.007	0.653
0.06	0.832	0.075	0.093	0.092	0.180	0.000	0.012	0.714
0.2	0.785	0.096	0.119	0.116	0.200	0.000	0.023	0.778
0.6	0.725	0.115	0.160	0.149	0.222	0.000	0.043	0.830
1.2	0.670	0.134	0.196	0.178	0.239	0.000	0.067	0.865
2.4	0.591	0.157	0.252	0.220	0.258	0.001	0.103	0.902
3.6	0.533	0.169	0.298	0.253	0.273	0.002	0.137	0.922
4.8	0.488	0.174	0.338	0.282	0.286	0.002	0.169	0.940

Doses printed in bold face meet the overdose criterion (P (overdose) < 0.25))

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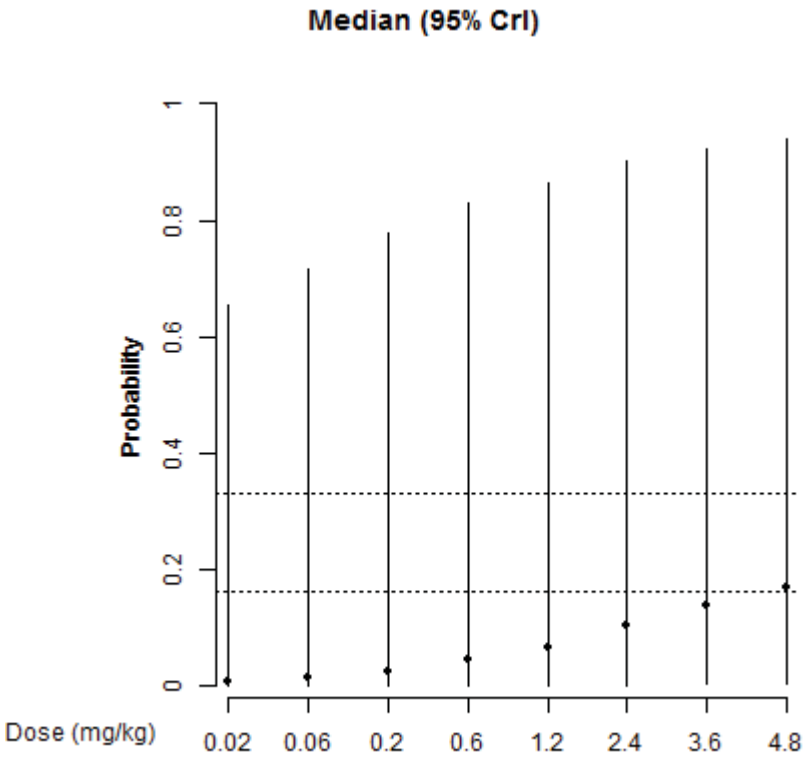

Figure 7.1: 1 Prior medians and 95% credible intervals

Beyond the abovementioned BLRM that considers mainly DLT probability, in order to select the dose(s) for phase Ib, we will also consider plasma PK data, biomarker and efficacy data as available. For example, a BLRM that computes the posterior probability of the plasma PK (AUC) falling in a target range (e.g. 80% maximal efficacy exposure) if applicable.

Phase Ib:
In this phase, patients will be randomised into five cohorts of BI 905711 with approximately 80 patients (see section 4.1.2.2). Dose(s) selection for phase Ib was made by a SMC with the aim to select a safe and potentially effective dose range of BI 905711 based on all data collected in phase Ia.

Data collected during this phase Ib will be recorded and presented by descriptive statistics.

If applicable, we may use Bayesian hierarchical models incorporating biomarker information to support decision-making in selecting the RP2D.

If the trial is terminated due to unexpected causes, only descriptive analysis will be provided.

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7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing is planned in this trial. All analyses in this trial are descriptive and exploratory in nature.

7.3 PLANNED ANALYSES

Analysis of efficacy and safety will be based on the treated set, which will consist of all patients who receive at least one dose of BI 905711.

For the determination of the MTD, only DLT evaluable patients will be considered. Patients will be analyzed according to their starting doses. Any other analysis sets will be defined in the TSAP. No per protocol set will be used in the analysis. However, important protocol violations will be summarised. The TSAP will specify the important protocol violations in detail.

7.3.1 Primary endpoint analyses

Phase Ia: In order to determine the MTD, the number of patients with DLTs will be assessed per dose level in phase Ia. The MTD will be determined as described in Section 7.1. Patients with DLTs that occurred during the first two treatment cycles and later cycles may be tabulated separately.

For doses that will be recommended for phase Ib, totality of data will be considered including efficacy and PK. Details are described in Section 3.1.1.

Time frame: Database lock (DBL) will occur when either MTD is found or the recommended dose range for phase Ib is determined, and all the patients have had at least 2 post-baseline tumor assessment timepoints excluding patients who have discontinued earlier.

Phase Ib:
The primary endpoints in the dose-expansion part are objective response (OR) and PFS derived from the data of all cycles. The PFS will be summarized using PFS4 rate, defined as the proportion of patients with PFS >= 4 months, and will be presented descriptively. Objective response will be analyzed in terms of objective response rate (ORR), defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR). For each dose level, the proportion of patients with objective response (CR and PR) will be calculated with 95% confidence interval.

The observed response rate and PFS4 rate for different dose levels will be compared to recommend the optimal dose level (RP2D). If applicable, a Bayesian hierarchical model will be used to get the adjusted response rate for each dose level, and comparisons will be made among different dose levels to make a recommendation on the optimal dose level (RP2D).

Time frame: The database lock will occur after all treated patients have had at least three post-baseline tumor assessment timepoints (unless patients discontinue the treatment early due to any reasons). A clinical trial report will follow.

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7.3.2 Secondary endpoint analyses

Secondary endpoints will be analyzed by descriptive statistics. PK analyses are specified in Section 7.3.5 and Section 5.3.

Time frame: the same as the primary endpoint analyses time frame.

Details will be provided in the TSAP.

[redacted]

7.3.4 Safety analyses

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

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

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

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

Laboratory data will be 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 summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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

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7.3.5 Pharmacokinetic and pharmacodynamic analyses

The PK parameters will be calculated by means of non-compartmental analysis. Descriptive statistics will be used to evaluate plasma concentration data and PK parameters. PK parameters will be calculated according to the relevant BI internal procedures.
Further details on analysis will be described in the TSAP.

7.4 INTERIM ANALYSES

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

For efficacy, in phase Ib, an arm 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 observed in patients enrolled in phase Ib, 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 analysis 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 analysis. This will be performed to support dose escalations 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 analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. No formal preliminary PK and immunogenicity report will be written.

7.5 HANDLING OF MISSING DATA

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

Pharmacokinetcis:

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.

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If the actual sampling time is not recorded or is missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.6 RANDOMISATION

For phase Ib, patients will be randomised into four cohorts of BI 905711 with approximately 60 patients. BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. Access to the randomisation list will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

No formal statistical power calculations to determine sample size were performed for this trial. In total, approximately up to 140 patients are planned (approximately 40 evaluable CRC patients and 20 non-CRC GI cancer patients for phase Ia, approximately 60 evaluable CRC patients and 20 PDAC patients for phase Ib) for this study.

For phase Ia:
Given the pre-specified possible dose levels (Table 4.1.2.1: 1) and the number of patients per dose level, approximately 28 CRC patients will be needed to complete dose escalation.

The actual number of patients will depend on the number of dose cohorts and the cohort sizes actually tested. Based on the simulation studies to evaluate operating characteristics of the BLRM (see Appendix 10.3), on average 20-36 evaluable patients are expected to be treated in the dose escalation part for safety evaluation for the model to have reasonable operating characteristics relating to its MTD recommendation.

In addition, 12 CRC patients are planned for efficacy evaluation in phase Ia. Thus, for planning purpose, a total of 40 CRC patients and 20 non-CRC patients are planned for phase Ia.

For phase Ib (Part B):
For planning purposes, up to 15 CRC patients per each dose group for up to 4 cohorts, i.e. total of up to 60 CRC patients, and up to 20 PDAC patients for the single arm cohort will be enrolled for this part.

A Bayesian Hierarchical Model (BHM) approach (R13-4803) will be used to analyze the PFS4/ORR rate based on all data from different arms. The simulation results in Table 7.7: 1 show that with the proposed sample size per arm, the BHM approach has reasonable performance under a wide range of scenarios. The probability of passing the positive boundaries under a negative scenario is well controlled per arm (<= 3%). The probability of passing the positive boundaries under a positive/mix scenario is at least 75% per arm.

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Table 7.7: 1 Operating characteristics of the BHM approach in dose expansion arms under different scenarios

Scenario: PFS4 (%)/ORR (%) **Prob.** $PFS4_{BHM}$ **≥ positive boundaries or** ORR_{BHM} **≥ positive boundaries**					
Arms	**0.6 mg/kg Biweekly**	**1.2 mg/kg Biweekly**	**2.4 mg/kg Biweekly**	**0.6 mg/kg Weekly**	**Prob.** $PFS4_{BHM}$ **≥ positive boundaries or** ORR_{BHM} **≥ positive boundaries in *at least one arm***
Positive boundaries	**50%/15%**	**50%/15%**	**50%/15%**	**50%/15%**	
Negative scenario: PFS4/ORR Prob. $PFS4_{BHM}$ ≥ boundaries or ORR_{BHM} ≥ boundaries	35%/1% 3%	35%/1% 3%	35%/1% 3%	35%/1% 3%	10%
Mixed scenario: PFS4/ORR Prob. $PFS4_{BHM}$ ≥ boundaries or ORR_{BHM} ≥ boundaries	60%/20% 75%	40%/10% 27%	40%/1% 19%	40%/1% 18%	79%
Positive scenario: PFS4/ORR Prob. $PFS4_{BHM}$ ≥ boundaries or ORR_{BHM} ≥ boundaries	60%/15% 95%	60%/15% 94%	60%/15% 95%	60%/15% 95%	99%

Prob. = Probability. $PFS4_{BHM}$ = Shrinkage estimator of the PFS4 rate based on the BHM. ORR_{BHM} = Shrinkage estimator of the ORR rate based on the BHM. Probabilities of $PFS4_{BHM}/ORR_{BHM}$ ≥ positive boundaries are based on 1000 simulations per scenario. Positive boundaries represent pre-specified PFS4/ORR rates.

If DLTs are observed at a certain dose level during phase 1b and the BLRM shows that the dose level does not fulfill the overdose risk control, it may be considered to stop that dose level due to over toxicity.

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

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

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

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

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Copies of source documents necessary for CT/MRIs or ECGs may be provided for safety review. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

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

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing 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, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The Sponsor will also monitor compliance with the protocol and GCP.

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

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8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in Section 8.7.
Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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

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

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

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

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8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed") 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 patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.

The "**Last Patient Last Visit Primary Endpoint (LPLV PE)**" is defined as the date at which the last patient was examined or received an intervention for the purposes of final collection of data for the primary endpoint (according to the protocol specified schedule or after premature discontinuation) for each part of the trial. Patient treatment and follow up may continue after this time point. For phase Ia, if the last patient is enrolled for dose escalation evaluation, this is the date when the patient has had Cycle 3 Day 1 visit or EOR visit (if the patient is discontinued early). If the last patient is enrolled for efficacy evaluation in phase Ia or Ib, this is the date when the patient has had at least three tumor assessment timepoints (unless the patient discontinues the treatment early due to any reasons).

