CLINICAL TRIAL PROTOCOL

BNT141-01

Version: 4.0 **Date:** 13 JUN 2022

Sponsor: BioNTech SE

Trial title:	Phase I/IIa, first-in-human, open-label, dose escalation trial with expansion cohorts to evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of BNT141 as a monotherapy and in combination with other anti-cancer agents in patients with CLDN18.2-positive solid tumors
Brief title:	Safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy trial of BNT141 in patients with unresectable or metastatic CLDN18.2-positive gastric, pancreatic, ovarian and biliary tract tumors
Trial phase:	I/IIa
Indication:	CLDN18.2-positive solid tumors
Product:	BNT141
Trial sites:	Approximately 20 sites in Europe and North America. Additional sites may be included during the trial. For details, see the Trial Master File.
Sponsor's responsible persons:	Leticia de Mattos Arruda, MD, PhD, Senior Director, Clinical Development
Sponsor:	BioNTech SE, An der Goldgrube 12, 55131 Mainz, Germany
Clinical Research Organization:	Syneos Health UK Ltd., Farnborough Business Park, 1 Pinehurst Road, Farnborough, Hampshire, GU14 7BF, UK
Regulatory identifiers:	IND number 27153 Clinicaltrials.gov identifier NCT04683939 EudraCT number: 2022-001843-25
Medical Monitor:	The sponsor's Medical Monitor name and contact information will be provided separately.

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* Sponsor approved

Statement of Compliance: This trial will be conducted in according to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, Good Clinical Practice (GCP), and applicable regulatory requirements.

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1 PROTOCOL SUMMARY

1.1 Trial synopsis

Trial number: BNT141-01

Trial title: Phase I/IIa, first-in-human, open-label, dose escalation trial with expansion cohorts to evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of BNT141 as a monotherapy and in combination with other anti-cancer agents in patients with CLDN18.2-positive solid tumors

Trial phase: I/IIa

Objectives and endpoints

Objective	Endpoints
Primary objectives	
To assess the safety and tolerability of BNT141 at different dose levels.	• Occurrence of treatment-emergent adverse events (TEAEs) within a patient including Grade ≥ 3, serious, fatal TEAE by relationship. • Occurrence of dose reductions and discontinuation of BNT141 due to TEAEs.
To identify the maximum tolerated dose (MTD) or maximally administered dose (MAD) /recommended Phase II dose (RP2D) of BNT141 based on the occurrence of dose-limiting toxicities (DLTs) using the following definitions: • The MTD will be defined as the highest tolerated dose, where less than one-third of the patients experience a DLT. • The MAD is defined as the highest dose administered, where all dose levels were tolerated during dose escalation. • The RP2D will be defined based on integrated evaluation of safety, tolerability, clinical benefit, pharmacokinetic (PK), and pharmacodynamic (PD) data, for all dose levels tested.	• Occurrence of DLTs within a patient during the DLT evaluation period.
Secondary objectives	
To characterize the PK profile of the BNT141-encoded protein RiboMab[redacted].	• PK parameters including but not limited to area-under-the-concentration-time curve (AUC), clearance (CL), volume of distribution (Vd), maximum concentration (C_{max}), time to C_{max} (t_{max})measured concentration at the end of a dosing interval [taken directly before next administration] (C_{trough}), and half-life ($t_{½}$).

Objective	Endpoints
To evaluate the anti-tumor activity of BNT141 according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.	• Objective response rate (ORR) is defined as the proportion of patients in whom a complete response (CR) or partial response ([PR], per RECIST 1.1) is confirmed as best overall response. • Disease control rate (DCR) is defined as the proportion of patients in whom a CR or PR or stable disease ([SD], per RECIST 1.1, SD assessed at least 6 weeks after first dose) is observed as best overall response. • Duration of response (DOR) is defined as the time from first objective response (CR or PR per RECIST 1.1) to first occurrence of objective tumor progression (progressive disease per RECIST 1.1) or death from any cause, whichever occurs first.
Exploratory objectives	
To evaluate the efficacy of BNT141.	• Progression-free survival (PFS) is defined as the time from first dose of BNT141 to first objective tumor progression (progressive disease per RECIST 1.1), or death from any cause, whichever occurs first. • Overall survival (OS) is defined as the time from first dose of BNT141 to death from any cause.
To assess Claudin 18.2 (CLDN18.2) expression level as a potential biomarker to predict clinical response to BNT141.	• Correlation of CLDN18.2 expression level with clinical outcomes.
To assess potential PD biomarkers of BNT141.	• Evaluation of PD biomarkers compared to baseline.
To evaluate the immunogenicity of BNT141.	• Anti-drug antibodies [ADAs] response.
To assess other exploratory markers that may be collected in the study to better understand BNT141 treatment.	• Evaluate pre-treatment lipid status and potential influence on BNT141 response.

Trial design

This trial is an open-label, multi-site, Phase I/IIa dose escalation, safety, and PK trial of BNT141 followed by expansion cohorts in patients with CLDN18.2-positive tumors. CLDN18.2 positivity will be determined by a central laboratory during the pre-screening phase using a validated immunohistochemistry assay, and is defined as moderate-to-strong CLDN18.2 expression.

The trial design consists of three parts:

- **Part 1A is a dose escalation of BNT141 as monotherapy** in patients with unresectable or metastatic CLDN18.2-positive solid tumors for which there is no available standard therapy likely to confer clinical benefit, or the patient is not a candidate for such available therapy. Patients must have received all available standard therapies and failed at least first-line standard of care (SOC) therapy prior to enrolment. The dose of BNT141 will be escalated until the MTD and/or RP2D of BNT141 as monotherapy are defined. Eligible tumor types are gastric cancer,

gastroesophageal junction (GEJ) and esophageal adenocarcinoma, pancreatic, biliary tract (cholangiocarcinoma and gallbladder cancer), and mucinous ovarian cancers. Additionally, patients with specific tumors (including colorectal cancer, non-small-cell lung cancer, gastric subtype of endocervical adenocarcinoma) where there is scientific evidence that the CLDN18.2 could be elevated can be tested for CLDN18.2 expression.

- **Part 1B is a dose escalation of BNT141 in combination with nab-paclitaxel and gemcitabine** in patients with advanced unresectable or metastatic CLDN18.2-positive pancreatic adenocarcinoma or cholangiocarcinoma who are eligible for treatment with nab-paclitaxel and gemcitabine. Part 1B intends to define the MTD and/or RP2D of the combination.
- **Part 2 (Expansion)** consists of the following pre-defined expansion cohorts:
  - CLDN18.2-positive [redacted] eligible for treatment with nab-paclitaxel and gemcitabine.
  - CLDN18.2-positive [redacted] eligible for treatment with nab-paclitaxel and gemcitabine.

Part 2 will be further defined via an amendment after careful evaluation of all available safety, PK and PD, and efficacy data generated in Parts 1A and 1B by the Safety Review Committee (SRC).

Trial duration

The trial is considered completed when all patients have had at least 12 months survival follow up or are lost to follow up or have withdrawn consent or have died or the sponsor discontinues the trial. However, the maximum trial duration is 3 years after the last subject's first treatment in the trial.

Population

A maximum of approximately 48 DLT-evaluable patients will be enrolled to trial treatment in each of the trial Parts 1A and 1B, depending on the DLTs which may occur. Non-DLT-evaluable patients will be replaced. Once the MTD is reached, up to 10 additional patients with CLDN18.2 expressing pancreatic and biliary tract cancers will be enrolled at the MTD level in Part 1A and up to 10 additional patients with CLDN18.2 expressing pancreatic adenocarcinoma and cholangiocarcinoma in Part 1B, to obtain additional data on safety, PK and PD. The sample size and design in Part 2 will be further determined after careful evaluation of all available safety, PK and PD, and efficacy data generated in Parts 1A and 1B by the SRC and will be further defined via an amendment.

Key inclusion criteria

Patients who meet the following inclusion criteria will be eligible for trial entry:

For all parts:

- Metastatic or unresectable solid tumor.
- Histological or cytological documentation of a solid tumor via a pathology report.

- CLDN18.2-positive tumor sample defined as moderate-to-strong CLDN18.2 protein expression defined as intermediate (2+) to strong (3+) staining intensity in ≥ 50% of tumor cells as assessed by central testing using a CLIA-validated immunohistochemistry assay in formalin-fixed, paraffin-embedded (FFPE) neoplastic tissues. New biopsies and archival bio-samples are allowed. Bone biopsies are not allowed. Cytology specimens (including fine needle aspirates) will not be accepted for CLDN18.2 examination. If archival tissue samples from several points of time are available, the most recent one is preferred. Patients with a lower expression level or with CLDN18.2-negative cancers are not eligible.

Trial part-specific inclusion criteria:

- **For Part 1A:** Patients with solid tumors, for which there is no available standard therapy likely to confer clinical benefit, or the patient is not a candidate for such available therapy. Patients must have received all available standard therapies and failed at least first-line SOC therapy prior to enrolment. Measurable or evaluable disease per RECIST 1.1. Eligible tumor types are gastric cancer, gastroesophageal junction (GEJ) and esophageal adenocarcinoma, pancreatic, biliary tract (cholangiocarcinoma and gallbladder cancer), and mucinous ovarian cancers. Additionally, patients with specific tumors (including colorectal cancer, non-small-cell lung cancer, gastric subtype of endocervical adenocarcinoma) where there is scientific evidence that the CLDN18.2 could be elevated can be tested for CLDN18.2 expression.
- **For Part 1B:** Patients with advanced pancreatic adenocarcinoma or cholangiocarcinoma who are eligible for treatment with nab-paclitaxel and gemcitabine. Measurable or evaluable disease per RECIST 1.1.
- **For Part 2 (Expansion):**
  - **Cohort 1 –** [redacted] eligible for treatment with nab-paclitaxel and gemcitabine. Measurable disease per RECIST 1.1.
  - **Cohort 2 –** [redacted] eligible for treatment with nab-paclitaxel and gemcitabine. Measurable disease per RECIST 1.1.

Key exclusion criteria

Patients who meet at least one of the following exclusion criteria will not be eligible for trial entry:

- Receiving: radiotherapy, chemotherapy, or molecularly-targeted agents within 3 weeks or 5 half-lives (whichever is longer) of the start of trial treatment; immunotherapy/monoclonal antibodies within 3 weeks of the start of trial treatment (excluding BNT141); nitrosoureas, antibody-drug conjugates, or radioactive isotopes within 6 weeks of the start of trial treatment. Palliative radiotherapy will be allowed.
- Receives concurrent systemic (oral or intravenous [IV]) steroid therapy > 10 mg prednisone daily or its equivalent for an underlying condition.

Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is permitted.

- Major surgery within 4 weeks before the first dose of BNT141.
- Prior treatment with a CLDN18.2 targeting mAb other than BNT141.
- Ongoing or active infection requiring IV treatment with anti-infective therapy that has been administered less than 2 weeks prior to the first dose of BNT141.
- Side effects of any prior therapy or procedures for any medical condition not recovered to National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) v.5 Grade ≤ 1, with the exception of anorexia, fatigue, hyperthyroidism, hypothyroidism, and peripheral neuropathy, which must have recovered to ≤ Grade 2. Alopecia of any grade is allowed.
- Current evidence of new or growing brain or leptomeningeal metastases during screening. Patients with known brain or leptomeningeal metastases may be eligible if they have:
  - Radiotherapy, surgery or stereotactic surgery for the brain or leptomeningeal metastases.
  - No neurological symptoms (excluding Grade ≤ 2 neuropathy).
  - Stable brain or leptomeningeal disease on the computer tomography (CT) or magnet resonance imaging (MRI) scan within 4 weeks before signing the informed consent form (ICF).
  - Not undergoing acute corticosteroid therapy or steroid taper.

Trial treatments:

Part 1A: Each treatment cycle at Part 1A has a duration of 3 weeks (21 d).

BNT141 will be administered IV once every three weeks (Q3W) at eight main dose levels: 0.15, 0.3, 0.6[redacted] mg/kg.

Part 1B: Each treatment cycle in Part 1B has a duration of 4 weeks (28 d).

BNT141 will be administered IV [redacted] of the first 28-day cycle and Q3W thereafter. The BNT141 starting dose level will be determined in the Part 1A monotherapy dose escalation and will be subsequently escalated to the MTD.

Nab-paclitaxel will be administered IV on [redacted] of each 28-day cycle at a dose of [redacted].

Gemcitabine will be administered IV on [redacted] of each 28-day cycle at a dose of [redacted].

Statistics: For Parts 1A and 1B, the MTD as monotherapy and in combination with nab-paclitaxel/gemcitabine respectively will be determined using a 3+3 design.

The Part 2 expansion cohort will be conducted in [redacted] types. The sample size and design in Part 2 will be further determined based on careful evaluation of all available safety, PK and PD, and efficacy data generated in Parts 1A and 1B and will be further defined via an amendment.