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the Sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

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The following committees will be established to evaluate data and allow transition between components of the study.

SMC (Safety Monitoring Committee)
The SMC served for decision regarding dose escalation in phase Ia and dose(s) determination for phase Ib. SMC will be composed of participating investigators in dose escalation and members of the BI trial team. SMC reviewed individual and aggregated safety data at regular intervals to determine the safety profile and risk/benefit ratio and recommend next dose level and appropriateness of further enrollment into dose level cohorts following escalation rules as described in the CTP. Details of the SMC responsibilities and procedures were described in the SMC charter.

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

BI has appointed a CT Leader, responsible for coordinating all required activities, in order to
- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

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

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

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF. An IRT vendor will be used in this trial. Details will be provided in the IRT Manual, available in the ISF.

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10. APPENDICES

10.1 PHARMACOKINETIC ANALYSES

If feasible, BI 905711 PK parameters will be calculated according to the relevant BI internal procedures.

After the first doses:

- Cmax (maximum measured concentration)
- AUC0-∞ (area under the concentration-time curve over the time interval from zero extrapolated to infinity)
- AUC0-tz (area under the concentration-time curve over the time interval from 0 up to the last quantifiable data point)
- t_z (time point of the last quantifiable plasma concentration)
- %AUCtz-∞ (the percentage of the AUC0-∞ that is obtained by extrapolation)
- AUCt1-t2 (area under the concentration time curve over the time interval t1 to t2)
- tmax (time from dosing to the maximum measured concentration)
- Cpre,N (the pre-dose concentration of the analyte in plasma immediately before administration of the Nth dose after N-1 doses were administered)
- t1/2 (terminal half-life)
- CL (total clearance of the analyte)
- Vz (apparent volume of distribution during the terminal phase)
- Vss (volume of distribution after intravenous infusion)

If feasible, the following additional PK parameters may be determined after repeated doses [e.g. if steady state can reasonably be assumed, the parameters will be denoted with ss as shown; otherwise, they will be denoted with the dose number of the last dose]:

- Cmax,ss (maximum measured concentration at steady state)
- Cmin,ss (minimum concentration at steady state)
- tmin,ss (time to reach minimum concentration at steady state)
- Cavg (average concentration at steady state)
- Cpre, N,ss (pre-dose concentration at steady state immediately before administration of the next dose)
- AUCτ,ss (area under the concentration-time curve at steady state over a uniform dosing interval τ)
- AUCt1-t2,ss (area under the concentration time curve over the time interval t1 to t2 at steady state)
- tmax,ss (time from last dosing to maximum concentration at steady state)
- $t_{z,ss}$ (time of last measurable concentration within the dosing interval τ at steady state)
- λz,ss (terminal rate constant at steady state)
- t1/2,ss (terminal half-life at steady state)
- MRTinf,ss (mean residence time in the body after intravenous infusion at steady state)
- CLss (total clearance at steady state)
- Vz,ss (volume of distribution during the terminal phase after multiple intravascular administrations at steady)

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- Vss,ss (volume of distribution after multiple intravascular administrations at steady state)
- RA,Cmax (accumulation ratio based on Cmax)
- RA,AUC (accumulation ratio based on AUC0-τ)
- RA,$C_{pre,N}$ (accumulation ratio based on $C_{pre,N}$)
- LI (linearity index, $AUC_{\tau,ss}/AUC_{0-\infty}$)
- PTF (Peak-Trough Fluctuation)

If deemed necessary, further appropriate pharmacokinetic parameters might be calculated.

10.2 TIME SCHEDULE FOR PK AND BIOMARKER BLOOD SAMPLING – NO LONGER APPLICABLE PER CTP V7.0

Table 10.2: 1 Time schedule for PK and Biomarker blood sampling for phase Ia - No longer applicable per CTP v7.0

Treatment Course	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK	ADA	[redacted]
Pre-Cycle 1	Screening	001	-28 to -5	0:00	0:00	Blood sampling			
Cycle 1	C01_D01	101	1	Just before start of infusion (SOI)	-0:05	Blood sampling	X	X	
				0:00	0:00	SOI	---		
				Immediately before end of infusion[b]	0:30	Blood sampling	X		
				7 hours post SOI	7:00	Blood sampling	X		
	C01_D02	102	2	24 hours post SOI	24:00	Blood sampling	X		
				Just before SOI of the further infusion[f]	23:55	Blood sampling	X		
				Immediately before end of further infusion [f]	24:30	Blood sampling [f]	X		
	C01_D03	103	3	48 hours post SOI	48:00	Blood sampling	X		
	C01_D08	108	8	168 hours post SOI	168:00	Blood sampling	X		

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Table 10.2: 1 Time schedule for PK and Biomarker blood sampling for phase Ia (cont.) - No longer applicable per CTP v7.0

Treatment Course	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK	ADA	[redacted]
Cycle 2 and 4	C02_D01 /C04_D01	201/ 401	1	Just before SOI	-0:05	Blood sampling	X	X	
				0:00	0:00	SOI	---		
				Immediately before end of infusion[b]	0:30	Blood sampling	X		
	C02_D02 /C04_D02	202/ 402	2	24 hours post SOI	24:00	Blood sampling	X		
				Just before SOI of the further infusion[f]	23:55	Blood sampling	X		
				Immediately before end of further infusion [f]	24:30	Blood sampling [f]	X		
Cycle 3	C03_D01	301	1	Just before SOI	-0:05	Blood sampling	X	X	
				0:00	0:00	SOI	---		
				Immediately before end of infusion[b]	0:30	Blood sampling	X		
				7 hours post SOI	7:00	Blood sampling	X		
	C03_D02	302	2	24 hours post SOI	24:00	Blood sampling	X		
				Just before SOI of the further infusion[f]	23:55	Blood sampling	X		
				Immediately before end of further infusion [f]	24:30	Blood sampling [f]	X		
	C03_D03	303	3	48 hours post SOI	48:00	Blood sampling	X		
	C03_D08	308	8	168 hours post SOI	168:00	Blood sampling	X		

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Table 10.2: 1 Time schedule for PK and Biomarker blood sampling for phase Ia (cont.) - No longer applicable per CTP v7.0

Treatment Course	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK	[redacted]
Cycle 5 and Cycle 7	C05_D1/ C07_D1	501/ 701	1	Just before SOI	-0:05	Blood sampling	X	
Cycle 9 and Cycle 11	C09_D1/C11_D01	901/ 1101	1	Just before SOI	-0:05	Blood sampling	X	
Cycle 13[d]	C13_D01	1301	1	Just before SOI	-0:05	Blood sampling	X	
EOT[e]	EOT	9960				Blood sampling	X	
30-Day Safety Follow-up	EOR	9961				Blood sampling	X	

PTM = Planned Time; SOI=Start of Infusion
[a]The following windows of time are allowed for PK sampling:
1. Pre-dose (PTM -0:05): within 1 hour before next drug infusion/drug administration.
2. 7h: within ± 15 min of designated time
3. 24- 48h: within ±60 min of designated time.
4. 168h ±24 hour

Time windows are specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.
[b]In the event that infusion duration is >60 minutes longer than planned, the subsequent time points for PK blood collection on the day of drug infusion should be adjusted accordingly.

[redacted]

[d]PK and ADA sampling is to be collected pre-dose (-0:05) at Day 1 of Cycle 13 and every 3 months thereafter (Cycle 19, Cycle 25, etc.).
[e]If the patient will not continue treatment in the next scheduled cycle, pre-dose sampling scheduled for Day 1 of the next cycle needs to be performed at the EOT visit.
[f]Per section 4.1.4.1.1, if less than 50% of the planned dose of BI 905711 was administered due to an infusion-related reaction, a further dose of 50% of the intended total dose may be administered on the following day and after recovery to baseline for at least 24 hours. If this scenario occurs, the PK sample should be collected just before the start of the further infusion. A second PK sample should also be collected before the end of the further infusion.

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Table 10.2: 2 Time schedule for PK and Biomarker blood sampling for phase Ib-Biweekly dosing - No longer applicable per CTP v7.0

Treatment Course	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK	ADA	[redacted]
Pre-Cycle 1	Screening	001	-28 to -5	0:00	0:00	Blood sampling			
Cycle 1	C01_D01	101	1	Just before start of infusion (SOI)	-0:05	Blood sampling	X	X	
				0:00	0:00	SOI	---		
				Immediately before end of infusion[b]	0:30	Blood sampling	X		
				7 hours post SOI	7:00	Blood sampling	X		
	C01_D02	102	2	24 hours post SOI	24:00	Blood sampling	X		
				Just before SOI of the further infusion[e]	23:55	Blood sampling	X		
				Immediately before end of further infusion[e]	24:30	Blood sampling	X		
	C01_D03	103	3	48 hours post SOI	48:00	Blood sampling	X		
	C01_D08	108	8	168 hours post SOI	168:00	Blood sampling	X		

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Table 10.2: 2 Time schedule for PK and Biomarker blood sampling for phase Ib-Biweekly dosing (cont.) - No longer applicable per CTP v7.0

Treatment Course	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK	ADA	[redacted]
Cycle 2	C02_D01	201	1	Just before SOI	-0:05	Blood sampling	X	X	
				0:00	0:00	SOI	---		
				Immediately before end of infusion[b]	0:30	Blood sampling	X		
	C02_D03	203	3	48 hours post SOI	48:00	Blood sampling	X		
				Just before SOI of the further infusion[e]	47:55	Blood sampling	X		
				Immediately before end of further infusion[e]	48:30	Blood sampling	X		
Cycle 3	C03_D01	301	1	Just before SOI	-0:05	Blood sampling	X	X	
				0:00	0:00	SOI	---		
				Immediately before end of infusion[b]	0:30	Blood sampling	X		
				7 hours post SOI	7:00	Blood sampling	X		
	C03_D02	302	2	24 hours post SOI	24:00	Blood sampling	X		
				Just before SOI of the further infusion[e]	23:55	Blood sampling	X		
				Immediately before end of further infusion[e]	24:30	Blood sampling	X		
	C03_D03	303	3	48 hours post SOI	48:00	Blood sampling	X		
	C03_D08	308	8	168 hours post SOI	168:00	Blood sampling	X		

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Table 10.2: 2 Time schedule for PK and Biomarker blood sampling for phase Ib-Biweekly dosing (cont.) - No longer applicable per CTP v7.0

Treatment Course	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK	ADA	[redacted]
Cycle 4	C04_D 01	401	1	Just before SOI	-0:05	Blood sampling	X	X	
				0:00	0:00	SOI	---		
				Immediately before end of infusion[b]	0:30	Blood sampling	X		
	C04_D 02	402	2	24 hours post SOI	24:00	Blood sampling	X		
				Just before SOI of the further infusion[e]	23:55	Blood sampling	X		
				Immediately before end of further infusion[e]	24:30	Blood sampling	X		
Cycle 5 and Cycle 7	C05_D 1/ C07_D 1	501/ 701	1	Just before SOI	-0:05	Blood sampling	X	X	
Cycle 8	C08_D 1	801	1	Just before SOI	-0:05	Blood sampling	X	X	
Cycle 9 and Cycle 11	C09_D 1/C11_ D01	901/ 1101	1	Just before SOI	-0:05	Blood sampling	X	X	
Cycle 14	C14_D 01	1401	1	Just before SOI	-0:05	Blood sampling	X[g]	X[g]	
EOT[d]	EOT	9960				Blood sampling	X	X	
30-Day Safety Follow-up	EOR	9961				Blood sampling	X	X	

PTM = Planned Time; SOI=Start of Infusion
[a]The following windows of time are allowed for PK sampling:
1. Pre-dose (PTM -0:05): within 1 hour before next drug infusion/drug administration.
2. 7h: within ± 15 min of designated time
3. 24- 48h: within ±60 min of designated time.
4. 168h ±24 hour

Time windows are specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.
[b]In the event that infusion duration is >60 minutes longer than planned, the subsequent time points for PK blood collection on the day of drug infusion should be adjusted accordingly.
[redacted]

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[d]If the patient will not continue treatment in the next scheduled cycle, pre-dose sampling scheduled for Day 1 of the next cycle needs to be performed at the EOT visit.
[e]Per section 4.1.4.1.1, if less than 50% of the planned dose of BI 905711 was administered due to an infusion-related reaction, a further dose of 50% of the intended total dose may be administered on the following day and after recovery to baseline for at least 24 hours. If this scenario occurs, the PK sample should be collected just before the start of the further infusion. A second PK sample should also be collected before the end of the further infusion. [redacted]
[g]PK, and ADA collection is to be performed at Cycle 14 Day 1 and, at every sixth cycle thereafter (e.g. C20D1, C26D1, etc.), and at EOT.

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Table 10.2: 3 Time schedule for PK and Biomarker blood sampling for phase Ib-Weekly dosing - No longer applicable per CTP v7.0

Treatment Course	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK	ADA	[redacted]
Pre-Cycle 1	Screening	001	-28 to -5	0:00	0:00	Blood sampling			
Cycle 1	C01_D01	101	1	Just before start of infusion (SOI)	-0:05	Blood sampling	X	X	
				0:00	0:00	SOI	---		
				Immediately before end of infusion[b]	0:30	Blood sampling	X		
				7 hours post SOI	7:00	Blood sampling	X		
	C01_D02	102	2	24 hours post SOI	24:00	Blood sampling	X		
				Just before SOI of the further infusion[e]	23:55	Blood sampling	X		
				Immediately before end of further infusion[e]	24:30	Blood sampling	X		
	C01_D03	103	3	48 hours post SOI	48:00	Blood sampling	X		
	C01_D08	108	8	Just before start of infusion (SOI)	167:55	Blood sampling	X		
				168:00	168:00	SOI	---		

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Table 10.2: 3 Time schedule for PK and Biomarker blood sampling for phase Ib – Weekly dosing (cont.) - No longer applicable per CTP v7.0

Treatment Course	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK	ADA	[redacted]
Cycle 2	C02_D01	201	1	Just before SOI	-0:05	Blood sampling	X	X	
				0:00	0:00	SOI	---		
				Immediately before end of infusion[b]	0:30	Blood sampling	X		
	C02_D03	203	3	48 hours post SOI	48:00	Blood sampling	X		
				Just before SOI of the further infusion[e]	47:55	Blood sampling	X		
				Immediately before end of further infusion[e]	48:30	Blood sampling	X		
Cycle 3	C03_D01	301	1	Just before SOI	-0:05	Blood sampling	X	X	
				0:00	0:00	SOI	---		
				Immediately before end of infusion[b]	0:30	Blood sampling	X		
				7 hours post SOI	7:00	Blood sampling	X		
	C03_D02	302	2	24 hours post SOI	24:00	Blood sampling	X		
				Just before SOI of the further infusion[e]	23:55	Blood sampling	X		
				Immediately before end of further infusion[e]	24:30	Blood sampling	X		
	C03_D03	303	3	48 hours post SOI	48:00	Blood sampling	X		
	C03_D08	308	8	Just before start of infusion (SOI)	167:55	Blood sampling	X		
				168:00	168:00	SOI	---		

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Table 10.2: 3 Time schedule for PK and Biomarker blood sampling for phase Ib-Weekly dosing (cont.) - No longer applicable per CTP v7.0

Treatment Course	Visit	Visit No.	Day	Time Point[a] [hh:min]	CRF Time /PTM	Event	PK	ADA	[redacted]
Cycle 4	C04_D 01	401	1	Just before SOI	-0:05	Blood sampling	X	X	
				0:00	0:00	SOI	---		
				Immediately before end of infusion[b]	0:30	Blood sampling	X		
	C04_D 02	402	2	24 hours post SOI	24:00	Blood sampling	X		
				Just before SOI of the further infusion[e]	23:55	Blood sampling	X		
				Immediately before end of further infusion[e]	24:30	Blood sampling	X		
Cycle 5 and Cycle 7	C05_D 1/ C07_D 1	501/ 701	1	Just before SOI	-0:05	Blood sampling	X	X	
Cycle 8	C08_D 1	801	1	Just before SOI	-0:05	Blood sampling	X	X	
Cycle 9 and Cycle 11	C09_D 1/C11_ D01	901/ 1101	1	Just before SOI	-0:05	Blood sampling	X	X	
Cycle 14	C14_D 01	1401	1	Just before SOI	-0:05	Blood sampling	X[g]	X[g]	
EOT[d]	EOT	9960				Blood sampling	X	X	
30-Day Safety Follow-up	EOR	9961				Blood sampling	X	X	

PTM = Planned Time; SOI=Start of Infusion

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

1. Pre-dose (PTM -0:05): within 1 hour before next drug infusion/drug administration.
2. 7h: within ± 15 min of designated time
3. 24- 48h: within ±60 min of designated time.
4. 168h ±24 hour

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

[b]In the event that infusion duration is >60 minutes longer than planned, the subsequent time points for PK blood collection on the day of drug infusion should be adjusted accordingly.

[redacted]

[d]If the patient will not continue treatment in the next scheduled cycle, pre-dose sampling scheduled for Day 1 of the next cycle needs to be performed at the EOT visit.

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[e]Per section 4.1.4.1.1, if less than 50% of the planned dose of BI 905711 was administered due to an infusion-related reaction, a further dose of 50% of the intended total dose may be administered on the following day and after recovery to baseline for at least 24 hours. If this scenario occurs, the PK sample should be collected just before the start of the further infusion. A second PK sample should also be collected before the end of the further infusion. [redacted]

[g]PK, and ADA collection is to be performed at Cycle 14 Day 1 and, at every sixth cycle thereafter (e.g. C20D1, C26D1, etc.), and at EOT.

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10.3 DETAILS OF BLRM SETUP AND OPERATING CHARACTERISTICS

The BLRM was assessed by two different metrics: hypothetical on-study data scenarios and long-run operating characteristics. The simulations for scenarios and operating characteristics were produced using R version 3.4.2 and Jags version 4.3.0. Both the hypothetical data scenarios and the operating characteristics are based on the CRC patients data for safety evaluation only. Note that in the real trial more data will be available from the non-CRC GI cancer patients and also from additional patients enrolled for efficacy evaluation which will lead to improved data scenarios and operating characteristics

Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.3: 1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model. For each scenario, the probability of overdose for the current dose is shown, as well as the next optimal dose recommended by the model in terms of the probability of target dose, and the related probabilities of under-dosing, target dose, and overdosing for the next optimal dose. The actual dose chosen for the next cohort, not shown in Table 10.3: 1, will be determined by the SMC after taking into consideration of the recommended dose from the model as well as other relevant data from this study.

For example, scenario 1 represents the case that no DLT is observed in the first patient at the starting dose of 0.02 mg/kg. In this case, the next dose permitted by the model and by the escalation rule is 0.06 mg/kg. Similarly scenarios 3 and 6 represent cases where no DLTs are observed, and the model will recommend escalating to the next dose level that is permitted by escalation rule. In scenario 2, one DLT is observed already in the patient at the lowest dose level. In this case, the model cannot provide the next recommended dose level. However, according the escalation rule specified in Section 3.1.1, two more patients may be enrolled into this dose level. The same holds for scenario 4.

Scenarios 17 illustrate a case where dose level 2.4 mg/kg has probability of overdose exceeds 25%, per BLRM with the given provisional dose levels, the next optimal dose recommended would be 1.2 mg/kg. However, BLRM has flexibility to explore intermediate dose level, in both scenarios, if intermediate dose levels of 1.6 mg/kg and 1.8 mg/kg are explored, 1.6 mg/kg would be recommended as the next dose level because it has the highest probability of target dose, and overdose probability less than 25%.

Scenario 20 illustrates a case where low dose cohorts have no DLT, or 1 DLT, and the highest dose level 4.8 mg/kg has 1 DLT. In such cases, BLRM would continue to put patients on 4.8 mg/kg, but if higher dose levels are allowed, higher level e.g. 6.4 mg/kg would be recommended.

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Table 10.3: 1 Hypothetical data scenarios

Scenario	Dose (mg/kg)	# Pat	# DLT	Current Dose: P(OD)	Next recommended dose based on EWOC and escalation rule	Next recommended dose		
						P(UD)	P(TD)	P(OD)
1	0.02	1	0	0.033	0.06	0.885	0.068	0.047
2	0.02	1	1	0.591	NA	NA	NA	NA
2a	0.02	3	1	0.236	0.02	0.503	0.261	0.236
3	0.02 0.06	1 1	0 0	0.019	0.2	0.886	0.071	0.043
4	0.02 0.06	1 1	0 1	0.394	NA	NA	NA	NA
4a	0.02 0.06	1 3	0 1	0.165	0.06	0.541	0.294	0.165
5	0.02 0.06	1 4	0 1	0.114	0.2	0.477	0.308	0.216
6	0.02 0.06 0.2	1 1 4	0 0 0	0.005	0.6	0.913	0.069	0.018
7	0.02 0.06 0.2	1 1 4	0 0 1	0.108	0.6	0.470	0.305	0.225
8	0.02 0.06 0.2	1 1 4	0 0 2	0.374	0.06	0.421	0.374	0.205
9	0.02 0.06 0.2 0.6	1 1 4 4	0 0 0 1	0.053	1.2	0.565	0.299	0.136
10	0.02 0.06 0.2 0.6	1 1 4 4	0 0 0 2	0.210	0.6	0.369	0.421	0.210
11	0.02 0.06 0.2 0.6	1 1 4 4	0 0 1 1	0.198	0.6	0.369	0.432	0.198
12	0.02 0.06 0.2 0.6	1 4 4 4	0 1 1 1	0.315	0.2	0.372	0.492	0.136
13	0.02 0.06 0.2 0.6	1 4 6 4	0 1 1 1	0.232	0.6	0.258	0.510	0.232
14	0.02 0.06 0.2 0.6 1.2	1 1 4 4 4	0 0 0 0 1	0.025	2.4	0.584	0.279	0.138

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Table 10.3: 1 Hypothetical data scenarios (cont.)