Adverse events will be presented using summary statistics.

Individual curves of plasma concentration for RiboMab[redacted] will be presented for all patients.

PK parameters will be calculated based on non-compartmental methods and will be calculated separately.

RECIST 1.1 will be used to define response. Summaries of objective response and disease control will be presented by dose cohort/indication and total.

The PFS, OS, and DOR will be summarized using survival analysis methods.

SRC: The SRC will review safety, clinical, and available PK and PD data on an ongoing basis. At a minimum the data will be reviewed at each dose level after all patients enrolled in this dose level have completed the DLT period. A comprehensive review of all available safety, PK and PD, and efficacy data will occur prior to starting Part 2 (Expansion).

Formal statistical analysis will occur at the end of the trial.

1.2 Schema (graphical representation of the trial)

Figure 1: Trial design

Part 1A is a dose escalation of BNT141 as monotherapy in patients with advanced unresectable or metastatic CLDN18.2-positive solid tumors for which there is no available standard therapy likely to confer clinical benefit, or the patient is not a candidate for such available therapy. Eligible tumor types are gastric cancer, gastroesophageal junction (GEJ) and esophageal adenocarcinoma, pancreatic, biliary tract (cholangiocarcinoma and gallbladder cancer), and mucinous ovarian cancers. Additionally, patients with specific tumors (including colorectal cancer, non-small-cell lung cancer, gastric subtype of endocervical adenocarcinoma) where there is scientific evidence that the CLDN18.2 could be elevated can be tested for CLDN18.2 expression. CCI

CCI [redacted]

CCI [redacted] CLDN18.2 = Claudin 18.2; CLDN18.2^{pos} = Claudin 18.2 positive; CCI [redacted] DL = dose level; DLT = dose-limiting toxicity; GEJ = gastroesophageal junction; monoTx = monotherapy treatment; MTD = maximum tolerated dose; N = number of patients; PD = pharmacodynamics; PDAC = pancreatic adenocarcinoma; PK = pharmacokinetics; pts = patients; RP2D = recommended Phase II dose; SOC = standard of care; Tx = treatment.

1.3 Schedule of activities

The schedule of activities (SoA) and procedures for Part 1A (BNT141 monotherapy dose escalation) is shown in Table 1, with the schedule of central laboratory assessments (PK, PD, immunogenicity, and lipids) shown in Table 2, and local laboratory assessments in Table 3.

The SoA and procedures for Part 1B (BNT141 dose escalation in combination with nab-paclitaxel and gemcitabine) is shown in Table 4, with the schedule of central laboratory assessments (PK, PD, immunogenicity and lipids) shown in Table 5, and local laboratory assessments in Table 6.

Assessments should be performed before trial treatment administration (on the applicable days) or any planned intervention, with the exception of post-dose blood sampling for exploratory PD, PK, immunogenicity assessments and any samples required for supplementary R&D. On the days of tumor imaging, blood sampling can be before or after imaging assessments.

For Part 1A, 1 cycle is defined as 21 d and the DLT evaluation period is also 21 d.
For Part 1B, 1 cycle is defined as 28 d, with the DLT evaluation period lasting 28 d.

Details regarding the expansion cohorts in Part 2 will be further determined after careful evaluation of all available safety, PK and PD, and efficacy data generated in Parts 1A and 1B by the SRC and will be submitted by a major amendment to this protocol.

Investigators must make every effort to adhere to the given visit schedule and to perform all assessments within the given time window for each visit as specified in the SoA in Table 1 and Table 4. This is especially true for the extensive PK assessments according to the SoA (Table 2 and Table 5).

Please refer to Section 7.1 and Section 7.3 for treatment discontinuation and lost to follow-up criteria. Please note, however, that lost to follow-ups should be avoided by all means and every effort should be taken by the trial site to follow-up on the whereabouts of the patients and their survival status.

Table 1: Schedule of activities and procedures: Part 1A – BNT141 monotherapy dose escalation

Treatment Cycle (21 d)	Pre-screening	Screening [1] ≤ 21 d prior Cycle 1 Day 1	Cycle 1						Cycle 2			Cycle 3					Cycle 4			Cycle 5, 7, 9 etc.	Cycle 6, 8, 10 etc.		EOT [2]	Safety FU1 30d after last dose	Safety FU2 60d after last dose	Survival FU Every 12 weeks	Unscheduled [3]
Day			1	2	3	4	8	15	1	8	15	1	2	4	8	15	1	8	15	1	1	8					
Visit window (days)						+1	±1	±1	+3	±1	±1	±3		±1	±1	±1	±3	±1	±1	±3	±3	±1		+5	±7	±14	
Administrative procedures																											
ICF for pre-screening	X																										
ICF for main trial		X																									
Demographics	X																										
Tumor tissue	X [4]		X [5]							X [6]																	
Eligibility	X	X																									
Medical history [7]		X																									
Clinical procedures/interventions																											
Height, body weight [8]		X	X				X	X	X	X	X	X			X	X	X	X	X	X	X		X	X	X		X
Physical examination [9]		X	X				X	X	X	X	X	X					X			X	X		X	X	X		X
Vital signs [10]		X	X				X	X	X	X	X	X					X			X	X		X	X	X		X
ECG [11]		X	X	X	X	X	X	X	X			X	X	X	X	X	X			X	X		X	X	X		X
Tumor assessments [12]		X									X		Refer to Footnote 12										X				
ECOG Performance Status		X	X						X			X					X			X	X		X	X	X		X
AEs [13]		X	X				X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X		X
Prior/concomitant medication [14]		X	X				X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X		X
BNT141 administration [15]		CCI																									
New anti-cancer treatment [16]																							X	X	X	X	
Survival follow-up [17]																										X	
Local lab: Blood sample [18]		X	X	X			X	X	X	X	X	X	X				X			X	X		X	X	X		X
Local lab: Urine sample [18]		X	X						X			X					X			X	X		X	X	X		X
Central lab: Blood sample [19]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X		X

1 If ≥ 50% moderate-to-strong CLDN18.2 protein expression is detected, patient can enter the screening phase. For screening, all laboratory assessments must be performed ≤ 7 d prior the planned treatment start with BNT141. Results of SOC test or examinations performed prior to obtaining informed consent and within 21 d prior to Cycle 1 Day 1 may be used, such tests do not need to be repeated for screening.

2 If the patient has to go off treatment per treatment withdrawal criteria, the End of Treatment Visit should be performed as soon as possible after permanent discontinuation criteria but not later than 30 d after last dose (in this latter case, due to the End of Treatment Visit occurring close to Safety FU1, Safety FU1 can be skipped). The visit at which an imaging shows disease progression resulting in treatment discontinuation may be used as the End of Treatment Visit, at which time all assessment associated with the End of Treatment Visit should be performed.

3 Unscheduled visits can be performed at any time point when clinically indicated and can include assessments as indicated.

4 Both fresh and archival biopsies will be accepted.

5 Additional tumor tissue (10 µm thick tumor curls) should be sent from all patients receiving study drug to the central laboratory for further exploratory research on CLDN18-ARHGAP6/26 fusion.

6 On-treatment biopsy should be performed in patients where feasible/without a risk of complications for the patient. Preferred on Cycle 2 Day 8 (± 1 d), but can be performed at any time during the study treatment.

7 Medical history includes cancer history (including but not limited to, prior cancer therapies and procedures and tumor characteristics such as mutation status, cancer related somatic genomic alterations and germline status, other clinically relevant diseases, surgeries, use of alcohol and/or drugs abuse and, reproductive status).

8 Height will only be measured at screening. The body weight measurement taken at the visit prior to dosing should be used for IMP preparation.

9 Full physical examinations should be performed during screening, thereafter a symptom orientated limited physical examination should be performed.

10 Includes temperature, blood pressure (systolic and diastolic), heart rate, oxygen saturation and respiratory rate.

11 A 12-lead ECG will be performed in triplicate. Single ECG recordings may be obtained at an unscheduled time point as clinically indicated.

12 The same imaging method (CT/MRI) must be used for a patient throughout the trial at screening, at Week 6 (± 7 d), then every 6 weeks (± 7 d) for 24 weeks, and every 12 weeks (± 7 d) thereafter until disease progression. Tumor assessments will not be performed at the beginning of the trial if last tumor assessment was within 4 weeks before C1D1 and these images can be used. Imaging will be assessed by an experienced radiologist at site using RECIST 1.1 criteria and sent to an external service provider for storage. Monitoring of the liver and the spleen size will be performed as described in the Imaging Manual.

13 AEs/SAEs will be reported from the start of study drug treatment until Safety FU2. During pre-screening no AEs/SAEs will be reported, with the exception of AEs/SAEs related to the procedure of collection of a fresh biopsy.

14 Prior medications are any medications and non-drug therapies (see Section 6.5) used by the patient within 21 d prior to initiation of trial treatment and during screening. Concomitant medications are any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment (including prophylactic treatment after BNT141 administration and medications as a result of an adverse event). Prior/Concomitant medications and non-drug therapies include all previous and on-trial COVID-19 vaccinations.

15 BNT141 will be administered CCI .

16 New anti-cancer treatments will be collected from treatment discontinuation until death (unless the patient withdraws consent or the sponsor terminates the trial).

17 Information on survival FU, new anti-cancer therapy and cancer-related procedures will be collected for all patients via telephone calls, patient medical records, and/or clinic visits approximately every 12 weeks until death (unless the patient withdraws consent or the sponsor terminates the trial). If the patient withdraws from trial, the trial staff may use a public information source (e.g., county records) to obtain information about survival status only.

18 Local laboratory assessments can take place one day prior to patient visit apart from Cycle 2 Day 1. The screening samples must be obtained within 7 d of Cycle 1 Day 1. All Day 1 samples must be taken before study drug administration. Additional safety laboratory assessments can be performed at any time point when clinically indicated and can include assessments as indicated. Local laboratory assessments are detailed in Table 3.

19 Central laboratory assessments are given in Table 2.

AE = adverse event; ARHGAP = Rho GTPase Activating Protein 6; CLDN = Claudin; COVID = coronavirus disease; CT = computer tomography; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FU = follow-up; ICF = informed consent form; IMP = investigational medicinal product; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria Solid Tumors; SAE = serious AE; SOC = standard of care.

Table 2: Schedule of central laboratory assessments (PK, PD, immunogenicity and lipids) for Part 1A – BNT141 monotherapy dose escalation

Treatment Cycle (21 d)	Cycle 1									Cycle 2						Cycle 3								Cycle 4, 6, 8 etc. [1]		EOT	Safety FU1 30d after last dose	Safety FU2 60d after last dose	Unscheduled
Day	1				2	3	4	8	15	1				8	15	1				2	4	8	15	1	8				
[redacted]	CCI [redacted]	[redacted]	[redacted]	[redacted]						CCI [redacted]	[redacted]	[redacted]	[redacted]			CCI [redacted]	[redacted]	[redacted]	[redacted]					CCI [redacted]					
Blood collection window [3]	-24h	+10m	±15m	±15m							+10m	±15m	±15m			-24h	+10m	±15m	±15m					-24h					
Visit window [3]							+1d	±1d	±1d	+3d				±1d	±1d	±3d					+1d	±1d	±1d	±3d	±1d		+5d	±7d	
Pharmacokinetics (PK)																													
PK RiboMab[CCI] (serum)	X	X	X	X	X	X	X	X	X	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK lipids (plasma) [4]	X	X [4]	X	X	X			X	X	X	X					X	X			X			X						X
Pharmacodynamics (PD)																													
Cytokines/ chemokines (serum) [4, 5]	X	X [4]	X	X	X	X	X			X	X	X	X			X	X	X	X	X	X			X					X
ADCC (serum)	X						X									X					X								X
CDC (serum)	X						X									X					X								X
Immunogenicity (serum)																													
Anti-[CCI] lipid antibodies	X							X		X				X		X						X		X	X	X	X	X	X
Anti-RiboMab[CCI] antibodies	X								X	X					X	X							X	X	X	X	X	X	X
Additional samples																													
Extra sample for further analysis [6]	X							X		X				X		X						X		X	X	X	X	X	X
Apolipoprotein E	X																												

The PK sampling schedule may be adapted based on dose escalation PK results. Samples will be analyzed centrally. For details, please see the Laboratory Manual.

1 PK, PD samples should be collected only every second cycle from Cycle 4 (Cycle 4, 6, 8). No PK, PD samples should be taken in Cycle 5, 7, 9 etc.

2 [CCI]

3 [CCI] Investigators should adhere to the given time points. However, due to possible time deviations that may occur in clinical practice, those will not be reported as protocol deviations.

4 After start of infusion, an unscheduled sampling for cytokines or PK lipids may be considered if infusion-related reactions occur.

5 Cytokines/chemokines to be analyzed include, but are not limited to IFN-γ, IFN-α, TNF-α, IL-1b, IL-12, MCP-1, MIP-1b, IL-2, IL-15, and IL-6.