Scenario	Dose (mg/kg)	# Pat	# DLT	Current Dose: P(OD)	Next recommended dose based on EWOC and escalation rule	Next recommended dose		
						P(UD)	P(TD)	P(OD)
15	0.02 0.06 0.2 0.6 1.2	1 1 4 4 4	0 0 0 0 2	0.176	1.2	0.420	0.404	0.176
16	0.02 0.06 0.2 0.6 1.2 2.4	2 2 4 4 4 4	0 0 0 0 1 1	0.149	2.4	0.448	0.403	0.149
17*	0.02 0.06 0.2 0.6 1.2 2.4	2 2 4 4 4 4	0 0 0 0 1 2	0.384	1.2 1.6* 1.8*	0.465 0.309 0.259	0.454 0.517 0.516	0.082 0.174 0.225
18	0.02 0.06 0.2 0.6 1.2 2.4 3.6	1 1 4 4 4 4 4	0 0 0 0 0 0 1	0.048	4.8	0.609	0.245	0.146
19	0.02 0.06 0.2 0.6 1.2 2.4 3.6	1 4 4 4 4 4 4	0 1 0 0 0 0 1	0.027	4.8	0.665	0.291	0.044
20*	0.02 0.06 0.2 0.6 1.2 2.4 3.6 4.8	1 1 4 4 4 4 4 4	0 0 0 0 1 0 0 1	0.043	4.8 6.4*	0.649 0.553	0.308 0.355	0.043 0.092

*denote the cases where intermediate or higher doses are considered.

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation. Table 10.3: 2 describes

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7 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. Scenario 1 represents the DLT rates that are aligned with prior means per dose level. Scenarios 2 and 3 reflect the extreme cases of high and low toxicity probabilities, respectively. Scenario 4 represents an even more extreme case with very low toxicity probability. Scenario 5 covers the case of a true dose-toxicity relationship that does not have a logistic form. Finally, Scenarios 6 and 7 reflect the possibility of having non-monotonic true dose-toxicity relationship.

Table 10.3: 2 Assumed true dose-toxicity scenarios

Scenarios	**Provisional dose levels**							
	0.02	**0.06**	**0.2**	**0.6**	**1.2**	**2.4**	**3.6**	**4.8**
1: Prior	0.076	0.092	0.116	0.149	0.178	0.220	0.253	0.282
2: High Tox	0.100	0.221	0.305	0.356	0.408	0.454	0.486	0.498
3: Low Tox	0.009	0.018	0.057	0.100	0.122	0.160	0.174	0.180
4: Very low Tox*	0.001	0.008	0.010	0.020	0.050	0.065	0.080	0.100
5: Non-Logis-tic	0.020	0.050	0.065	0.090	0.130	0.250	0.321	0.508
6: Non-Monotonic 1	0.020	0.080	0.120	0.202	0.250	0.389	0.250	0.202
7: Non-Monotonic 2	0.010	0.050	0.090	0.210	0.327	0.389	0.327	0.210

* Additional dose level 300mg added (assumed true tox probability of 0.789) to allow R code to run

For each of these scenarios, 1000 trials were simulated. 4 patients per dose cohort were assumed as default cohort size for the simulations. It was then assessed how often a dose was declared as MTD with true DLT rate in the under-, targeted or over-dose range. Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 10.3: 3.

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Table 10.3: 3 Simulated operating characteristics

Scenario	% of trials declaring an MTD with true DLT rate in				# Patients	# DLT
	underdose	target dose	overdose	stopped	Mean (Min-Max)	Mean (Min- Max)
1	31.6	62.7	0.0	5.7	29.8 (4 - 52)	4.6 (1 - 13)
2	4.6	63.9	16.1	15.4	19.5 (4 - 48)	4.6 (2 - 13)
3	20.9	78.4	0.0	0.7	33.3 (8 - 52)	3.4 (0 -11)
4	98.3	0.0	0.0	1.7	35.7 (12 - 52)	2.1 (0 - 7)
5	45.8	47.4	5.6	1.2	33.9 (4 - 52)	5.3 (1 - 13)
6	21.5	72.9	5.0	0.6	28.1 (4 - 52)	4.5 (1 - 14)
7	17.4	78.2	4.2	0.2	28.0 (8 - 52)	4.7 (1 - 12)

*1 trial declared the additional dose 300mg/kg as MTD

In Scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, 62.7% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range.

Scenarios 4 and 5 (very low-toxicity scenario) shows, that when the true DLT rate is very low, i.e. the majority dose levels with true DLT rate below the target interval, then more likely the model will declare a underdose as MTD. Since in scenario 4 none of the dose levels has an assumed true toxicity rate in the target interval, none of the simulated trials has declared a MTD with true DLT rate in the target dose range. In scenario 5 only few dose level was assumed to have true DLT rate in the target range, but at the upper end of the target range, therefore only a low number of simulated trials declared MTD at this dose with true DLT rate in the target range. The probability of observing a DLT at 1.2mg/kg is 0.13 and therefore close to the lower bound of the target interval. Adding up the corresponding probability of declaring this dose as an MTD (35.8% leads to a target rate of 83.2). Both scenarios have a very low percentage of trials stopped since no MTD was reached (either because the maximum number of patients was reached before declaring MTD or because too many DLTs were simulated to continue escalation).

In Scenarios 6 and 7, dose-toxicity relationship is non-monotonic. Scenarios 6 and 7 illustrates that the majority simulated trials (over 70%) declare the target dose levels as MTD.

The mean patient numbers across different scenarios is around 28, though the maximum can go up to 52 during simulation. This shows that the planned maximum of 40 patients is reasonable for phase Ia.

In summary, the considered data scenarios show a reasonable behaviour of the model and the operating characteristics demonstrate a good precision of MTD determination.

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		10Dec2019
EudraCT number **EU number**		2018-003268-29
BI Trial number		1412-0001
BI Investigational Medicinal Product(s)		BI 905711
Title of protocol		A first-in-human phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in patients with advanced gastrointestinal cancers
Global Amendment due to urgent safety reasons		
Global Amendment		**X**
Section to be changed		Synopsis
Description of change		Revised to clarify Exclusion #1
Rationale for change		Revision to align description of Exclusion #1 with Section 3.3.3.
Section to be changed		Flowchart
Description of change		Revised to clarify that safety labs are to be performed at Cycle 4 Day 1.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Flowchart
Description of change		Revision to footnote #2
Rationale for change		Revision to clarify meaning of Eligibility for further treatment prior to dosing on Day 1 of each cycle from Cycle 2 onwards.
Section to be changed		Flowchart
Description of change		Revision to footnotes #10 and #12
Rationale for change		Revision to clarify that pre-treatment PET scan and fresh biopsy is to be performed during screening before the first day of treatment (Cycle 1 Day 1) after eligibility has been confirmed.
Section to be changed		Flowchart and Section 6.2.1
Description of change		Revised footnote #14 and section 6.2.1 to clarify use of tumor assessments performed prior to informed consent.
Rationale for change		Tumor assessments performed prior to informed consent as part of routine clinical practice will be accepted if they meet the requirements of the protocol and are performed within the Screening visit window (28 days) prior to treatment start.

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Section to be changed		Section 3.1.2
Description of change		Revised to remove statement that possible inclusion of non-CRC GI cancer patients into phase Ib will be considered if efficacy (OR) is observed in phase Ia
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 3.3.2 and Synopsis
Description of change		Revised Inclusion criterion #2 to describe that eligible patients must have disease progression on all available therapies known to confer clinical benefit for their disease.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 3.3.2 and Synopsis
Description of change		Revised inclusion criterion #5: a. to expand the bilirubin inclusion criterion from "within normal limits and ≤1.5 x ULN for patients with Gilbert's syndrome" to "bilirubin ≤1.5 x ULN; and ≤3 x ULN for patients with Gilbert's syndrome". b. to expand the ALT and AST inclusion criterion from "≤1.5 x ULN and ≤2.5 x ULN in patients with known liver metastases" to "ALT and AST ≤2.5 x ULN or ≤5 x ULN in patients with known liver metastases"
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 3.3.3 and Synopsis
Description of change		Revised Exclusion criterion #3 to clarify that 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 or active ulcers (gastro-intestinal tract, skin) or laboratory abnormality that may increase the risk associated with trial participation or trial drug administration, and in the judgment of the Investigator, would make the patient inappropriate for entry into the trial.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 3.3.3 and Synopsis
Description of change		Added Exclusion criterion #14 to provide guidance regarding cardiac criteria that would constitute a concomitant condition for exclusion from the study.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 3.3.3 and Synopsis

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Description of change		Added exclusion criterion #15 to exclude patients with known hypersensitivity to the trial medication and/or its components *i.e.* polysorbate 20, sodium citrate, lysine hydrochloride, sucrose, citric acid.
Rationale for change		Revision in response to PMDA (Japan) review comment.
Section to be changed		Section 3.3.4.1
Description of change		Revised to include specific criteria required to continue treatment beyond initial RECIST-defined radiological progression of disease and to clarify that written informed consent should be obtained.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 3.3.4.1
Description of change		Revised to remove references to temporary treatment discontinuation and to early treatment discontinuation.
Rationale for change		Dose modification is described in section 4.1.2.3. Procedures for treatment discontinuation and follow up are outlined in the Flowchart and Section 6.2.3
Section to be changed		Section 3.3.4.4
Description of change		Revised to clarify that patients without DLT during MTD evaluation period will not be included in the BLRM analysis and additional patient(s) will be entered at the same dose level according to the criteria listed. It is also clarified that 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.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 4.1.4
Description of change		Revised to clarify the post-infusion monitoring guidelines for the first three doses of BI 905711.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 4.1.4
Description of change		Revised to clarify that total storage time for ready-to-use solution.
Rationale for change		Revised to clarify that total storage time for ready-to-use solution at room temperature should not exceed 150 minutes between preparation and end of infusion time.
Section to be changed		Section 4.1.4.1.1
Description of change		Revised to clarify that during the first re-exposure, after a prior Infusion-Related Reaction

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		(IRR), a systematic hospitalisation for at least 24 hours for observation is no longer required. Instead, patients must remain under observation for at least 8 hours post start of infusion. If required, patients may be hospitalised for a longer observation period at the investigator's discretion.
Rationale for change		A systematic 24-hour hospitalisation is not justified given that Infusion-Related Reaction (IRR) is a rare event that typically occurs during or shortly after the end of the infusion, and in most cases, it is manageable without hospitalization.
Section to be changed		Section 4.1.4.1.2
Description of change		Revised to clarify the observation period for CRS.
Rationale for change		Revision included to clarify that 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 4.1.4.
Section to be changed		Section 4.1.4.1.5
Description of change		Revised to clarify that patients who experience a ≥ CTCAE grade 2 adverse event must undergo a full neurological investigation with treatment interruption.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 5.2.2
Description of change		Revised to add body temperature.
Rationale for change		Revision added to align with updates added for post-infusion observation period in section 4.1.4.
Section to be changed		Section 5.2.3
Description of change		Revised to clarify urinalysis.
Rationale for change		Analysis will be performed by routine analysis.
Section to be changed		Section 5.2.6.1.5
Description of change		Revised DLT criteria to include (a) any death not clearly due to the underlying disease or extraneous causes and (b) all Grade 4 events possibly related to study therapy, irrespective of whether patients received maximal supportive therapy.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 6.2.1

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Description of change		Revision to clarify the genomic alterations status such as BRAF, KRAS, HER2, BRCA...etc, and the immune markers status such as microsatellite instability and/or DNA mismatch repair deficiency...etc. will be collected in the eCRF.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Miscellaneous
Description of change		Revisions to formatting, punctuation, and/or spelling.
Rationale for change		Clarifications added as applicable to address minor formatting updates that do not affect protocol content and will not be listed as separate changes.