6 Samples will be used either for re-testing or for future analysis if required (see Section 8.9).

ADCC = antibody-dependent cellular cytotoxicity; [CCI]; CDC = complement-dependent cytotoxicity; d = day; EOI = end of infusion; EOT = end of treatment; FU = follow-up; h = hour; IFN = interferon; IL = interleukin; m = minute; MCP = monocyte chemoattractant protein; MIP = macrophage inflammatory protein; TNF = tumor necrosis factor.

Table 3: Local laboratory assessments: Part 1A – BNT141 monotherapy dose escalation

Treatment Cycle (21 d)	Test to be done	Screening	Cycle 1				Cycle 2			Cycle 3		Cycle 4 onwards	EOT	Safety FU1	Safety FU2	Unscheduled
Day		≤ 21 d prior C1D1	1	2	8	15	1	8	15	1	2	1		30 d after last dose	60 d after last dose	
Visit window (days)					±1	±1	±3	±1	±1	±3		±3		+5	±7	
Hematology	RBC count, hemoglobin, hematocrit, platelet count, WBC count, differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry	**Electrolytes**: sodium, potassium, chloride, phosphate, calcium **Liver**: total and direct bilirubin, ALP, ALT, AST, LDH **Kidney**: creatinine, eGFR **Proteins**: total protein, albumin, glucose, CRP, urate, BUN or urea	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation factors	PT, aPTT, INR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endocrine	TSH, free T3, total T3, free T4, total T4	X											X	X	X	X
Pregnancy test [1]	Urine or serum pregnancy test	X	X				X			X		X	X	X	X	X
Tumor marker [2]	CA 19-9	X								X		X	X			X
Hepatitis B and C	HbsAg, HCV (if positive for HCV RNA by PCR)	X														
Lipids	Total cholesterol, LDL, VLDL, HDL, triglycerides		X													
Urinalysis (dipstick)	pH, specific gravity, glucose, protein, ketones, blood	X	X				X			X		X	X	X	X	X

Local laboratory assessments can take place one day prior to patient visit apart from Cycle 2 Day 1. The screening samples must be obtained within 7 d of Cycle 1 Day 1. All Day 1 samples must be taken before study drug administration. Additional safety laboratory assessments can be performed at any timepoint when clinically indicated and can include assessments as indicated.

1 Serum pregnancy test for women of childbearing potential must be performed and documented as negative within 7 d of Cycle 1 Day 1. Urine or serum pregnancy test (for women of childbearing potential) will be performed at specified subsequent visits. If a urine pregnancy test is positive, hold dosing and confirm the result with a serum pregnancy test.

2 CA 19-9 measurements will be performed at screening, at Cycle 3 Day 1, then every 6 weeks (± 7 d) for 24 weeks, and every 12 weeks (± 7 d) thereafter until disease progression.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CA 19-9 = cancer antigen 19-9; CRP = C-reactive protein; d = days; eGFR = estimated glomerular filtration rate; EOT = end of treatment; FU = follow-up; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL = high-density lipoprotein; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; PCR = polymerase chain reaction; PT = prothrombin; RBC = red blood cell count; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; VLDL = very low-density lipoprotein; WBC = white blood cell.

Table 4: Schedule of activities: Part 1B – Combination dose escalation

Treatment Cycle [1] (28 d)	Pre-screening	Screening [2] ≤ 21 d prior C1D1	Cycle 1, 4, 7, etc.							Cycles 2, 5, 8, etc.						Cycles 3, 6, 9, etc.				EOT [3]	Safety FU1 30d after last dose	Safety FU2 60d after last dose	Survival FU Every 12 weeks	Unscheduled [4]
Day			1	2	3	4	8	15	22	1	8	15	16	18	22	1	8	15	22					
Visit window (days)							±1	±1	±1	+3	±1	±1			±1	±3	±1	±1	±1		+5	±7	±14	
Administrative procedures																								
ICF for pre-screening	X																							
ICF for main trial		X																						
Demographics	X																							
Tumor tissue	X [5]		X [6]								X [7]													
Eligibility	X	X																						
Medical history [8]		X																						
Clinical procedures/interventions																								
Height, body weight [9]		X	X				X	X		X	X	X				X	X	X		X	X	X		X
Physical examination [10]		X	X				X	X	X	X	X	X				X	X	X		X	X	X		X
Vital signs [11]		X	X				X	X	X	X	X	X				X	X	X		X	X	X		X
ECG [12]		X	X	X	X	X	X			X		X	X	X	X	X				X	X	X		X
Tumor assessments [13]		X	Refer to Footnote 13																	X				
ECOG Performance Status		X	X							X						X				X	X	X		X
AEs [14]		X	X				X	X	X	X	X	X				X	X	X		X	X	X		X
Prior/concomitant medication [15]		X	X				X	X	X	X	X	X				X	X	X		X	X	X		X
BNT141 administration [16]		CCI																						
Nab-paclitaxel + Gemcitabine [17]			X				X	X		X	X	X				X	X	X						
New anti-cancer treatment [18]																				X	X	X	X	
Survival follow-up [19]																							X	
Local lab: Blood sample [20]		X	X	X			X	X	X	X	X	X				X	X	X		X	X	X		X
Local lab: Urine sample [20]		X	X							X						X				X	X	X		X
Central lab: Blood sample [21]			X	X [22]	X [22]	X [22]	X	X [22]	X	X [22]	X [22]	X [22]	X [22]	X [22]	X [22]	X [22]	X [22]	X [22]		X	X	X		X

1 Trial visits will be performed weekly for Cycles 1, 2 and 4 (Days 1, 8, 15, 22). After the first 4 cycles, trial visits will be performed at the days where BNT141 and/or nab-paclitaxel and gemcitabine are administered. Treatment will continue until disease progression and until protocol-defined treatment discontinuation criteria are met.
2 If ≥50% moderate-to-strong CLDN18.2 protein expression is detected, patient can enter the screening phase. For screening, all laboratory assessments must be performed ≤ 7 d prior the planned treatment start with BNT141. Results of SOC test or examinations performed prior to obtaining informed consent and within 21 d prior to Cycle 1 Day 1 may be used, such tests do not need to be repeated for screening.
3 If the patient has to go off treatment per treatment withdrawal criteria, the End of Treatment Visit should be performed as soon as possible after permanent discontinuation criteria but not later than 30 d after last dose (in this latter case, due to the End of Treatment Visit occurring close to Safety FU1, Safety FU1 can be skipped). The visit at which an imaging shows disease progression resulting in treatment discontinuation may be used as the End of Treatment Visit, at which time all assessment associated with the End of Treatment Visit should be performed.
4 Unscheduled visits can be performed at any time point when clinically indicated and can include assessments as indicated.
5 Fresh and archival biopsies will be accepted.
6 Additional tumor tissue (10 µm thick tumor curls) should be sent from all patients receiving study drug to the central laboratory for further exploratory research on CLDN18-ARHGAP6/26 fusion.
7 On-treatment biopsy should be performed in patients where feasible/without a risk of complications for the patient. Preferred on Cycle 2 Day 8 (± 1d), but can be performed at any time during the study treatment.
8 Medical history includes cancer history (including but not limited to, prior cancer therapies and procedures and tumor characteristics such as mutation status, cancer related somatic genomic alterations and germline status, other clinically relevant diseases, surgeries, use of alcohol and/or drugs abuse and, reproductive status).
9 Height will only be measured at screening. The body weight measurement taken at the visit prior to dosing should be used for IMP preparation.
10 Full physical examinations should be performed during screening, thereafter a symptom orientated limited physical examination should be performed.
11 Includes temperature, blood pressure (systolic and diastolic), heart rate, oxygen saturation and respiratory rate.
12 A 12-lead ECG will be performed in triplicate. Single ECG recordings may be obtained at an unscheduled time point as clinically indicated.
13 The same imaging method (CT/MRI) must be used for a patient throughout the trial at screening, at Week 8 (± 7 d), then every 8 weeks (± 7 d) for 24 weeks, and every 12 weeks (± 7 d) thereafter until disease progression. Monitoring of the liver and the spleen size will be performed as described in the Imaging Manual.
14 AEs/SAEs will be reported from the start of study drug treatment until Safety FU2. During pre-screening no AEs/SAEs will be reported, with the exception of AEs/SAEs related to the procedure of collection of a fresh biopsy.
15 Prior medications are any medications and non-drug therapies (see Section 6.5) used by the patient within 21 d prior to initiation of trial treatment and during screening. Concomitant medications are any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment (including prophylactic treatment after BNT141 administration and medications as a result of an adverse event). Prior/Concomitant medications and non-drug therapies include all previous and on-trial COVID-19 vaccinations.
16 BNT141 will be administered [redacted].
17 Nab-paclitaxel and gemcitabine will be given per SmPC after administration of BNT141 [redacted]
18 New anti-cancer treatments will be collected from treatment discontinuation until death (unless the patient withdraws consent, or the sponsor terminates the trial).
19 Information on survival FU, new anti-cancer therapy and cancer-related procedures will be collected for all patients via telephone calls, patient medical records, and/or clinic visits approximately every 12 weeks until death (unless the patient withdraws consent or the sponsor terminates the trial). If the patient withdraws from trial, the trial staff may use a public information source (e.g., county records) to obtain information about survival status only.
20 Local laboratory assessments can take place one day prior to patient visit apart from Cycle 2 Day 1. The screening samples must be obtained within 7 d of Cycle 1 Day 1. All Day 1 samples must be taken before study drug administration. Additional safety laboratory assessments can be performed at any time point when clinically indicated and can include assessments as indicated. Local laboratory assessments are detailed in Table 6.
21 Central laboratory assessments are given in Table 5.
22 Cycles 1 to 3 only.

AE = adverse event; ARHGAP = Rho GTPase Activating Protein 6; CLDN = Claudin; COVID = coronavirus disease; CT = computer tomography; C1D1 = Cycle 1 Day 1; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; ICF = informed consent form; IMP = investigational medicinal product; MRI = magnetic resonance imaging; SAE = serious AE; SmPC = summary of product characteristics; SOC = standard of care.

Table 5: Schedule of central laboratory assessments (PK, PD, immunogenicity and lipids) for Part 1B – Combination dose escalation

Treatment Cycle (28 d)	Cycle 1													Cycle 2									Cycle 3			Cycle 4, 7, 10, 13, 16, etc.		EOT	Safety FU1	Safety FU2	Unscheduled
Day	1				2	3	4	8	15	22				1	8	15				16	18	22	1	8	15	1	8		30d after last dose	60d after last dose	
CCI	CCI									CCI						CCI								CCI		CCI					
Blood collection window [2]	-24h	+10 m	±15 m	±15 m							+10 m	±15 m	±15 m			-24h	+10 m	±15 m	±15 m					-24h		-24h					
Visit window [2]							+1d	±1d	±1d	+3d				±1d	±1d	+3d					+1d	±1d	±1d	+3d	±1d	+3d	±1d		+5d	±7d	
Pharmacokinetics (PK)																															
PK RiboMab CCI (serum)	X	X	X	X	X	X	X	X	X	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK lipids (plasma) [3]	X	X [3]	X	X	X			X	X	X	X					X	X			X			X								X
Pharmacodynamics (PD)																															
Cytokines/ chemokines (serum) [3, 4]	X	X [3]	X	X	X	X	X			X	X	X	X			X	X	X	X	X	X			X		X					X
ADCC (serum)	X						X									X					X										X
CDC (serum)	X						X									X					X										X
Immunogenicity (serum)																															
Anti- CCI lipid antibodies	X							X		X				X		X						X		X	X	X	X	X	X	X	X
Anti-RiboMab CCI antibodies	X								X	X					X	X							X	X	X	X	X	X	X	X	X
Additional samples																															
Extra sample for further analysis [5]	X							X		X				X		X						X		X	X	X	X	X	X	X	X
Apolipoprotein E	X																														

The PK sampling schedule may be adapted based on dose escalation PK results. Samples will be analyzed centrally. For details, please see the Laboratory Manual.

1 CCI

2 CCI Investigators must adhere to the given time points. However, due to possible time deviations that may occur in clinical practice, those will not be reported as protocol deviations.

3 After start of infusion, an unscheduled sampling for cytokines or PK lipids may be considered if infusion-related reactions occur.

4 Cytokines/chemokines to be analyzed include but are not limited to IFN-γ, IFN-α, TNFα, IL-1b, IL-12, MCP-1, MIP-1b, IL-2, IL-15, and IL-6.

5 Samples will be used either for re-testing or for future analysis if required (see Section 8.9).

ADCC = antibody-dependent cellular cytotoxicity; CCI; CDC = complement-dependent cytotoxicity; d = day; EOI = end of infusion; EOT = end of treatment; FU = follow-up; h = hour; IFN = interferon; IL = interleukin; m = minute; MCP = monocyte chemoattractant protein; MIP = macrophage inflammatory protein; TNF = tumor necrosis factor.

Table 6: Local laboratory assessments: Part 1B – Combination dose escalation

Treatment Cycle [1] (28 d)	Test to be done	Screening	Cycle 1, 4, 7, etc.					Cycle 2, 5, 8, etc.			Cycle 3, 6, 9, etc.			EOT	Safety FU1	Safety FU2	Unscheduled
Day		≤ 21 d prior C1D1	1	2	8	15	22	1	8	15	1	8	15		30 d after last dose	60 d after last dose	
Visit window (days)					±1	±1	±1	±3	±1	±1	±3	±1	±1	±1	+5	±7	
Hematology	RBC count, hemoglobin, hematocrit, platelet count, WBC count, differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry	**Electrolytes**: sodium, potassium, chloride, phosphate, calcium **Liver**: total and direct bilirubin, ALP, ALT, AST, LDH **Kidney**: creatinine, eGFR **Proteins**: total protein, albumin, glucose, CRP, urate, BUN or urea	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation factors	PT, aPTT, INR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endocrine	TSH, free T3, total T3, free T4, total T4	X												X	X	X	X
Pregnancy test [2]	Urine or serum pregnancy test	X	X					X			X			X	X	X	X
Tumor marker [3]	CA 19-9	X									X			X			X
Hepatitis B and C	HbsAg, HCV (if positive for HCV RNA by PCR)	X															
Lipids	Total cholesterol, LDL, VLDL, HDL, triglycerides		X														
Urinalysis (dipstick)	pH, specific gravity, glucose, protein, ketones, blood	X	X					X			X			X	X	X	X

Local laboratory assessments can take place one day prior to patient visit apart from Cycle 2 Day 1. The screening samples must be obtained within 7 d of Cycle 1 Day 1. All Day 1 samples must be taken before study drug administration. Additional safety laboratory assessments can be performed at any time point when clinically indicated and can include assessments as indicated.

1 Trial visits will be performed at Cycles 1, 2 and 4 (Days 1, 8, 15, 22). After the first 4 cycles, trial visits will be performed at the days where BNT141 and/or nab-paclitaxel and gemcitabine are administered. Treatment will continue until disease progression and until protocol-defined treatment discontinuation criteria are met.

2 Serum pregnancy test for women of childbearing potential must be performed and documented as negative within 7 d of Cycle 1 Day 1. Urine or serum pregnancy test (for women of childbearing potential) will be performed at specified subsequent visits. If a urine pregnancy test is positive, hold dosing and confirm the result with a serum pregnancy test.

3 CA 19-9 measurements will be performed at screening, at Week 8 (Cycle 3 Day 1), then every 8 weeks (± 7 d) for 24 weeks, and every 12 weeks (± 7 d) thereafter until disease progression.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CA 19-9 = cancer antigen 19-9; CRP = C-reactive protein; d = days; eGFR = estimated glomerular filtration rate; EOT = end of treatment; FU = follow-up; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL = high-density lipoprotein; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; PCR = polymerase chain reaction; PT = prothrombin; RBC = red blood cell count; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; VLDL = very low-density lipoprotein; WBC = white blood cell.

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TRIAL-SPECIFIC ABBREVIATIONS

Abbreviation	Explanation
ADCC	Antibody-dependent cellular cytotoxicity
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CDC	Complement-dependent cytotoxicity
CLDN18.2	Claudin 18.2
CRS	Cytokine release syndrome
EOX	The combination of epirubicin, oxaliplatin and capecitabine
FFPE	(Fresh) formalin-fixed paraffin-embedded
GEJ	Gastroesophageal junction
HRT	Hormone replacement therapy
CCI	[redacted]
IL	Interleukin
LNP	Lipid nanoparticles
NHP	Non-human primate
PDAC	Pancreatic adenocarcinoma
RP2D	Recommended Phase II Dose

For standard abbreviations, see Section 10.8.

2 INTRODUCTION

2.1 Trial rationale

Outcomes of SOC therapies remain poor for patients with relapsed or refractory advanced solid tumors, including but not limited to pancreatic, biliary tract and gastric cancers. Treatment options include further palliative chemotherapy, best supportive care and investigational treatments without proven benefit. Therapy in this population is not curative, with an expected OS of a few months. Immunotherapy with monoclonal antibodies (mAbs) has provided treatment options in at least some cancers with high unmet medical need. However, the prognosis of several tumor types, including pancreatic and biliary tract tumors, remains dismal. Safe and effective targeted therapies are needed.

Recent research has identified isoform 2 of the tight junction molecule Claudin-18 (CLDN18.2) as a promising anti-cancer target suitable for therapeutic antibody development (Sahin et al. 2008). CLDN18.2 is expressed in various high medical need cancers, e.g., gastric, gastroesophageal, colorectal, pancreatic, biliary tract and in the mucinous subtype of ovarian cancer, while expression in healthy tissues is restricted to the gastric epithelia. To date, no therapy targeting CLDN18.2 has been approved for any cancer indication.

BioNTech's first development candidate of the RiboMab platform, BNT141, is a CCI [redacted].

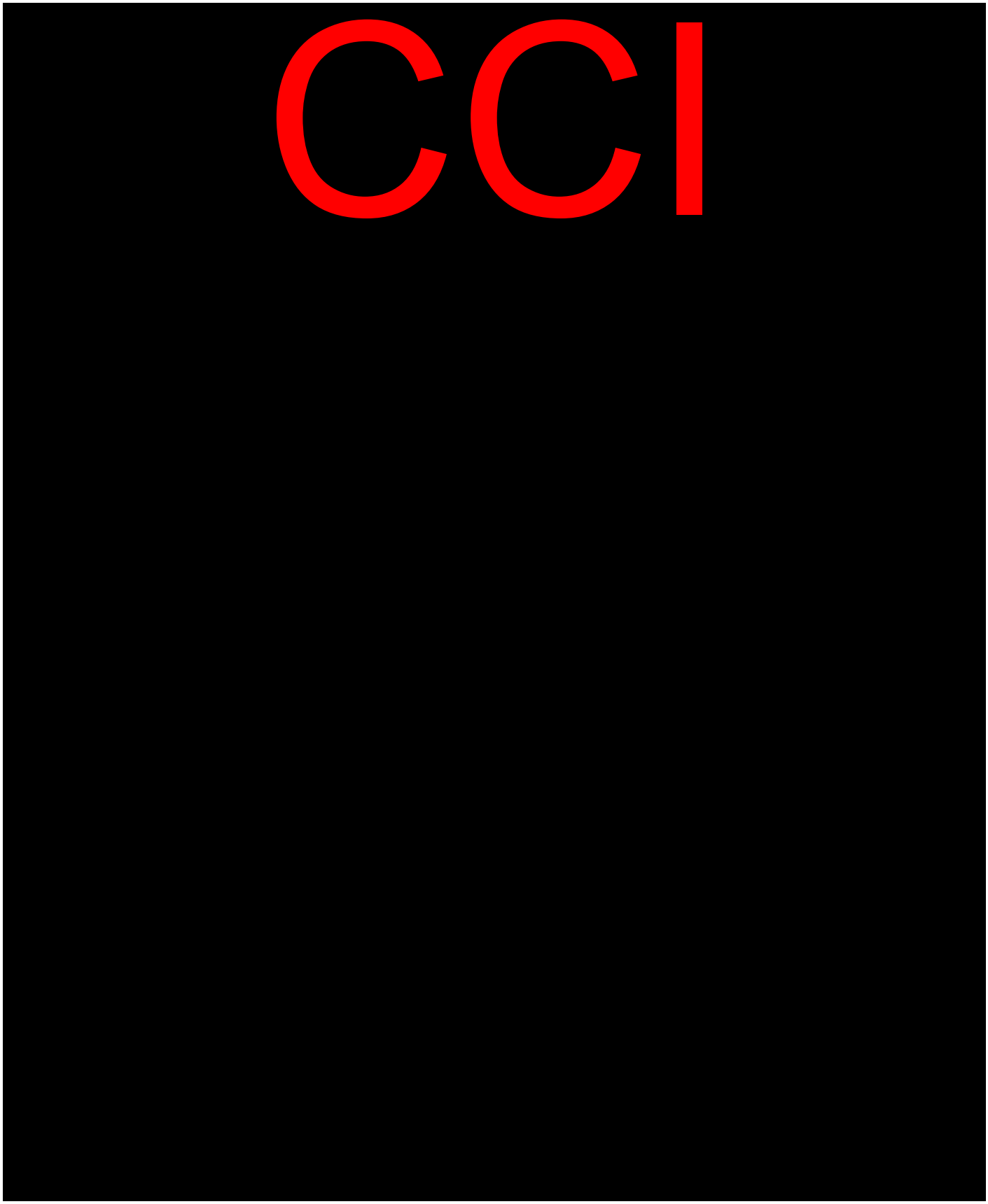
CCI [redacted]

[redacted]

The BNT141-01 trial requires expression of intermediate or high CLDN18.2 levels enriching the trial populations for patients with a higher probability of benefit from BNT141 and excluding patients not expressing this specific tumor target.

2.2 Background

[redacted]


CCI

2.2.1.1 Scientific rationale

BNT141 encodes the CCI antibody RiboMabCCI targeting CLDN18.2, which is a highly selective tumor-associated tight junction surface protein expressed in various cancers of high medical need, such as gastric, gastroesophageal, colorectal, pancreatic, biliary tract and mucinous ovarian cancer. The planned first-in-human (FIH), dose escalation trial will evaluate safety and preliminary efficacy of BNT141 as monotherapy and in combination with chemotherapy agents in patients with CLDN18.2-positive solid tumors. Eligibility for this trial requires expression of intermediate or high CLDN18.2 levels enriching the trial populations for patients with a higher probability of benefit from BNT141 and excluding patients not expressing the tumor target.

To date, no therapy targeting CLDN18.2 has been approved for any cancer indication. BNT141 is a novel RNA CCI where it encodes *in vivo* the protein RiboMabCCI. CCI

2.2.2 The target CLDN18.2

The target CLDN18.2 was selected based on the following key criteria:

- Limited expression in healthy tissues (only expressed in differentiated cells of the gastric epithelia).
- Luminal expression in gastric epithelia and thus inaccessible for immune effectors.
- Expression in a substantial fraction of primary and metastatic lesions in solid tumors.
- Exposition of CLDN18.2 epitopes on tumor cells due to malignant transformation and perturbations in cell polarity.
- Tumor biological role, as blockade of CLDN18.2 associates with anti-tumor activity in preclinical studies.

2.2.2.1 CLDN18.2 expression in healthy tissue

CLDN18.2 is a highly selective gastric lineage antigen (Sahin et al. 2008). Its expression is restricted to short-lived differentiated cells of gastric epithelia in the pit and base regions of gastric glands (Figure 3B). The stem cell zone, from which differentiated epithelial cells of the gastric glands are continuously replenished, is CLDN18.2-negative. No other normal cell type of the human body expresses CLDN18.2 at transcript level or at protein level (Figure 3A).