11.2 GLOBAL AMENDMENT 2

Date of amendment		21May2020
EudraCT number **EU number**		2018-003268-29
BI Trial number		1412-0001
BI Investigational Medicinal Product(s)		BI 905711
Title of protocol		A first-in-human phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in patients with advanced gastrointestinal cancers
Global Amendment due to urgent safety reasons		
Global Amendment		**X**
Section to be changed		Synopsis
Description of change		Update of contact information for Coordinating Investigator
Rationale for change		Administrative update due to change in Coordinator Investigator
Section to be changed		Synopsis
Description of change		Clarification added for the total number of patients.
Rationale for change		Revision to state up to approximately 140 patients.
Section to be changed		Synopsis, Section 3.3.1, Section 3.3.2
Description of change		Inclusion criteria #1

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Rationale for change		Inclusion of gallbladder carcinoma due to update of tumor type to be studied.
Section to be changed		Synopsis, Section 3.3.2, Section 3.3.3
Description of change		Inclusion criteria #6, Exclusion #4
Rationale for change		Clarification that Adverse Event grading is according to CTCAE v5.0
Section to be changed		Synopsis and Section 3.3.3
Description of change		Exclusion #8
Rationale for change		Exclusion criteria #8 has been removed due to heparin interaction testing results. Language regarding use of anticoagulation therapy has been moved from Exclusion criteria #8 to Section 4.2.2.1. Exclusion criteria renumbered from existing #7 onwards in the Synopsis and in Section 3.3.3.
Section to be changed		Synopsis and Section 3.3.3
Description of change		Exclusion criteria #13
Rationale for change		Removed reference to mean resting QTC as only one ECG reading is planned to be obtained.
Section to be changed		Flowchart
Description of change		Footnote #3
Rationale for change		Clarification added that Physical exam does not need to be repeated at Cycle 1 Day 1 if completed within 24hrs.
Section to be changed		Flowchart
Description of change		Footnote #4 added
Rationale for change		If for logistical purposes patient weight may need to be calculated prior to Cycle 1 Day 1 in order to prepare the pharmacy order, the Cycle 1 Day 1 dose may be calculated based upon a patient weight obtained up to 3 days before administration if the body weight change is by ≤10% compared to the reference weight. Footnotes in flowchart renumbered from #4 onwards.
Section to be changed		Flowchart
Description of change		Footnote #5
Rationale for change		Clarification added that ECOG does not need to be repeated at Cycle 1 Day 1 if completed within 24hrs.
Section to be changed		Flowchart
Description of change		Footnote #9
Rationale for change		Removed requirement to perform safety labs at Cycle 1 Day 3.

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		On Cycle 1 Day 1, patients also need to have safety labs performed between 4-6 hours post-dose (updated from 7-8 hours post-dose).
Section to be changed		Flowchart and Section 5.4.1
Description of change		Revision to footnote #11 and Section 5.4.1 to add an on treatment biopsy in phase Ib.
Rationale for change		An additional on treatment fresh tumor biopsy is mandatory in at least 20 CRC patients irrespective of the dose cohort and only in case a fresh biopsy has been successfully obtained before first study treatment. The biopsy should be taken on Cycle 2 Day 2, 24h after administration of BI 905711. Fresh on treatment biopsies should be obtained from additional patients and all indications (CRC and non CRC) if the patient agrees (optional). Timepoints are detailed in the Flow Chart
Section to be changed		Section 1.2
Description of change		Revision to remove section about BI 905711 mixed *in vitro* with plasma from blood collected in tubes containing heparin lead to cloudiness and microscopic examination revealed flocculation (c16856466).
Rationale for change		Revision based update of heparin use.
Section to be changed		Section 1.4
Description of change		Updated toxicology results to include a description of immune complex formation resulting in renal injury (glomerulonephropathy)
Rationale for change		Toxicology update
Section to be changed		Section 2.1.3
Description of change		Added PK parameters as secondary endpoints
Rationale for change		Update
Section to be changed		Section 3.1
Description of change		Revision to Figure 3.1:1
Rationale for change		Clarification added to align with for planned approach for recruitment in CRC and non-CRC cohorts.
Section to be changed		Section 3.1.1
Description of change		Reformatted into sub-sections 3.1.1.1 through 3.1.1.4
Rationale for change		Sub-sections created for ease of review. Additional clarifications included for planned approach for recruitment in CRC and non-CRC cohorts, MTD determination/recommended dose range for expansion, and expanded cohort for efficacy evaluation in Phase Ia.
Section to be changed		Section 3.1.1.2 and 4.1.2.1

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Description of change		Clarification about inclusion of China into phase Ia.
Rationale for change		If the first site in China is initiated while the phase Ia is ongoing, the first Chinese patient will be enrolled into the non-CRC dose level that is open at the time of site initiation. Thereafter, at least one Chinese patient will be enrolled in China at each subsequent dose level in Phase Ia.
Section to be changed		Section 3.3
Description of change		Revision to selection of trial population
Rationale for change		Clarification added to update the approximate number of sites and regions anticipated to participate in phase Ia.
Section to be changed		Section 3.3.3
Description of change		Exclusion criteria #3
Rationale for change		Alignment with text for exclusion criteria #3 in Synopsis
Section to be changed		Section 4.1.2.3
Description of change		Clarification added about dose escalation
Rationale for change		More than one dose-escalation can be considered if deemed appropriate by the Investigator. Dose cannot be escalated if it was previously reduced due to toxicity.
Section to be changed		Section 4.1.4
Description of change		Clarification about reference weight to be used for dose calculation.
Rationale for change		The Cycle 1 Day 1 dose will be calculated using the Cycle 1 Day 1 weight 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.
Section to be changed		Section 4.1.4
Description of change		Clarification regarding timeframe for the infusion and priming and flushing.
Rationale for change		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. Priming and flushing should not be included in the administration duration.
Section to be changed		Section 4.1.4.1.1
Description of change		Timeframe for administration
Rationale for change		If less than 50% of the planned dose of BI 905711 was administered due to an infusion-related

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		reaction, a further dose of 50% of the intended total dose may be administered on the following day and after recovery to baseline for at least 24 hours. Administration may occur within up to 3 days after the original planned dose.
Section to be changed		Section 4.1.4.1.5
Description of change		Clarification of guidelines for management of possible neurological toxicities
Rationale for change		During dose escalation phase (phase Ia), patients will undergo baseline brain MRI and should be followed for possible new neurological signs and symptoms at each visits of the study drug administration and at end of treatment.
Section to be changed		Section 4.2.2.1
Description of change		Clarification of heparin use
Rationale for change		Language regarding use of anticoagulation therapy has been moved from Exclusion criteria #8 to Section 4.2.2.1. Based on heparin interaction testing results, guidance regarding use of use of heparin (including flushing and locking of intravenous catheters) or LMWH has been updated.
Section to be changed		Section 5.1
Description of change		Revised to align with footnote #15 and section 6.2.1 to clarify use of tumor assessments performed prior to informed consent.
Rationale for change		Tumor assessments performed prior to informed consent as part of routine clinical practice will be accepted if they meet the requirements of the protocol and are performed within the Screening visit window (28 days) prior to treatment start.
Section to be changed		Flowchart, Section 5.1
Description of change		Clarification about monitoring of patients with a specific tumor marker (also added in footnote #15)
Rationale for change		If the patient's cancer is being monitored with a specific tumor marker (e.g. CEA, CA19.9, etc.), tumor marker levels should be obtained at baseline, and at every protocol-specified tumor assessment timepoint.
Section to be changed		Section 5.2.6.1.5
Description of change		Clarification added for definition of febrile neutropenia
Rationale for change		Grade ≥ 3 febrile neutropenia defined as ANC below ANC <1000/mm3 and a single temperature of ≥ 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F)

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		for more than one hour; or where there are life-threatening consequences or urgent intervention indicated.
Section to be changed		Section 5.3.2
Description of change		Clarification about derivation of exact time points of plasma sampling
Rationale for change		Exact time points of plasma sampling will be documented in the CRFs by the medical personnel or sent as electronic files to the Trial Data Manager.
Section to be changed		Section 5.4
Description of change		Clarification about assessment of biomarkers
Rationale for change		Wording updated for ease of review and to include reference to on treatment biopsy. The determination of cell death biomarkers will be performed in plasma and tumor tissue.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		Section 5.5.1
Description of change		Revision to the methods and timing of sample collection
Rationale for change		If the patient has not consented to optional biobanking (see section 5.5), trial samples left over after primary analysis will be discarded after completion of these additional investigations but not later than 5 years after the final trial report has been signed.
Section to be changed		Section 7.3.1
Description of change		Clarification of the timeframe for the primary endpoint analysis
Rationale for change		Time frame: Database lock (DBL) will occur when either MTD is found or the recommended dose range for Phase Ib is determined, and all the patients have had at least 2 tumor assessment

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		timepoints excluding patients who have discontinued earlier.
Section to be changed		Section 9.1
Description of change		Revision to references
Rationale for change		References added for R20-1190, R20-1191, R20-1196, R20-1209
Section to be changed		Section 10.2
Description of change		Clarification of PK sampling scheduled at 24 hours post SOI and clarification of the windows for PK sampling.
Rationale for change		If less than 50% of the planned dose of BI 905711 was administered due to infusion-related reactions, a further dose of 50% of the intended total dose may be administered on the following day and after recovery to baseline for at least 24 hours. If this scenario occurs, the PK sample should be collected just before the start of the further infusion. A second PK sample should also be collected before the end of the further infusion. The window for sampling at 7h has been revised to ± 15 min of the designated time. In the event that infusion duration is >60 minutes longer than planned, the subsequent time points for PK blood collection on the day of drug infusion should be adjusted accordingly.
Section to be changed		Miscellaneous
Description of change		Revisions to formatting, punctuation, and/or spelling.
Rationale for change		Clarifications added as applicable to address minor formatting updates that do not affect protocol content and will not be listed as separate changes.