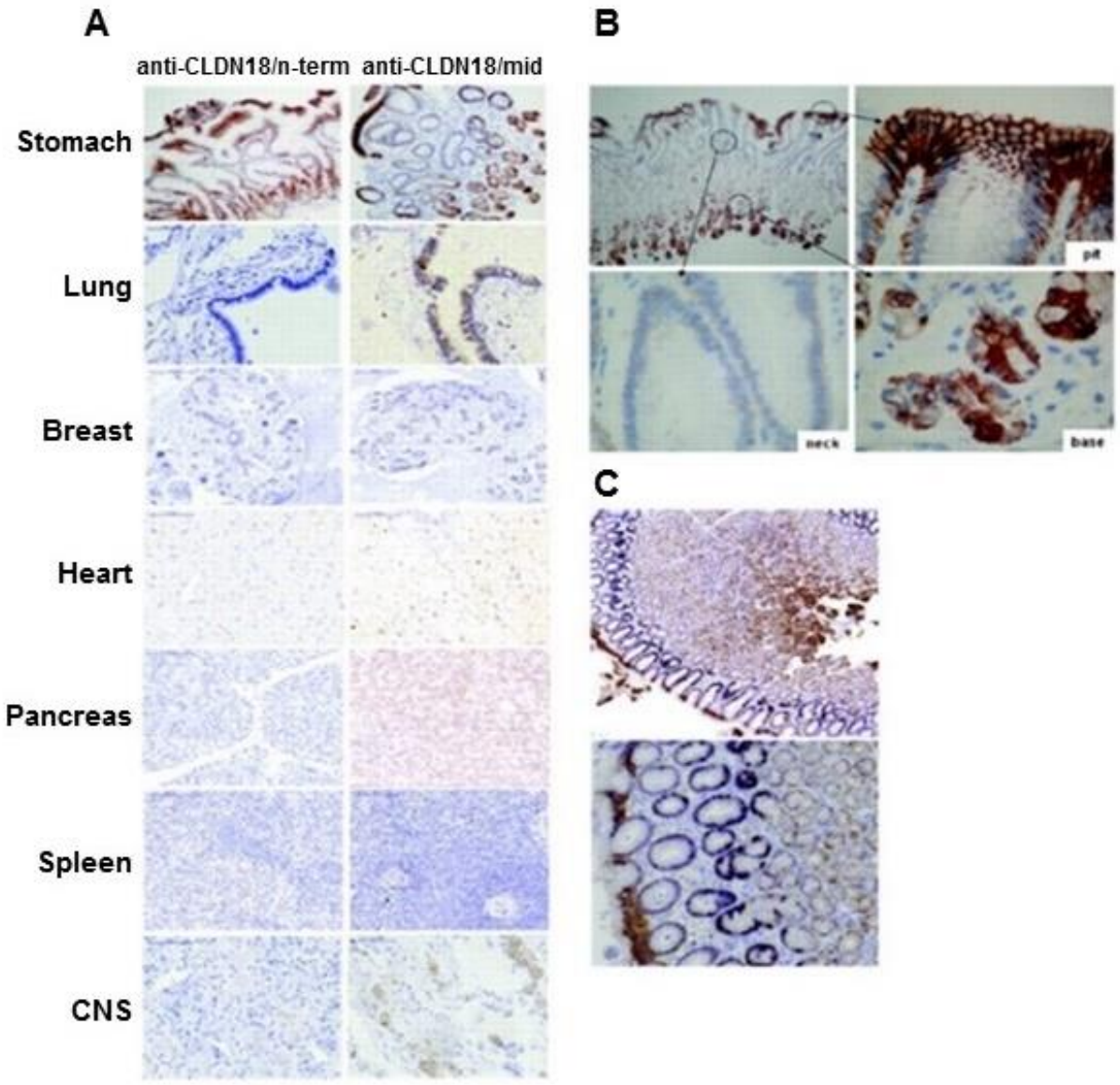


Figure 3: Immunohistochemistry of normal human tissues with CLDN18.2 antibodies

(A) Sections prepared from normal human tissues were stained with anti-claudin-18/n-term antibody (1:300), which is specific for CLDN18.2, and anti-claudin-18/mid (1:50) antibody detecting CLDN18.1 and CLDN18.2 (Zymed). The anti-claudin-18/mid antibody labels lung due to cross-reactivity with variant CLDN18.1. (B) Epithelia from the antral gastric region were stained with the anti-claudin-18/n-term antibody (top left). Close-ups show CLDN18.2 protein expression at the tip and the base of glands, but not in the neck region. (C) Double staining of gastric tissue sections with Ki67 (dark purple) and anti-claudin-18/mid antibodies (brown).

CLDN = Claudin; CNS = central nervous system.

Source: Sahin et al. 2008.

2.2.2.2 CLDN18.2 expression in cancer

CLDN18.2 is expressed in various human cancers including gastric, gastroesophageal, biliary tract and pancreatic cancers (Karanjawala et al. 2008; Shinozaki et al. 2011) (Figure 4, Figure 5), as well as precancerous lesions (Wöll et al. 2014; Tanaka et al. 2011). Tumor-associated expression of CLDN18.2 has also been detected in ovarian (Sahin et al. 2008) and lung cancers (Micke et al. 2014). Expression has also been seen in colorectal cancer based on sponsor's investigations.

Sahin et al. (2008) showed that 77% of primary gastric adenocarcinomas are CLDN18.2-positive. About half of gastric adenocarcinomas display intermediate (2+) to strong (3+) CLDN18.2 expression by immunohistochemical analysis in at least 60% of tumor cells. CLDN18.2 expression is more frequent in diffuse than in intestinal gastric cancers. The CLDN18.2 protein is also frequently detected in lymph node metastases of gastric cancer and in distant ovarian metastases (so-called Krukenberg tumors). Moreover, 50% of esophageal adenocarcinomas display significant expression of CLDN18.2.

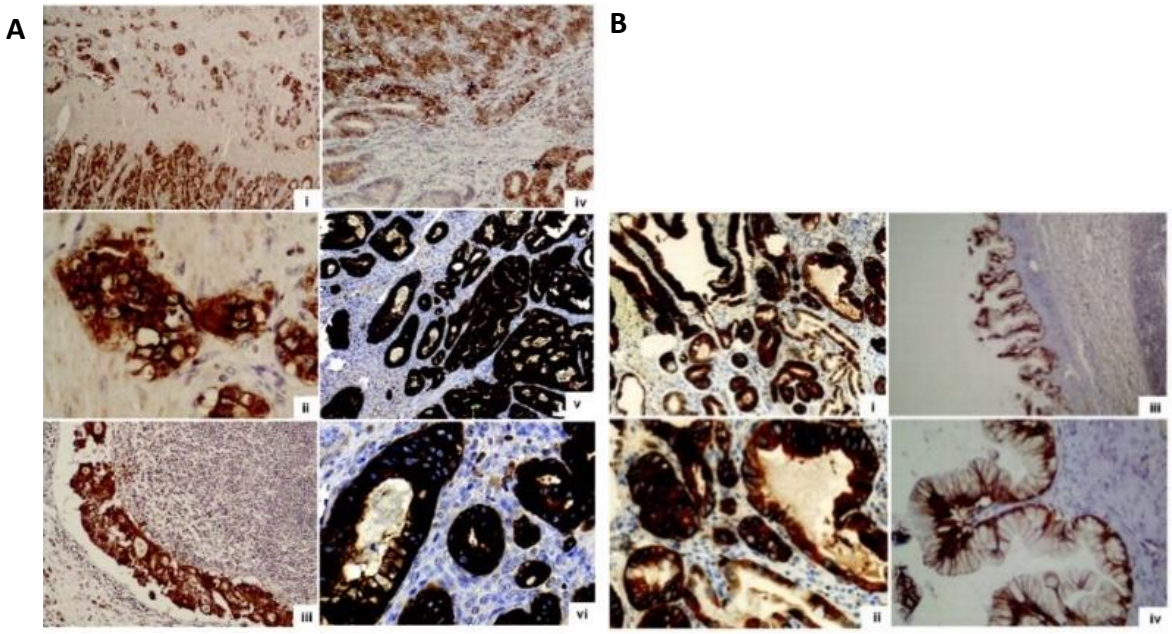


Figure 4: Immunohistochemistry of gastric tumor tissues with CLDN18.2 antibodies

(A) Tissue sections obtained from gastric tumors expressing CLDN18.2. Overview (i) and close-up (ii) of a primary lesion and a lymph node metastasis (iii) obtained from the same patient. Gastric cancer specimen from a second patient (iv). Overview (v) and close-up (vi) from a gastric cancer metastasis in the ovary obtained from a third patient. (B) Overviews and close-ups of an adenocarcinoma of the esophagus (i, ii) and of a mucinous ovarian cancer (iii, iv), respectively. All cases shown in (A) and (B) had been scored as 3+ staining in 90% to 95% of cells.

CLDN18.2 = Claudin 18.2.

Source: Sahin et al. 2008.

In pancreatic cancers, CLDN18.2 is expressed with a prevalence of 60 to 90% (Karanjawala et al. 2008; Wöll et al. 2014). Almost 60% of patients with pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer, express membrane-bound CLDN18.2 and in 20% of patients with pancreatic neuroendocrine

neoplasms, CLDN18.2 is ectopically activated. CLDN18.2 is expressed in primary and metastatic PDAC lesions (Wöll et al. 2014) (Figure 5). CLDN18.2 is also known to be expressed in patients with biliary tract cancer (6.3%) (Hong et al. 2020). In addition, it has been shown that CLDN18 is frequently expressed in various kinds of biliary neoplasms, including precancerous lesions and gallbladder cancer (Espinoza et al. 2019; Shinozaki et al. 2011).

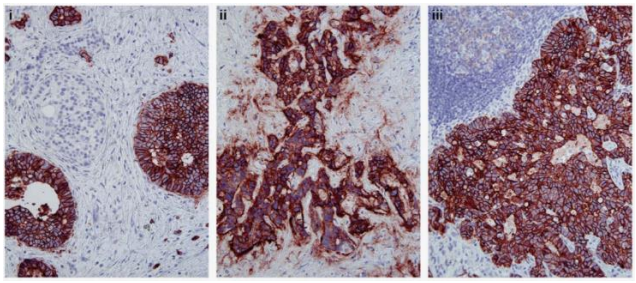


Figure 5: Expression of CLDN18.2 in matched sets of primary PDAC tumors and metastases

Representative sections of the (i) PDAC (ii) liver metastasis and the corresponding intra-individual (iii) lymph node metastasis in a single patient (100x magnification).
CLDN18.2 = Claudin 18.2; PDAC = pancreatic ductal adenocarcinoma.
Source: Wöll et al. 2014.

Downregulation of CLDN18.2 by small interfering RNA results in inhibition of proliferation of gastric cancer cells (Niimi et al. 2001), indicating its involvement in the proliferation of CLDN18.2-positive tumor cells. Independent antibody-based anti-CLDN18.2 approaches have also shown effective induction of tumor cell death in vitro as well as in animal models of gastric and/or pancreatic cancer (Zhu et al. 2019), further consolidating this strategy as a suitable therapeutic approach for CLDN18.2-positive tumors. Interestingly, gemcitabine, a first-line chemotherapeutic drug used in the treatment of pancreatic cancer, has been associated with upregulation of CLDN18.2 expression on the surface of cancer cells (Türeci et al. 2018). This represents an opportunity for synergy between chemotherapy and anti-CLDN18.2 targeting for increased efficacy.

For this trial, patients will only be eligible if they have tumors displaying moderate-to-strong CLDN18.2 protein staining intensity in tumor cells using a validated immunohistochemistry assay.

2.2.3 Overview of the diseases

2.2.3.1 Solid tumors

Cancer is the second leading cause of death globally and in 2018 was predicted to be responsible for an estimated 9.6 million deaths (Bray et al. 2018). In general, once a solid tumor has metastasized, with a few exceptions such as germ cell and some carcinoid tumors, 5-year survival rarely exceeds 25%. Incidence of CLDN18.2-positive tumors is described above in Section 2.2.2.

Refinements in conventional therapies such as chemotherapy, radiotherapy, surgery, and targeted therapies and recent advances in immunotherapies have improved outcomes in patients with advanced solid tumors. In the last few years, the (United States) Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved several checkpoint inhibitors for the treatment of patients with multiple cancer types, mainly solid tumors. These approvals have dramatically changed the landscape of cancer treatment. However, this revolution in cancer care has not benefited patients suffering from cancers such as advanced/metastatic pancreatic adenocarcinoma and biliary tract cancers that have not been shown to respond to existing immunotherapies.

The poor prognosis of these cancer types highlights the need for additional treatment approaches. One such approach is that of targeted therapies, an ever-evolving field with promising modalities including RNA-encoded antibodies such as BNT141. Identifying a specific tumor-associated antigen for an oncology target that has limited normal tissue expression is critical. CLDN18.2 represents a potentially attractive tumor-associated antigen because it fulfills this criterion. The capability for RiboMab[redacted] to induce ADCC and CDC could augment the cytotoxic effect of chemotherapy, potentially translating into improved outcomes. To date, no therapy targeting CLDN18.2 has been approved for any cancer indication.

2.2.3.2 PDAC

The most common type of pancreatic cancer is exocrine pancreatic cancer, of which 90% are PDACs (ACS 2020a, Kleeff et al. 2016). Although there have been advances in treatments, clinical outcomes of patients with PDAC remain poor, with the 5-year OS rate being reported as 8% (Siegel et al. 2018, Luberice et al. 2017). This prognosis is due to diagnosis at an advanced stage, as well as limited response to available treatments which include chemotherapy, surgery and radiotherapy. Only a small proportion (10 to 20%) of patients present with resectable PDAC, where surgical resection followed by adjuvant chemotherapy is the only curative option. The majority of patients (80 to 90%) present with locally advanced, unresectable disease or distance metastases, and are treated up-front with systemic chemotherapy (Gillen et al. 2010; Werner et al. 2013). Chemotherapy regimens include nucleoside analogs, such as gemcitabine and capecitabine, or the pyrimidine analog 5-fluorouracil (5-FU) as single agents or in combination with other treatments such as radiotherapy. Some regimens, such as FOLFIRINOX (a combination of oxaliplatin, irinotecan, 5-FU, and leucovorin) have improved OS in patients with early stage pancreatic cancer, but have limited efficacy in the advanced setting (Orth et al. 2019, Conroy et al. 2011). The SOC for patients with locally advanced or metastatic disease and a good performance status (PS) is systemic therapy. The National Comprehensive Cancer Network (NCCN) recommends nab-paclitaxel and gemcitabine in patients with an Eastern Cooperative Oncology Group (ECOG) PS of 1 to 2, and FOLFIRINOX/modified FOLFIRINOX (both with the option of subsequent chemoradiation) in patients with ECOG PS 0 to 1 (NCCN guidelines Version 1.2020. Pancreatic adenocarcinoma).

There have been recent advances in treatments for this high medical need group of patients, including targeted and biomarker-driven treatments. Erlotinib, an epidermal growth factor receptor inhibitor, is approved in the United States (US) in combination with gemcitabine for the first-line treatment of patients with locally advanced, unresectable or

metastatic pancreatic cancer. Patients with metastatic pancreatic adenocarcinoma with germline *BRCA* mutations also have the option of maintenance olaparib treatment. The poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitor extended PFS vs placebo treated patients from 3.8 to 7.4 months in a randomized, double-blind Phase III trial, although no benefit to OS was detected in the interim analysis (Golan et al. 2019).

Despite these advances, this remains a patient population with a high unmet medical need. BNT141 could potentially benefit the subpopulation of tumors with CLDN18.2-positive pancreatic adenocarcinoma. The sponsor aims to accelerate the clinical development of BNT141 in this indication by establishing a safe dose to be carried forward with the SOC (chemotherapy) during the FIH trial.

2.2.3.3 Biliary tract cancers

Biliary tract cancers comprise a group of rare epithelial tumors, and include gallbladder cancer and intrahepatic and extrahepatic bile duct cancer (cholangiocarcinoma). Together, they constitute approximately 1% of adult cancers worldwide, and are associated with poor survival rates, in general due to late-stage diagnosis (Athauda et al. 2020). The 5-year survival rate for gallbladder cancer and cholangiocarcinoma is 19% and 8%, respectively (ACS 2020b, ACS 2020c).

Treatments for biliary tract cancers are stratified according to the stage of the disease. Surgical resection and adjuvant chemotherapy remain the mainstay of cure for localized disease, although this represents a small minority of patients (10 to 40%), as disease is typically diagnosed in patients with an advanced stage or unresectable disease (Cidon 2016). For the first-line treatment of advanced disease, the Phase III trial ABC-02 confirmed the superiority of the combination of gemcitabine and cisplatin over single-agent gemcitabine (Valle et al. 2010).

Anti-tumor activity was also suggested for first-line therapy with weekly gemcitabine plus nab-paclitaxel in advanced or metastatic cholangiocarcinoma. The ORR was 30%, median PFS was 7.7 months, and median OS was 12.4 months. The most common Grade 3 or worse treatment-related AEs were neutropenia (43%) and fatigue (14%) (Sahai et al. 2018).

Several clinical trials are also exploring targeted therapies and immunotherapy for biliary tract cancers, but their use is yet to be established (Athauda et al. 2020). Although the therapeutic landscape for this disease is improving, there is an urgent need for more optimal, personalized management of biliary tract cancer in order to achieve durable clinical benefit.

2.2.4 Introduction to the investigational treatment

Trial treatment includes both investigational medicinal product (IMP) and non-investigational medicinal products (NIMP). The IMP under evaluation in this trial is BNT141; all other combination anti-cancer agents are part of SOC and are considered NIMPs.

2.2.4.1 Investigational medicinal product

BNT141

[redacted]

2.2.4.2 Non-investigational medicinal products

Gemcitabine

Gemcitabine kills cells undergoing deoxyribonucleic acid (DNA) synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized by nucleoside kinases to diphosphate and triphosphate (dCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually results in the initiation of apoptotic cell death.

Nab-paclitaxel

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nm. It is a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes

microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or 'bundles' of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

2.3 Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) applicable for this trial are given in the BNT141 Investigator's Brochure.

2.3.1 Risk assessment of BNT141 as monotherapy (Part 1A)

As this trial will be the first time BNT141 will be tested in humans, all precautions indicated when testing a new systemically active compound in a FIH trial will be taken, including choosing a high medical need patient population. There will be a minimum of 48 h between the first and second patient, and between the second and third patient, in each dose cohort in Parts 1A and 1B in order to account for any acute safety signals in each new dose level. To further augment patient safety, there will be a minimum of 14 d between the first, second and third patient enrolled in the first dosing cohort in each of the monotherapy (Part 1A) and the combination (Part 1B) escalation parts of the trial. The trial will be conducted at sites experienced in FIH trials, and trial-related procedures will only be performed by qualified physicians and trained nurses. The sponsor will also prepare and train the investigators to closely monitor, dose delay, or withdraw patients if AEs occur after administration of BNT141 in monotherapy and in combination.

Furthermore, regular safety data reviews will be performed by the sponsor and by the SRC to identify and evaluate potential safety concerns. All patients enrolled in this trial will be monitored by qualified health care professionals who will provide care and evaluate the patient's response to the trial drug in terms of its safety and efficacy.

Beyond that, the sponsor has performed a risk assessment to identify and assess risks specific to BNT141 related to either the translated proteins, i.e., RiboMab[redacted] antibody, or to the formulation of the RNA drug substance within LNPs. In particular, the following data sources were used: (i) the preclinical data package obtained for BNT141, and (ii) non-clinical and (iii) clinical literature data published on other similar therapies either still in development or approved.

One of the identified risks is associated with the intended target of BNT141, which is CLDN18.2, which may present as "on-target/off-tumor" toxicity, resulting from a direct interaction with normal tissues that express the targeted antigen. The stomach is the only human, NHP and murine organ in which CLDN18.2 is expressed in healthy tissues. [redacted] Furthermore, BNT141 does not bind to any other claudin family member, including the closely related splice variant CLDN18.1, that is predominantly expressed in the lung (Sahin et al. 2008). In summary, potential risk for "on-target/off-tumor" toxicity is low and will be mitigated by close clinical observation in patients including regular safety laboratory assessments.

Previous clinical trials using IV administered LNP-formulated RNA mixtures have reported incidence of mild to moderate infusion-related reactions (IRRs) at relatively higher

administered doses (Coelho et al. 2013, Tabernero et al. 2013). These reactions readily responded to temporary interruption of the infusion and resumption of drug administration at a slower rate, and associated in some cases with transient elevation of pro-inflammatory cytokines (interleukin [IL]-6, tumor necrosis factor-α). Since the risk of IRRs cannot be excluded due to the given limited experience with BNT141, in the FIH trial BNT141-01, BNT141 will be administered [redacted]. In addition, treatment guidelines for the management of IRRs are provided in Section 6.6.3.1 and cytokine measurements are included in the scheduled assessments.

[redacted]

Another potential risk associated with BNT141 is the induction of ADA against RiboMab[redacted]. This potential risk could affect the exposure of the antibody translating in a decrease of efficacy. This clinical trial protocol will further monitor this potential risk with ADA measurements in accordance with regulatory guidelines.

In conclusion, the non-clinical and literature data collected so far do not show any potential unacceptable toxicities that cannot be mitigated or managed in the clinical setting. The anticipated benefits of BNT141 in patient populations with high, unmet medical needs outweigh the potential risks with the compound.

2.3.2 Risk assessment of BNT141 in combination with nab-paclitaxel and gemcitabine (Part 1B and Part 2)

As this is an FIH trial, the risk of synergistic and/or potentiating toxicities when BNT141 is combined with nab-paclitaxel and gemcitabine cannot be completely ruled out. [redacted]

[redacted]

To safeguard patient safety, the sponsor will generate sufficient monotherapy safety data in Part 1A before initiation of the Part 1B combination escalation and will ensure that prior to the combination initiation, the starting dose level of BNT141 in the Part 1B combination is fully evaluated and deemed safe as monotherapy in the 3+3 design.

2.3.3 Benefit assessment

As summarized in Section 2.1, with cures remaining scarce in patients with advanced or metastatic CLDN18.2-positive solid tumors, there is an unmet medical need for more effective therapies. This trial will determine the safety, PD, PK, and preliminary efficacy of BNT141 in monotherapy and combination therapy. This information will provide the basis for subsequent combination trials, and thus ultimately support the development of new therapies for patients with advanced or metastatic solid tumors.

2.3.4 Overall benefit/risk conclusion

Taking into account the measures taken to minimize risk to patients participating in this trial, the potential risks identified in association with BNT141 are justified by the anticipated benefits that may be afforded to patients with advanced or metastatic solid tumors. Additional information is provided in the BNT141 Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Objective	Endpoints
Primary objectives	
To assess the safety and tolerability of BNT141 at different dose levels.	• Occurrence of treatment-emergent adverse events (TEAEs) within a patient including Grade ≥ 3, serious, fatal TEAE by relationship. • Occurrence of dose reductions and discontinuation of BNT141 due to TEAEs.
To identify the maximum tolerated dose (MTD) or maximally administered dose (MAD) /recommended Phase II dose (RP2D) of BNT141 based on the occurrence of dose-limiting toxicities (DLTs) using the following definitions: • The MTD will be defined as the highest tolerated dose, where less than one-third of the patients experience a DLT. • The maximally administered dose (MAD) is defined as the highest dose administered, where all dose levels were tolerated during dose escalation. • The RP2D will be defined based on integrated evaluation of safety,	• Occurrence of DLTs within a patient during the DLT evaluation period.

Objective	Endpoints
tolerability, clinical benefit, pharmacokinetic (PK), and PD data, for all dose levels tested.	
Secondary objectives	
To characterize the PK profile of the BNT141-encoded protein RiboMab[redacted].	• PK parameters including but not limited to area-under-the-concentration-time curve (AUC), clearance (CL), volume of distribution (Vd), maximum concentration (C_{max}), time to C_{max} (t_{max}), measured concentration at the end of a dosing interval [taken directly before next administration] (C_{trough}), and half-life ($t_{½}$).
To evaluate the anti-tumor activity of BNT141 according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.	• Objective response rate (ORR) is defined as the proportion of patients in whom a complete response (CR) or partial response ([PR], per RECIST 1.1) is confirmed as best overall response. • Disease control rate (DCR) is defined as the proportion of patients in whom a CR or PR or SD (per RECIST 1.1, SD assessed at least 6 weeks after first dose) is observed as best overall response. • Duration of response (DOR) is defined as the time from first objective response (CR or PR per RECIST 1.1) to first occurrence of objective tumor progression (progressive disease per RECIST 1.1) or death from any cause, whichever occurs first.
Exploratory objectives	
To evaluate the efficacy of BNT141.	• Progression-free survival (PFS) is defined as the time from first dose of BNT141 to first objective tumor progression (progressive disease per RECIST 1.1), or death from any cause, whichever occurs first. • Overall survival (OS) is defined as the time from first dose of BNT141 to death from any cause.
To assess Claudin 18.2 (CLDN18.2) expression level as a potential biomarker to predict clinical response to BNT141.	• Correlation of CLDN18.2 expression level with clinical outcomes.
To assess potential PD biomarkers of BNT141.	• Evaluation of PD biomarkers compared to baseline.
To evaluate the immunogenicity of BNT141.	• Anti-drug antibodies [ADAs] response.
To assess other exploratory markers that may be collected in the trial to better understand BNT141 treatment.	• Evaluate pre-treatment lipid status and potential influence on BNT141 response.

4 TRIAL DESIGN

4.1 Overall design

This trial is an open-label, multi-site, Phase I/IIa dose escalation, safety, and PK trial of BNT141 followed by expansion cohorts in patients with CLDN18.2-positive tumors. CLDN18.2 positivity will be determined by a central laboratory during the pre-screening phase using a validated immunohistochemistry assay, and is defined as moderate-to-strong CLDN18.2 expression.

The trial design consists of three parts:

- **Part 1A is a dose escalation of BNT141 as monotherapy** in patients with advanced unresectable or metastatic CLDN18.2-positive solid tumors for which there is no available standard therapy likely to confer clinical benefit, or the patient is not a candidate for such available therapy. Patients must have received all available standard therapies and failed at least first-line SOC therapy prior to enrolment. The dose of BNT141 will be escalated until the MTD and/or RP2D of BNT141 as monotherapy are defined. Once the MTD is reached, up to 10 additional patients with CLDN18.2 expressing pancreatic and biliary tract cancers will be enrolled at the MTD level to obtain additional data on safety, PK and PD. Eligible tumor types are gastric cancer, gastroesophageal junction (GEJ) and esophageal adenocarcinoma, pancreatic, biliary tract (cholangiocarcinoma and gallbladder cancer), and mucinous ovarian cancers. Additionally, patients with specific tumors (including colorectal cancer, non-small-cell lung cancer, gastric subtype of endocervical adenocarcinoma) where there is scientific evidence that the CLDN18.2 could be elevated can be tested for CLDN18.2 expression.
- **Part 1B is a dose escalation of BNT141 in combination with nab-paclitaxel and gemcitabine** in patients with locally advanced unresectable or metastatic CLDN18.2-positive pancreatic adenocarcinoma or cholangiocarcinoma who are eligible for treatment with nab-paclitaxel and gemcitabine. Part 1B intends to define the MTD and/or RP2D of the combination. Once the MTD is reached, up to 10 additional patients with CLDN18.2-expressing pancreatic adenocarcinoma or cholangiocarcinoma will be enrolled at the MTD level to obtain additional data on safety, PK and PD. The MTD of BNT141 in combination with nab-paclitaxel and gemcitabine in Part 1B will not exceed the monotherapy BNT141 MTD determined in Part 1A.
- **Part 2 (Expansion)** consists of the following pre-defined expansion cohorts:

  [redacted]

  [redacted]

The sample size and design in Part 2 will be further determined based on careful evaluation of all available safety, PK and PD, and efficacy data generated in Parts 1A and 1B by the SRC and will be further defined via an amendment.