11.3 GLOBAL AMENDMENT 3

Date of amendment		29Jun2021
EudraCT number **EU number**		2018-003268-29
BI Trial number		1412-0001
BI Investigational Medicinal Product(s)		BI 905711
Title of protocol		A first-in-human phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in patients with advanced gastrointestinal cancers
Global Amendment due to urgent safety reasons		

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Global Amendment	**X**

Section to be changed		Flowchart, Section 5.4.1.2, Section 5.4.2.3, Section 10.2
Description of change		[redacted]
[redacted]		[redacted]
Section to be changed		Flowchart, Synopsis, Section 3.3.2, Section 5.4.1.1
Description of change		Footnote #11 and the aforementioned sections include clarification regarding significant risk procedures.
Rationale for change		Adjustment to remove the statement defining significant risk biopsy sites. The risk of a biopsy is based upon investigator judgment.
Section to be changed		Flowchart, Section 2.2.2, Section 5.1, Section 5.4, Section 5.4.2.6
Description of change		Footnote #13 and the aforementioned sections include clarification regarding FDG-PET
Rationale for change		FDG-PET will be performed in CRC patients in phase Ia and phase Ib. FDG-PET/CT should be performed at baseline within 14 days (±7 days) prior to treatment start (Cycle 1 Day 1) and at the 8 week tumor assessment timepoint.
Section to be changed		Flowchart and Section 5.1
Description of change		Footnote #15 and section 5.1 include adjustments to the planned tumor assessment schedule from every 6 weeks (± 7 days)(for the first 6 months) and every 12 weeks (± 7 days) thereafter to every 8 weeks (± 7 days).
Rationale for change		Planned tumor assessment schedule adjusted to allow for better comparability of results between 1412-0001 and similar trials which follow a planned 8 week tumor assessment schedule.
Section to be changed		Flowchart and Section 5.1
Description of change		Footnote #16 and section 5.1 include clarification regarding a brain MRI in phase Ia.
Rationale for change		In case of contraindication for MRI, a brain CT scan can be performed after agreement between the investigator and Sponsor
Section to be changed		Flowchart, Section 6.2.3.3

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Description of change		Body of flowchart, footnotes #3, 5, and 9, and Section 6.2.3.3 include adjustments to procedures at the Followup for progression visit
Rationale for change		ECOG, physical examination, and safety labs added to align with BI standard for patient monitoring during follow-up for progression.
Section to be changed		Section 1.4
Description of change		Addition of language regarding potential identification of a confirmed SARS-CoV-2 infection.
Rationale for change		Adjustment added based upon an assessment of the COVID-19 related risks to trial participants.
Section to be changed		Section 3.1
Description of change		Figure 3.1: 1
Rationale for change		Revision to remove references to backfill for non-CRC patients in Dose level 1 and Dose level 2 per agreement with the SMC to not consider backfill enrollment until Dose level 3.
Section to be changed		Synopsis, Section 3.3.1, Section 3.3.2
Description of change		Inclusion criteria #1
Rationale for change		Revision to clarify the gastrointestinal tumor types to be studied.
Section to be changed		Synopsis, Section 3.3.3
Description of change		Exclusion criteria #1
Rationale for change		Revision to clarify use of previous systemic anti-cancer therapy prior to study treatment start.
Section to be changed		Synopsis, Section 3.3.3
Description of change		Exclusion criteria #2
Rationale for change		Revision to clarify use of radiation therapy prior to study treatment start.
Section to be changed		Synopsis, Section 3.3.3
Description of change		Exclusion criteria #3
Rationale for change		Revision to serious concomitant disease or medical condition to specify that patients with any history of stroke or myocardial infarction within 6 months prior to screening are not eligible for participation.
Section to be changed		Section 3.3.4.1
Description of change		Revision to the criteria for discontinuation of trial treatment to address if a patient experiences an infection with SARS-CoV-2.
Rationale for change		Adjustment added based upon an assessment of the potential COVID-19 impact to trial participants.
Section to be changed		Section 4.1.4

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Description of change		Clarification of visit handling due to potential disrupting circumstances.
Rationale for change		Adjustment added based upon an assessment of the potential COVID-19 impact to trial participants.
Section to be changed		Section 4.1.8
Description of change		Clarification of investigational drug handling
Rationale for change		Unused and partially used trial drug may be destroyed onsite according to local site procedure.
Section to be changed		Section 4.2.2.1
Description of change		Clarification of restricted medication
Rationale for change		Gonadotropin-releasing hormone or luteinizing hormone releasing hormone analogs for patients with prostate cancer or breast cancer can be continued, but should not be initiated during trial.
Section to be changed		Section 4.2.2.1
Description of change		Revision to include information regarding COVID-19 vaccination
Rationale for change		Adjustment added based upon an assessment of the potential COVID-19 impact.
Section to be changed		Section 5.1
Description of change		Clarification of radiomics definition. Clarification added that FDG-PET/CT at baseline should be performed within 14 days (±7 days) prior to treatment start (Cycle 1 Day 1).
Rationale for change		Revisions included to align with current BI template definition.
Section to be changed		Section 5.2.6.1.4
Description of change		Clarification of hepatic injury definition
Rationale for change		Revisions included to align with current BI template definition.
Section to be changed		Section 5.2.6.2.1
Description of change		Clarification of trial completion
Rationale for change		Adjustment to include a statement to refer to the description of trial completion for an individual patient in section 6.2.3.4.
Section to be changed		Flowchart, Section 5.4, Section 10.2
Description of change		Adjustment to add determination of cell death biomarkers at screening (phase Ib only).
Rationale for change		Sampling added to measure the longitudinal variation of these markers in CRC patients in phase Ib.
Section to be changed		Section 5.4.1.1
Description of change		Revision to collection of archival tissue sample
Rationale for change		Archival tumor tissue sample should be provided as FFPE-preserved tissue, preferably as an

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		embedded block and less preferably as mounted tissue sections (at least 19 sections of 4-5 µm thickness) prepared under RNase free conditions.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 6.1
Description of change		Clarification of handling of disruption from planned schedule of visits and procedures.
Rationale for change		Adjustment added based upon an assessment of the potential COVID-19 impact to trial participants.
Section to be changed		Section 8.3.2
Description of change		Clarification regarding direct access to source data
Rationale for change		Adjustment added based upon an assessment of the potential COVID-19 impact.
Section to be changed		Miscellaneous
Description of change		Clarification of laboratory units throughout
Rationale for change		Laboratory values used for determination of patient eligibility or other medical decisions are presented in SI and conventional units.
Section to be changed		Miscellaneous
Description of change		Revisions to formatting, punctuation, and/or spelling.
Rationale for change		Clarifications added as applicable to address minor formatting updates that do not affect protocol content and will not be listed as separate changes.

11.4 GLOBAL AMENDMENT 4

Date of amendment		11Apr2022
EudraCT number **EU number**		2018-003268-29
BI Trial number		1412-0001
BI Investigational Medicinal Product(s)		BI 905711
Title of protocol		A first-in-human phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in patients with advanced gastrointestinal cancers
Global Amendment due to urgent safety reasons		
Global Amendment		**X**

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Section to be changed		Synopsis
Description of change		Clarification added for the total number of patients.
Rationale for change		Revision to state approximately 120 evaluable patients.
Section to be changed		Synopsis, Section 2.1.2
Description of change		Clarification of primary endpoint
Rationale for change		Update PFS from a secondary endpoint to a primary endpoint for phase Ib.
Section to be changed		Synopsis, Section 2.1.3
Description of change		Addition of secondary endpoint
Rationale for change		Addition of number of patients with treatment-emergent AEs as a secondary endpoint for phase Ib to align with the main objective for phase Ib.
Section to be changed		Synopsis, Section 3.3.2
Description of change		Inclusion criteria #1
Rationale for change		Clarification of tumor types for inclusion in phase Ia and phase Ib.
Section to be changed		Synopsis, Section 3.3.2
Description of change		Inclusion criteria #5
Rationale for change		Clarification of the parameters for Hemoglobin (Hb) ≥ 8.5 g/dl, ≥ 85 g/L, or ≥ 5.3 mmol/L (without transfusion within previous week)
Section to be changed		Synopsis, Section 3.1, Section 3.1.2, Section 7
Description of change		Confirmation of the number of planned patients in phase Ib
Rationale for change		Phase Ib will be opened with 3 dose levels in 4 cohorts
Section to be changed		Synopsis, Section 1.2, Section 3.1, Section 3.1.2, Section 4.1.1, Section 4.1.2.2, Section 4.1.3, Section 7
Description of change		Confirmation of dose levels for phase Ib
Rationale for change		Three dose levels for phase Ib will be administered on a biweekly regimen and 1 dose level for phase Ib will be administered on a weekly regimen (3 weeks on, 1 week off).
Section to be changed		Flowchart
Description of change		Clarification of Flowchart applicable for patients in phase Ia and phase Ib
Rationale for change		Clarification of the label for the Flowchart applicable to patients enrolled in phase Ia. Update of the description of the procedure in the phase Ia flowchart to circulating tumor DNA.

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		Addition of a Flowchart applicable to patients enrolled in phase Ib- Biweekly dosing. Addition of a Flowchart applicable to patients enrolled in phase Ib- Weekly dosing.
Section to be changed		Flowcharts for phase Ia and phase Ib
Description of change		Clarification of echocardiography (or multigated acquisition scan)
Rationale for change		Procedure added to flowchart to clarify that measurement of ejection fraction at may be needed per Exclusion criteria #13.
Section to be changed		Synopsis, Section 3.3.2
Description of change		Clarification of Inclusion criteria #4 for biopsy collection in phase Ib
Rationale for change		Availability and willingness to provide an archived tumor tissue specimen and undergo tumor biopsy before treatment. Pre-treatment fresh tumor biopsy collections for biomarker analyses are considered optional in phase Ia and mandatory in phase Ib. Only non-significant risk procedures per the investigator's judgment will be used to obtain any biopsies specified in this study. In case a fresh tumor biopsy cannot be obtained due to before mentioned reasons an archived tumor tissue specimen obtained within ≤6 months of screening must be submitted. In case the patient undergoes baseline tumor biopsy, an archived tumor tissue specimen must be submitted regardless of the date of collection.
Section to be changed		Flowcharts for phase Ib, Section 5.4.1
Description of change		Clarification of biopsy collection in phase Ib
Rationale for change		Clarification added that in phase Ib an additional on-treatment fresh tumor biopsy should be taken on Cycle 2 Day 3 and/or at disease progression for a patient in which a fresh biopsy has been successfully obtained before first study treatment. Clarification added that in phase Ib in case a fresh biopsy before treatment start has been collected, an archival tumor tissue must also be submitted (mandatory). Removal of the requirement that an on-treatment fresh biopsy is mandatory in at least 20 CRC patients in phase Ib.
Section to be changed		Flowcharts for phase Ib, Section 6.2.1
Description of change		Addition of collection of previous tumor response data if available.
Rationale for change		Support analyses relative to tumor response.
Section to be changed		Flowcharts

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Description of change		Footnote 9 (phase Ia), Footnote 10 (phase Ib)
Rationale for change		Addition of the requirement to have safety labs performed post-dose after the second and third administrations to assess ALT and AST values for a patient that experiences an elevated ALT and/or AST value after Cycle 1 Day 1 administration.
Section to be changed		Section 1.1
Description of change		Addition of prevalence data
Rationale for change		Addition of BI prevalence data for gastrointestinal cancers expressing CDH17.
Section to be changed		Section 1.2
Description of change		Update of Drug Profile
Rationale for change		Addition of updated information based upon phase Ia.
Section to be changed		Section 1.3
Description of change		Update of rationale for performing the trial
Rationale for change		Addition of updated information based upon phase Ia.
Section to be changed		Section 1.4
Description of change		Update of benefit-risk assessment
Rationale for change		Addition of updated information based upon phase Ia.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 3.1
Description of change		Update of Figure 3.1: 1
Rationale for change		Updated schematic included for phase Ib design.
Section to be changed		Section 3.1.1.4, Section 10.4
Description of change		Removal of the sections
Rationale for change		Sections 3.1.1.4 (Expanded cohort for efficacy evaluation in phase Ia) and 10.4 (Details of Dose Expansion and Operating Characteristics) were removed because the approach was not used in phase Ia.
Section to be changed		Section 3.2
Description of change		Update of trial design
Rationale for change		Addition of the dose levels and dose regimens selected for phase Ib and rationale for the weekly dosing regimen.
Section to be changed		Section 3.3
Description of change		Clarification of patient population
Rationale for change		For phase Ib, approximately 60 evaluable patients are planned to be entered in 8 regions.