Section 1.2 depicts the overall trial design. Details of Part 1A are described in Section 4.1.4.1.

Dose escalation in Part 1A and Part 1B will follow a classical 3+3 design. In each dose level, 3 to 6 DLT-evaluable patients will be enrolled (2 patients where 2 DLTs have occurred). There will be a minimum of 48 h between the first and second patient, and between the second and third patient, in each dose cohort to account for any acute safety signals in each new dose level. To further augment patient safety, there will be a minimum of 14 d between the first, second and third patient enrolled in the first dosing cohort in each of the monotherapy (Part 1A) and the combination (Part 1B) escalation parts of the trial.

Part 1A monotherapy dose escalation will be initiated first. In Part 1A, a pharmacology guided dose escalation (PGDE) approach will be taken into consideration for guiding the dose range of BNT141, where anti-tumor activity is expected, and the timing of Part 1B initiation. [redacted] Based on extrapolation from preclinical in vitro data and considering patient variability, a C_{trough} of [redacted] is considered as pharmacologically active and able to trigger the MoA-mediated anti-tumor activity in all patients throughout the treatment cycle. Part 1B dose escalation of BNT141 in combination with nab-paclitaxel and gemcitabine is planned to start before the MTD/RP2D is reached in Part 1A or at latest at the MTD dose level using a bifurcated trial design. Bifurcation in Part 1B is planned to start when a dose level with the target C_{trough} is reached in Part 1A and after this dose level is fully evaluated and deemed safe as monotherapy in the 3+3 design. [redacted] The sponsor together with the SRC may explore intermediate dose levels to bifurcate from monotherapy to combination dose escalation based on safety, PK, PD and preliminary efficacy data generated. For further understanding of the safety, tolerability and PK of BNT141, up to 6 additional patients may be enrolled at preceding dose levels or to intermediate dose levels in Parts 1A and 1B, while proceeding with further dose escalation or even thereafter.

The dose level of BNT141 [redacted] This shall lead to the timely optimization of the combination schedule that will be taken to Part 2 (Expansion). At the same time, patient safety is safeguarded by generating sufficient monotherapy data before bifurcation, and clear rules for parallel dose escalations are outlined.

In Part 2, two pre-defined expansion cohorts will be opened. The sample size and statistical design of those cohorts will be further defined via an amendment, based on careful evaluation of all available safety, PK and PD, and efficacy data obtained in Parts 1A and 1B. [redacted]

[redacted] Furthermore, more expansion cohorts to test safety, as well as to confirm the treatment dose and schedule may be opened and operationalized according to a protocol amendment. The decision to have additional cohorts will be based on the totality of data generated in Parts 1A and 1B of the trial. All decisions for cohort expansion will be endorsed by the SRC.

In Part 1A, efficacy will be assessed by on-treatment imaging assessed locally by the investigator at Week 6 (±7 d), every 6 weeks (±7 d) for 24 weeks, and every 12 weeks (±7 d) thereafter. In Part 1B efficacy will be assessed by on-treatment imaging at Week 8 (±7 d), every 8 weeks (±7 d) for 24 weeks, and every 12 weeks (±7 d) thereafter. Efficacy assessments will continue until disease progression is assessed by the investigator, withdrawal of consent, trial termination by the sponsor, or death, whichever occurs first. The RECIST 1.1 criteria will be used for secondary endpoint response evaluation including PFS (Eisenhauer et al. 2009). All images obtained must be submitted and stored to the central imaging vendor.

Patients who discontinue treatment for reasons other than radiographic disease progression (e.g., toxicity) will continue scheduled tumor assessments at the same frequency as would have been followed if the patient had remained on trial treatment.

Safety will be assessed on a regular basis by means of clinical and laboratory parameters, as defined in the SoA.

PK and various PD markers, which might act as anti-tumor, and safety indicators of activity of BNT141 monotherapy and in combination with nab-paclitaxel and gemcitabine, will be evaluated, as defined in the SoA.

The overall trial design is shown in Section 1.2.

4.1.1 MTD, MAD and RP2D definitions

The MTD is defined as the highest tolerated dose. The MAD is defined as the highest dose administered, where all dose levels were tolerated during dose escalation.

The RP2D will be determined based on integrated evaluation of safety, tolerability, clinical benefit, PK and PD data, for all dose levels tested. The RP2D will not exceed the MTD.

Toxicities other than DLTs will be considered, including: TEAEs assessed as related to BNT141 treatment but not considered dose-limiting, the nature and frequency of toxicities, and the emergence of any specific category of toxicities. Further data will be considered, including:

- Evidence of clinical activity, as available
- Available PK and PD data

If the RP2D cannot be distinguished using the criteria above, cohort expansion for optimized RP2D determination may take place at preceding dose levels or to intermediate dose levels for up to six additional patients per dose level. If serious related toxicities are observed in later cycles beyond Cycle 1, a reduction of the MTD and/or adjustment of RP2D may be considered. This determination will be made by the SRC.

4.1.2 Pre-screening

The pre-screening is intended to identify patients with CLDN18.2-positive tumors, before they sign the trial-specific informed consent and they enter into trial screening. Patients will sign a pre-screening ICF to specifically allow the collection and testing of tumor tissue by a validated immunohistochemistry assay. Patients undergoing pre-screening must have tumor types eligible for the trial, as defined in Part 1A, Part 1B and Part 2 eligibility criteria.

Tumor tissue must be obtained from each patient. Both fresh and archival biopsies will be accepted. Both biopsies should be sent preferably as slides from FFPE or as FFPE blocks. Bone biopsies are not allowed. Cytology specimens (including fine needle aspirates (FNA)) will not be accepted for this trial.

After completion of the pre-screening assay, the remaining (unused) part of a sample will be either banked for future research (optional), destroyed or, in case tumor blocks were sent, returned to trial sites upon request.

Demographic information including sex, year of birth/age, and self-reported race/ethnicity will be also collected during pre-screening.

4.1.3 Screening

Screening will occur ≤ 21 d prior to Visit C1. Patients will sign an ICF prior to any screening related procedures.

Eligibility status will be determined and be provided to the physician that submitted the patient's tissue for testing.

Medical history includes cancer history (including but not limited to, prior cancer therapies and procedures and tumor characteristics such as mutation status, cancer related somatic genomic alterations and germline status, other clinically relevant diseases, surgeries, use of alcohol and/or drugs abuse and reproductive status).Refer to Section 1.3 for the assessments to be performed at screening.

4.1.4 Dose escalation part

4.1.4.1 Part 1A: monotherapy dose escalation

Monotherapy dose escalation (Part 1A) will follow a classical 3+3 design. In each dose level, 3 to 6 DLT-evaluable patients will be enrolled (2 patients where 2 DLTs have occurred). There will be a minimum of 48 h between the first and second patient, and between the second and third patient, in each dose cohort to account for any acute safety signals in each new dose level. To further augment patient safety, there will be a minimum of 14 d between the first, second and third patient enrolled in the first dosing cohort in Part 1A of the trial.

Hospitalization [redacted] in Cycle [redacted] for all patients is at the discretion of the investigator. For the assessment of each cohort, the DLTs will be collected for the first treatment cycle, i.e., a DLT evaluation period of 21 d.

Dose escalation will follow a classical 3+3 design and continue until DLTs are observed in 2/3 or 2/6 patients as described in the following dose escalation table (Table 7).

Table 7: Dose escalations

Number of evaluable patients with DLT at a given dose level after the first treatment cycle	Escalation decision rule
0 out of 3 OR 1 out of 6	Enter patients at the next higher dose level
1 out of 3	Enter more patients at this dose level to a total of at least six evaluable patients or two patients with DLT
2 out of 3 OR at least 2 out of 6	Dose escalation will be stopped, the MTD will be considered to be reached at one dose level below. The sponsor will decide, based on SRC recommendation, if additional patients need to be enrolled and at which dose to finalize the trial
Any condition which would require further clarification of safety	A cohort of six patients can eventually be extended and more patients can be enrolled in a cohort if decided by the sponsor based on SRC recommendation

DLT = dose-limiting toxicity; MTD = maximal tolerated dose; SRC = Safety Review Committee.

The dose escalation will potentially (dependent on data collected during the trial) evaluate BNT141 at eight main dose levels as shown in Table 8.

Table 8: BNT141 dose increments

Dose level	Dose[1]	Dose increment
1	0.15 mg/kg	Starting dose
2	0.30 mg/kg	100%
3	0.60 mg/kg	100%
4	CCI	[redacted]
5	CCI	[redacted]
6	CCI	[redacted]
7	CCI	[redacted]
8	CCI	[redacted]

1 Can be reduced or increased as a function of the observed biologic activity and based on other data generated during the trial for dose optimization. Intermediate dose levels may be investigated.

In this FIH trial, the BNT141 starting dose is 0.15 mg/kg every 3 weeks (wks). This is based on a comprehensive evaluation of the toxicology program in mice and cynomolgus monkeys supporting 1.5 mg/kg once weekly as a safe dose, a safety margin of 10 to account for unexpected toxicities, and the utilization of a less frequent dosing regimen of BNT141 in the clinic (every 3 wks), which is anticipated to provide benefit based on the pharmacokinetic properties of the translated protein RiboMab[CCI]. More detailed information about the BNT141 starting dose in this FIH trial is found in the BNT141 Investigator's Brochure.

On the basis of the pharmacokinetic profile of RiboMab[CCI] in preclinical NHP studies [CCI] [redacted]

CCI we expect that a pharmacologically active dose can be delivered at the safe starting dose of 0.15 mg/kg, corresponding to approximately 7 µg/mL RiboMab01 at C_{max}. Further, based on the non-clinical toxicology profile, which does not suggest a steep dose- or exposure-response curve and showed no severe toxicity findings, initial dose doubling or tripling is permitted. CCI Furthermore, the sponsor proposes CCI optional, intermediate dose levels at CCI 0.45, CCI mg/kg. Once the MTD is reached, up to 10 additional patients with CLDN18.2-expressing pancreatic and biliary tract cancers will be enrolled at the MTD level to obtain additional data on safety, PK and PD.

To be eligible for DLT assessment, patients should receive one administration of BNT141 during Cycle 1 (DLT assessment period). Patients who will not be able to fulfill the criteria for the DLT assessment will be replaced (this only applies to patients who do not experience a DLT). Replaced patients can continue with BNT141 treatment and follow the same trial procedures except for DLT assessment until they meet the protocol-defined treatment discontinuation criteria.

After completion of the DLT period for each cohort, the SRC will review the data from the DLT period – including but not limited to all relevant safety, clinical, and available PK and PD data – to propose a dose level for the next cohort of patients.

4.1.4.2 Dose escalation in Part 1B

The rules and details on the bifurcated design are outlined in Section 4.1. Part 1B will involve dose escalation of BNT141 in combination with nab-paclitaxel and gemcitabine in patients with CLDN18.2-positive unresectable locally advanced or metastatic pancreatic adenocarcinoma and cholangiocarcinoma who are eligible for treatment with nab-paclitaxel and gemcitabine, until the MTD and/or RP2D are defined.

The dose escalation in Part 1B follows the classical 3+3 design as described above in Section 4.1.4.1. In each dose level, 3 to 6 DLT-evaluable patients will be enrolled (2 patients where 2 DLTs have occurred). There will be a minimum of 48 h between the first and second patient, and between the second and third patient, in each dose cohort to account for any acute safety signals in each new dose level. To further augment patient safety, there will be a minimum of 14 d between the first, second and third patient enrolled in the first dosing cohort in Part 1B of the trial.

Bifurcation in Part 1B is planned to start when a BNT141 dose level with the target C_{trough} is reached in Part 1A dose escalation, and after this dose level is fully evaluated and deemed safe as monotherapy in the 3+3 design. At this point, Part 1B may start CCI Nab-paclitaxel and gemcitabine will be administered as SOC regimen. BNT141 will be subsequently escalated to define the MTD and/or RP2D of the combination. Dose escalation will follow a classical 3+3 design and continue until DLTs are observed in 2/3 or 2/6 patients as outlined in Table 8. Once the MTD is reached, up to 10 additional patients with CLDN18.2-expressing pancreatic adenocarcinoma or cholangiocarcinoma will be

enrolled at the MTD level to obtain additional data on safety, PK and PD. The MTD of BNT141 in combination with nab-paclitaxel and gemcitabine in Part 1B will not exceed the monotherapy BNT141 MTD determined in Part 1A.

Hospitalization [redacted] in Cycle 1 [redacted] for all patients is at the discretion of the investigator. For the assessment of each cohort, the DLTs will be collected for the first treatment cycle, i.e., a DLT evaluation period of 28 d. BNT141 will be administered IV [redacted] of the first 28-day cycle and Q3W thereafter. Nab-paclitaxel and gemcitabine will be administered IV on [redacted] of each 28-day cycle. The days of administration of BNT141 and nab-paclitaxel and gemcitabine are shown in Table 9 and the recommended doses in Section 6.1.2. Based on Part 1B PK, PD, PK/PD modeling and clinical data, [redacted]. In the event that a dose level in Part 1B meets the classification for MTD, dosing in Part 1B will stop. To be eligible for DLT assessment, patients should receive:

- [redacted]
- [redacted]
- [redacted]

Patients who will not be able to fulfill the criteria for the DLT assessment will be replaced (this only applies to patients who do not experience a DLT). Replaced patients can continue with BNT141 treatment and follow the same trial procedures except for DLT assessment until they meet the protocol-defined treatment discontinuation criteria.

The monotherapy dose escalation in Part 1A can proceed independently of Part 1B until MTD and/or RP2D of BNT141 monotherapy are established. Refer to Section 6.6.4 for safety stopping criteria.

4.1.5 Expansion part

Once Parts 1A and 1B are completed, the trial will proceed with Part 2 (Expansion). This will be conducted in the two following indication-specific cohorts:

- CLDN18.2-positive [redacted] eligible for treatment with nab-paclitaxel and gemcitabine.
- CLDN18.2-positive [redacted] eligible for treatment with nab-paclitaxel and gemcitabine.

The sample size and statistical design of Part 2 will be further defined via an amendment, based on careful evaluation of all available safety, PK and PD, and efficacy obtained in Parts 1A and 1B.

4.1.6 Safety follow-up period

Safety monitoring assessments will be performed from the last dose of BNT141 or nab-paclitaxel and gemcitabine until 60 d after and the last Safety Follow-up Visit.

4.1.7 Survival follow-up

Information on survival follow-up, new anti-cancer therapy (including targeted therapy and immunotherapy) and cancer-related procedures will be collected for all patients via telephone calls, patient medical records, and/or clinic visits from BNT141 treatment discontinuation and approximately every 12 weeks until death (unless the patient withdraws consent or the sponsor terminates the trial). If the patient withdraws from trial, the trial staff may use a public information source (e.g., county records) to obtain information about survival status only.

4.1.8 Adaptive trial design elements

The following adaptive design elements define conditions under which changes to the trial design may be implemented based on the SRC recommendation. Further changes not specified here will only be introduced via an amendment to this protocol.

- Addition or removal of PK time points depending on emerging data on BNT141 can be performed based on SRC recommendation. Samples at various time points post-injection may be added based on emerging data from this trial. If the PK data are uninformative, one or more time points may be removed.
- Addition or removal of safety time points depending on emerging data on BNT141 can be performed based on SRC recommendation.
- Time points for measurement of correlative and PD assays may be added or reduced at the sponsor's discretion.
- For further understanding of the safety, tolerability and PK of BNT141, up to 6 additional patients may be enrolled at preceding dose levels or to intermediate dose levels in Parts 1A and 1B, while proceeding with further dose escalation or even thereafter. However, the data collected will not influence the determination of MTD in the leading dose escalation part of the trial.
- Intermediate dose levels or an alternative dosing schedule can be implemented based on SRC recommendation.
- Based on careful evaluation of PK and PD data, PK/PD modeling and after endorsement by the SRC committee, an alternative dosing schedule of BNT141 may be investigated, [redacted]

4.1.9 Planned number of patients

The sample size for trial Part 1A and Part 1B is driven by the classical 3+3 trial design and will range from three to six DLT-evaluable patients per cohort depending on the occurrence of DLTs. In both trial Parts 1A and 1B, the sample size will be up to 48 DLT-

evaluable patients in each part depending on the DLTs, which may occur. Once the MTD is reached, up to 10 additional patients with CLDN18.2 expressing pancreatic and biliary tract cancers will be enrolled at the MTD level in Parts 1A and up to 10 additional patients with CLDN18.2 expressing pancreatic adenocarcinoma and cholangiocarcinoma in Part 1B respectively, to obtain additional data on safety, PK and PD. Non-DLT-evaluable patients will be replaced. The sample size and design in Part 2 will be further determined after careful evaluation of all available safety, PK and PD, and efficacy data generated in Parts 1A and 1B by the SRC and will be further defined via an amendment.

4.2 Scientific rationale for the trial design

Part 1A of this trial is an FIH, open-label, dose escalation trial of BNT141 monotherapy in patients with different types of CLDN18.2-positive solid malignant tumors in order to determine the safety, PK and preliminary efficacy of BNT141. Part 1B aims to determine the safety profile, PK and preliminary efficacy of BNT141 in combination with nab-paclitaxel and gemcitabine. The trial continues with the expansion phase (Part 2) to explore further BNT141 in combination with nab-paclitaxel and gemcitabine in selected tumor indications. Different treatment schedules may also be explored in Part 2.

4.2.1 Trial design rationale for Part 1A: Monotherapy dose escalation

In the monotherapy dose escalation Part 1A, a PGDE approach will be taken into consideration for guiding the dose range of BNT141 where anti-tumor activity is expected, and the timing of Part 1B initiation. CCI

Based on extrapolation from these data the target PK parameter to inform further dose escalation for Part 1A is C_{trough} and is set to CCI (see Section 4.3).

CCI The target C_{trough} of CCI should be high enough to trigger CCI in all patients throughout the 21-day dosing cycle, considering patient variability, while limiting potential toxicity with the higher dose that may be related to the LNP-formulated RNA drug product.

CCI

CCI

Furthermore, the PGDE method is appropriate because:

- Real-time PK results will be obtained, which are required to determine the safety of the subsequent dose escalation.

- CCI
- Since the structure of the expressed RiboMabCCI is based on an CCI antibody, its metabolism is similar to that of endogenous CCI molecules.

The approach is also in line with the EMA Guideline on strategies to identify and mitigate risks for FIH and early clinical trials with investigational medicinal products.

4.2.2 Trial design rationale for bifurcated design

The development rationale for combination therapy is to leverage many different pathways to target both safe and effective tumor cell death. This is to be achieved by combining BNT141 with an already efficient but not durable cytotoxic treatment. Therefore, rapid triggering of combination testing is desired where BNT141 upon target binding mediates cell killing by ADCC and CDC. One of the common approaches to assess the effect of combining an IMP with another drug early on in clinical development, is to use a bifurcated design, which is used in Part 1 of this trial.

This approach will allow for rapid and safe combination dose escalation for timely optimization of the combination schedule that will be taken into the Part 2 part of the trial. At the same time, patient safety is safeguarded by generating enough monotherapy data before bifurcation. In addition, clear rules for parallel dose escalations are outlined.

4.2.3 Trial design rationale for Part 2: Expansion Phase

The trial design in the expansion cohorts will be either a Simon two-stage design or a Khan one-stage design.

The Simon two-stage design is often used for Phase II cancer clinical trials. A trial proceeds to the second stage unless the null hypothesis, that the true tumor response rate is below some specified value, is already accepted at the end of stage one. This limits exposing more patients to a compound without sufficient anti-tumor activity.

The one-stage design (per Khan et al. 2012) is used to examine several sample sizes for the same treatment effect and choose one that is the smallest. This would be especially useful for trials of novel agents (where little is known about the treatment) or for rare disorders, where it is appropriate to minimize the sample size.

4.3 Justification for dose

The proposed starting dose for the FIH trial of BNT141 is 0.15 mg/kg every 3 weeks. This is based on a comprehensive evaluation of the toxicology program in mice and NHP supporting 1.5 mg/kg once weekly as a safe dose, a safety margin of 10 to account for unexpected toxicities, and the utilization of a less frequent dosing regimen of BNT141 in the clinic (every 3 weeks as compared to the once weekly schedule utilized in the toxicology studies), which is anticipated to provide benefit based on the pharmacokinetic properties of the intact translated protein RiboMabCCI. For further details on dose justification, please refer to Section 4.1.4.

4.4 End of trial definition

The trial is considered completed when all patients:

- have had at least 12 months survival follow up OR
- are lost to follow up OR
- have withdrawn consent OR
- have died

OR the sponsor discontinues the trial.

However, the maximum trial duration is 3 years after the last subject's first treatment in the trial.

A patient is considered to have completed the trial if they have discontinued BNT141 treatment and have completed safety follow up (Day 60).

5 TRIAL POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Each patient who meets all of the following criteria is eligible to enroll in the trial.

5.1.1 Disease-specific inclusion criteria

For all parts

1. Metastatic or unresectable solid tumor.
2. Histological or cytological documentation of a solid tumor via a pathology report.
3. CLDN18.2-positive tumor sample defined as moderate-to-strong CLDN18.2 protein expression defined as intermediate (2+) to strong (3+) staining intensity in ≥ 50% of tumor cells as assessed by central testing using a CLIA-validated immunohistochemistry assay in FFPE neoplastic tissues. New biopsies and archival bio-samples are allowed. Bone biopsies are not allowed. Cytology specimens (including fine needle aspirates) will not be accepted for CLDN18.2 examination. If archival tissue samples from several points of time are available, the most recent one is preferred. Patients with a lower expression level or with CLDN18.2-negative cancers are not eligible.
4. **Trial part-specific inclusion criteria:**
   - **For Part 1A:** Patients with unresectable or metastatic histologically or cytologically confirmed solid tumors for which there is no available standard therapy to confer clinical benefit, or the patient is not a candidate for such available therapy. Patients must have received all available standard therapies and failed at least first-line SOC therapy prior to enrolment. Measurable or evaluable disease per RECIST 1.1. Eligible tumor types are gastric cancer, gastroesophageal junction (GEJ) and

esophageal adenocarcinoma, pancreatic, biliary tract (cholangiocarcinoma and gallbladder cancer), and mucinous ovarian cancers. Additionally, patients with specific tumors (including colorectal cancer, non-small-cell lung cancer, gastric subtype of endocervical adenocarcinoma) where there is scientific evidence that the CLDN18.2 could be elevated can be tested for CLDN18.2 expression.

- **For Part 1B:** Patients with histologically confirmed advanced unresectable or metastatic pancreatic adenocarcinoma or cholangiocarcinoma who are eligible for treatment with nab-paclitaxel and gemcitabine. Measurable or evaluable disease per RECIST 1.1.
- **For Part 2**:
  - **Cohort 1 –** [redacted] eligible for treatment with nab-paclitaxel and gemcitabine. Measurable disease per RECIST 1.1.
  - **Cohort 2 –** [redacted] eligible for treatment with nab-paclitaxel and gemcitabine. Measurable disease per RECIST 1.1.

5.1.2 Other inclusion criteria

For all parts

5. Signed an ICF prior to any trial-related assessments or procedures indicating that he or she understands the purpose of and procedures required for the trial and is willing to participate in the trial.
6. ECOG PS of 0 to 2.
7. Life expectancy of at least 3 months.
8. ≥ 18 years of age.
9. Adequate coagulation function at screening as determined by:
   - International normalized ratio (INR) or prothrombin time ≤ 1.5 x upper limit normal (ULN; unless on therapeutic anticoagulants with values within therapeutic window).
   - Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN (unless on therapeutic anticoagulants with values within therapeutic window).
10. Adequate hematologic function at screening as determined by:
    - White blood count (WBC) ≥ 3 × 10^9/L.
    - Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L (patient may not use granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor to achieve these WBC and ANC levels in the past 7 d).
    - Platelet count ≥ 100 × 10^9/L.
    - Hemoglobin ≥ 8.5 g/dL (may not transfuse or use erythropoietin to obtain this level in the past 7 d).

11. Adequate hepatic function at screening as determined by:
    - Total bilirubin ≤ 1.5 mg/dL (or ≤ 3.0 mg/dL for patients with known Gilbert's syndrome or liver metastasis).
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN; ≤ 3 ULN for patients with liver metastasis.
    - Albumin ≥ 25 g/L
12. Adequate renal function at screening as determined by:
    - Glomerular filtration rate ≥ 30 mL/min/1.73 m² – according to the abbreviated Modification of Diet in Renal Disease equation:

      Glomerular filtration rate (GFR) = $186 \times (S_{creatinin}^{-1.154}) \times (age^{-0.203})$

    (where the serum creatinine level is expressed in mg/dL; multiply it by 0.742 if the patient is female; multiply it by 1.212, if the patient is African-American [Levey et al. 1999]).
13. Able to attend trial visits as required by the protocol.
14. Women of childbearing potential (WOCBP) must have a negative serum (beta-human chorionic gonadotropin) at screening. For a definition of WOCBP