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Section to be changed		Section 4.2.2.1
Description of change		Clarification regarding restrictions regarding concomitant treatment
Rationale for change		The restriction regarding use of hematopoietic growth factor agents has been clarified to indicate it applied in phase Ia.
Section to be changed		Section 5.3.2
Description of change		Clarification of methods of sample collection
Rationale for change		Update added to describe use of samples for further methodological investigations.
Section to be changed		Section 5.4, Section 5.4.2.4
Description of change		Added biomarker assessment for NGS
Rationale for change		A broad mutational analysis will be performed via NGS to determination if there is a correlation of cancer-related mutations/biomarkers with clinical signals and/or PD biomarker modulation and/or mRNA gene expression.
Section to be changed		Section 5.4.1
Description of change		Collection of tissue samples
Rationale for change		Clarification added that in case a tissue block and/or tissue sections cannot be collected as indicated, the site needs to contact the Sponsor for agreement regarding collection.
Section to be changed		Section 5.4.1.2
Description of change		[redacted]
[redacted]		
[redacted]		
[redacted]		
Section to be changed		
Description of change		
Rationale for change		

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		[redacted]
Section to be changed		[redacted]
[redacted]		
		[redacted]
Section to be changed		Section 7
Description of change		Addition of phase Ib updates
Rationale for change		Updates added throughout Section 7 to describe the statistical design for phase Ib.
Section to be changed		Section 7.4
Description of change		Update to interim analysis
Rationale for change		Revisions added to describe that preliminary, exploratory analysis 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 analysis.
Section to be changed		Section 7.7
Description of change		Revision to analysis approach
Rationale for change		Due to addition of PFS as a second endpoint, revisions added to describe the use of BHM for phase Ib based on two endpoints (ORR, PFS). The previous method was based upon one endpoint (ORR).
Section to be changed		Section 9.1
Description of change		Revision to references
Rationale for change		References added for P22-01934 and R22-1028.
Section to be changed		Section 10.2
Description of change		Clarification of biomarker sampling when there is a further 50% infusion in phase Ib.
Rationale for change		If less than 50% of the planned dose of BI 905711 was administered due to infusion-related reactions, a further dose of 50% of the intended total dose may be administered on the following day and after recovery to baseline for at least 24 hours. [redacted]
Section to be changed		Section 10.2
Description of change		Tables 10.2:2 and 10.2:3 – footnote f, Section 5.4.1.2

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Rationale for change		[redacted]
Section to be changed		Section 10.2
Description of change		Clarification of PK and Biomarker Blood Sampling
Rationale for change		Clarification that Table 10.2: 1 is applicable to patients enrolled in phase Ia. References to phase Ib sampling removed from Table 10.2:1. Table 10.2:2 has been added and is applicable for patients enrolled in phase Ib- Biweekly dosing. Table 10.2:3 has been added and is applicable for patients enrolled in phase Ib- Biweekly dosing.
Section to be changed		Miscellaneous
Description of change		Revisions to verb tense
Rationale for change		Clarifications added as applicable throughout the document to reference activity that occurred in phase Ia.
Section to be changed		Miscellaneous
Description of change		Revisions to formatting, punctuation, and/or spelling.
Rationale for change		Clarifications added as applicable to address minor formatting updates that do not affect protocol content and will not be listed as separate changes.

11.5 GLOBAL AMENDMENT 5

Date of amendment		13Oct2022
EudraCT number **EU number**		2018-003268-29
BI Trial number		1412-0001
BI Investigational Medicinal Product(s)		BI 905711
Title of protocol		A first-in-human phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in patients with advanced gastrointestinal cancers
Global Amendment due to urgent safety reasons		
Global Amendment		**X**

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Section to be changed		Title Page
Description of change		Update of contact information for Clinical Trial Leader
Rationale for change		Administrative update due to change in Clinical Trial Leader
Section to be changed		Synopsis, 3.3.2
Description of change		Updated inclusion criteria 1 and 5 for PDAC cohort in Phase Ib: serum lipase > 1.5 – 2.0 x ULN or asymptomatic >2.0 – 5.0 x ULN if related to PDAC; Cancer histology of pancreatic adenocarcinoma with CDH17 positive expression as assessed by central testing.
Rationale for change		Specific requirement added considering patient background.
Section to be changed		Synopsis, Figure 3.1.1
Description of change		Addition of 1 cohort of PDAC patients which will be treated weekly on 0.6 mg/kg dose level
Rationale for change		Addition of PDAC cohort
Section to be changed		Synopsis
Description of change		Statistical methods text for Phase Ib updated from “may be applied if more than one dose level is expanded” to “will be applied to the multiple dose levels.”
Rationale for change		Updated to reflect that more than one dose level was expanded in Phase Ib
Section to be changed		Synopsis, Miscellanous
Description of change		Total number of evaluable patients increased from approximately 120 to 140, updated throughout document
Rationale for change		Addition of 20 patients in PDAC cohort
Section to be changed		Flowcharts
Description of change		Addition of safety laboratory parameters and physical examination at EOR visit.
Rationale for change		Revision implemented in accordance with French Health Authority (ANSM) regulatory recommendation.
Section to be changed		Flowcharts
Description of change		Update of footnote to describe that echocardiography (or multigated acquisition scan) may be performed at any time during the study if clinically indicated.

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Rationale for change		Revision implemented in accordance with Belgian Health Authority (FAMHP) regulatory recommendation.
Section to be changed		Flowchart: Phase Ia
Description of change		Removed the tickbox included at Cycle 2 Day 2 for Fresh Tumor Biopsy, which is not applicable for phase Ia.
Rationale for change		The tickbox was inadvertently included during formatting.
Section to be changed		Flowchart: Phase Ia
Description of change		Row for additional archival tumor tissue deleted for clarity, and footnote 12 updated.
Rationale for change		Archival tumor tissue is mandatory for Phase Ia.
Section to be changed		Flowchart: Phase Ib (Weekly Dosing)
Description of change		Added a tickbox for Adverse Events at Cycle 5 Day 8. Added a tickbox for Concomitant Therapy at Cycle 5 Day 8. Updated formatting for the tickbox for Tumor Assessment by CT/MRI to apply for the full Treatment Period and Post-treatment.
Rationale for change		The tickboxes were inadvertently not included when the Flowchart was formatted.
Section to be changed		Flowchart: Phase Ib (Weekly Dosing)
Description of change		Addition of screening visit 1 (SV1) and update footnote 12 for CDH17 status analysis by central vendor. Tissue must be sent to designated vendor for CDH17 positivity. Screening visit 2 (SV2) added and is for entry into main study after CDH17 positivity is confirmed. Addition of foonote 18 that this is only applicable for PDAC patients and that SV1 and SV2 can occur in parallel.
Rationale for change		CDH17 positive expression is part of inclusion criteria for PDAC patients.
Section to be changed		Flowcharts: Phase Ib (Biweekly dosing) and Phase Ib (Weekly dosing)
Description of change		Row added for tumor markers, and footnote 16 updated. Collection of tumor markers was optional and changed to mandatory.
Rationale for change		Updated based on additional procedure for better clarification and understanding of efficacy.
Section to be changed		Flowchart: Phase Ib (Weekly Dosing)
Description of change		Added column for even cycles; Cycle 5 and beyond separated into odd and even cycles for clarity.

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Rationale for change		Clarify difference in requirements between odd and even cycles.
Section to be changed		Flowcharts: Phase Ib (Weekly dosing)
Description of change		Footnote β, "The interval between two dose administration must be always at least 8 days" updated to "7 days".
Rationale for change		Correction to typo
Section to be changed		Abbreviations
Description of change		Addition of PDAC Pancreatic Ductal Adenocarcinoma
Rationale for change		Addition of PDAC cohort
Section to be changed		1.2
Description of change		Added the following text under non-clinical studies "Anticancer activity of BI 905711 in PDAC was tested in vivo using 11 patient-derived PDAC xenograft models (PDX) characterized by target expression of TRAILR2 and CDH17 in the range of 45 to 174 TPM (transcripts per million) and 26 to 604 TPM, respectively. Upon treatment with BI 905711, 4/11 PDX models showed tumor growth inhibition [TGI] ranging from 107 to 126% and 2/11 models showed moderate response (TGI 61% and 76%). First in vivo experiments (two PDAC PDX models) to study synergistic anticancer effect of BI 905711 in combination with chemotherapy (irinotecan) showed deepened response." Updated AE information and median duration of treatment under data from clinical studies.
Rationale for change		Information update
Section to be changed		1.3
Description of change		The last statement in the section updated to state "Safety, pharmacokinetic, and pharmacodynamic profiles, as well as preliminary antitumor activity assessments, acquired in this trial will provide the basis for further development of BI 905711."
Rationale for change		The statement was inadvertently truncated during formatting.
Section to be changed		[redacted]

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Description of change		[redacted]
Rationale for change		
Section to be changed		2.2.2, 5.1, 5.4, 5.4.2.6
Description of change		[^{18}F]FDG-PET should be performed for CRC patients and phase Ib PDAC patients. Updated throughout document.
Rationale for change		Addition of PDAC cohort
Section to be changed		3.1.2
Description of change		Moved CRC cohort into separate subsection 3.1.2.1 Randomized CRC expansion cohort Added the following text to new subsection 3.1.2.2 Single Arm PDAC expansion cohort "Approximately 20 evaluable patients with CDH17-positive PDAC will be enrolled into phase Ib. Patients will be enrolled on one dose level in weekly regimen (3 weeks on, 1 week off) of BI 905711. CDH17 analysis must be performed by a designated vendor and results reviewed prior to patient enrollment."
Rationale for change		Addition of PDAC cohort
Section to be changed		3.3
Description of change		Updated total number of patients in phase Ib from 60 to 80 patients. Added the following text "All PDAC patients in phase Ib will be required to undergo central testing of tumour tissue for CDH17 status at screening visit 1 (SV1) before proceeding to full screening assessments at screening visit 2 (SV2). There are no inclusion/exclusion criteria at screening visit 1 except that the patient must have tissue available for analysis and must be expected, as far as is possible to determine, to meet all inclusion and exclusion criteria at the time of screening visit 2."
Rationale for change		Addition of PDAC cohort

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Section to be changed		3.3.1
Description of change		Added text "and CDH17 positive pancreatic ductal adenocarcinoma in" at end of first paragraph.
Rationale for change		Addition of PDAC cohort
Section to be changed		5.1
Description of change		Text modified from "If the patient's cancer is being monitored" to "Patient's cancer will be monitored".
Rationale for change		Tumor markers changed from optional to mandatory. Updated based on additional procedure for better clarification and understanding of efficacy.
Section to be changed		5.2.3
Description of change		Addition of amylase to safety lab parameters, and note that this will be collected for Phase Ib patients. Footnote added accordingly.
Rationale for change		Revision implemented in accordance with French Health Authority (ANSM) regulatory recommendation.
Section to be changed		5.3.1
Description of change		Deleted from the last paragraph "The final preliminary analysis will be performed at the end of the phase Ia part prior to proceeding to the phase Ib part."
Rationale for change		Phase Ia is complete
Section to be changed		5.3.2
Description of change		[redacted]
Rationale for change		Based on BI internal discussion and decision for better understanding of product.
Section to be changed		5.4

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Description of change		First bullet point updated from "Determination of CDH17 protein expression by IHC" to "Determination of target protein expression by IHC, including but not limited to CDH17"
Rationale for change		Updated for clarity and addition of PDAC patients
Section to be changed		5.4.1.1
Description of change		The following text was moved to section for Phase Ia: • In phase Ia, an archived tumor tissue specimen must be submitted (mandatory). The following text was deleted: In phase Ia, in case a fresh pre-treatment tumor biopsy cannot be obtained due to before mentioned reasons, an archived tumor tissue specimen must be submitted (mandatory).
Rationale for change		Updated for clarity, archival tissue is mandatory for Phase Ia and fresh tumor biopsy is optional.
Section to be changed		5.4.1.1
Description of change		The following text was added to first bullet point under Tumor tissue collection in Phase Ib "For PDAC patients, CDH17 expression measured in archival tumor tissue within < 6 months or a fresh biopsy sample must be completed as part of screening visit 1 for PDAC cohort. If archival tumor tissue is submitted for screening visit 1, then a fresh biopsy must be provided prior to treatment start on Day 1."
Rationale for change		Addition of PDAC cohort
Section to be changed		5.4.1.1
Description of change		"Optional" added to second bullet point under Tumor tissue collection in Phase for timepoints Cycle 2 Day 3 and disease progression.
Rationale for change		Updated for consistency and clarity
Section to be changed		5.4.1.1
Description of change		The following text was moved to section Phase Ib • "In case a fresh pre-treatment tumor biopsy cannot be obtained due to the below-mentioned reasons, an archived tumor tissue specimen obtained within ≤6 months of screening must be submitted (mandatory)." The following text was moved to section Phase Ib and updated from "For phase Ib, in case the patient undergoes baseline tumor biopsy, an archival tumor tissue must also be submitted (mandatory) regardless of the date of collection.

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		An additional fresh tumor biopsy should be taken on Cycle 2 Day 3 (optional) and/or at disease progression (optional) for a patient in which a fresh biopsy has been successfully obtained before first study treatment." to "In case the patient undergoes baseline tumor biopsy, an archival tumor tissue must also be submitted (mandatory) regardless of the date of collection."
Rationale for change		Updated for clarity and also deletion of repeated information in same section.
Section to be changed		5.4.1.1
Description of change		The following text was deleted from second to last bullet point "at least 19 sections of 4-5 µm thickess".
Rationale for change		Information listed in lab manual, removed to avoid inconsistent information.
Section to be changed		5.4.1.2, 10.2
Description of change		Optional predose plasma samples removed.
Rationale for change		Based on BI internal discussion and decision. Samples are optional and were removed to reduce study complexity.
Section to be changed		5.4.1.2
Description of change		[redacted]
Rationale for change		Updated for consistency with Flowchart and Appendix 10.2
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		
Description of change		

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Rationale for change		[redacted]
Section to be changed		5.5
Description of change		Text updated from "Leftover nucleic acids from patient's plasma (e.g. cfDNA) to "Leftover from patient's plasma"
Rationale for change		Updated for clarity as samples are not limited to nucleic acids.
Section to be changed		6.2.1
Description of change		Added details and figure for screening visits for Phase Ib PDAC patients
Rationale for change		Addition of PDAC cohort
Section to be changed		7.1
Description of change		The following text was deleted "Details will be specified in the TSAP".
Rationale for change		Updated for consistency.
Section to be changed		7.6
Description of change		Number of cohorts updated from four to five. Number of patients for Phase Ib updated from 60 to 80.
Rationale for change		Addition of PDAC cohort
Section to be changed		7.7
Description of change		The following text in the first paragraph was updated from "In total, approximately up to 120 CRC patients are planned… approximately 60 for phase Ib)" to "In total, approximately up to 140 patients are planned… approximately 60 evaluable CRC patients and 20 PDAC patients for phase Ib)".
Rationale for change		Updated to reflect inclusion of PDAC (non-CRC) patients.
Section to be changed		10.2
Description of change		In [redacted]
Rationale for change		The tickbox was inadvertently included during formatting
Section to be changed		10.2
Description of change		In [redacted]

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		Day 8 and Cycle 5 Day 1, which is not applicable for phase Ib. Footnotes have been updated accordingly.
Rationale for change		The tickbox was inadvertently included during formatting.
Section to be changed		10.2
Description of change		In Tables 10.2:2 and 10.2:3, a tickbox has been added at Cycle 8 to add collection of PK and ADA. In addition, footnote g updated to describe that in phase Ib, PK and ADA collection is be performed at Cycle 14 Day 1 and at every sixth cycle thereafter (e.g. Cycle 20 Day 1 pre-dose, etc.), and at EOT.
Rationale for change		Addition of PK and ADA samples [redacted] cycle beyond Cycle 14 Day 1 at pre-dose.
Section to be changed		10.2
Description of change		[redacted]
Rationale for change		Updated for clarity
Section to be changed		10.2
Description of change		Visit no for Tables 10.2:2 and 10.2:3 updated from 9970 to 9961
Rationale for change		Updated for consistency with BI standards
Section to be changed		Miscellaneous
Description of change		Updated from four to five cohorts to reflect new cohort added, updated patient numbers from 60 to 80 in phase Ib throughout document.
Rationale for change		Addition of PDAC cohort
Section to be changed		Miscellaneous
Description of change		Revisions to formatting, punctuation, and/or spelling.
Rationale for change		Clarifications added as applicable to address minor formatting updates that do not affect protocol content and will not be listed as separate changes.

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11.6 GLOBAL AMENDMENT 6

Date of amendment		17Apr2023
EudraCT number **EU number**		2018-003268-29
BI Trial number		1412-0001
BI Investigational Medicinal Product(s)		BI 905711
Title of protocol		A first-in-human phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in patients with advanced gastrointestinal cancers
Global Amendment due to urgent safety reasons		
Global Amendment		**X**
Section to be changed		Flowcharts
Description of change		Section amended to clarify visits, assessments and procedures that are mandatory/not mandatory for cycles $\geq$ 6
Rationale for change		Recruitment in this trial was discontinued prematurely during the Phase I expansion cohort. Reduced procedures and assessments for ongoing patients to those needed for safety monitoring.
Section to be changed		1.3
Description of change		Added text "Based on available preliminary data from phase I clinical studies (1412.1 and 1412.3), the decision was made to terminate BI 905711 (TRAILR2/CDH17) development program. This decision is not related to any safety concerns or unfavorable benefit/risk balance, but to the lack of predictive biomarkers and the limited efficacy particularly in the context of the evolving treatment landscape for advanced CRC and other GI cancers. The purpose of CTP v7.0 is to reduce the study related activities to the minimum required to monitor patient safety and to avoid undue burden on patients."
Rationale for change		Explain rationale for CTP v7.0
Section to be changed		3.1.1
Description of change		Added text "Recruitment in Phase Ia is complete"
Rationale for change		Recruitment in Phase Ia is complete.

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Section to be changed		3.1.2
Description of change		Added text "Recruitment in this trial was discontinued during Phase I expansion, and no PDAC patients were enrolled in this expansion cohort."
Rationale for change		Recruitment in Phase Ib discontinued prematurely.
Section to be changed		3.3.4.3
Description of change		Updated #2: "Emergence of any efficacy/safety information ~~with or without invalidating the earlier positive benefit-risk assessment~~ that could significantly affect the continuation of the trial."
Rationale for change		To describe discontinuation of trial without changes to benefit-risk ratio.
Section to be changed		5.1
Description of change		Updated to reflect that tumor assessments will be assessed per institutional practice, and only overall response and disease progression will be collected in the eCRF.
Rationale for change		To be consistent with flowchart revision.
Section to be changed		5.2.1, 5.2.2, 5.2., 5.2.4
Description of change		Physical examination, vital signs, safety labs, and ECGs will be done as per institutional practice.
Rationale for change		To be consistent with flowchart revision.
Section to be changed		5.3.1, 7.3.5, 7.5, 10.1
Description of change		Updated text related to PK to align with standard Phase 1 protocol language
Rationale for change		To align with standard Phase 1 protocol language
Section to be changed		5.3.2, 5.4.1
Description of change		Effective from CTP v7.0, PK, ADA, Biomarker and Optional Tumor Biopsy samples are no longer collected for ongoing patients.
Rationale for change		Blood and optional tissue samples no longer collected.
Section to be changed		[redacted]
Description of change		
Rationale for change		

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Section to be changed		6.2.3.1
Description of change		Deleted "If the patient finishes study treatment without having progressive disease, tumor assessment/imaging must be performed at the time of treatment discontinuation, unless it has been done within the past 4 weeks."
Rationale for change		To be consistent with flowchart revision.
Section to be changed		6.2.3.3
Description of change		Section amended to define EOR as end of study. No further follow-up visits after EOR are required, unless follow-up is for S(AE) that occurred before EOR period.
Rationale for change		To be consistent with flowchart revision.
Section to be changed		7.6
Description of change		Updated five to four cohorts, and 80 to 60 patients.
Rationale for change		Typo
Section to be changed		10.2
Description of change		Sampling tables for PK and Biomarkers no longer applicable per CTP v7.0
Rationale for change		To be consistent with flowchart revision.
Section to be changed		10.2
Description of change		Sampling tables updated to clarify timepoint for PK sample collection in case of infusion related reactions and further infusion is performed.
Rationale for change		Clarification
Section to be changed		10.2
Description of change		Visit no for Tables 10.2:1 updated from 9970 to 9961
Rationale for change		Updated for consistency with BI standards

APPROVAL / SIGNATURE PAGE

Document Number: c17895778 **Technical Version Number:8.0**

Document Name: clinical-trial-protocol-version-07

Title: A first-in-human phase Ia/b, open label, multicentre, dose escalation study of BI 905711 in patients with advanced gastrointestinal cancers

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	19 Apr 2023 09:57 CEST
Approval-Team Member Medicine		19 Apr 2023 15:54 CEST
Approval-Biostatistics		19 Apr 2023 16:21 CEST
Verification-Paper Signature Completion		19 Apr 2023 16:24 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed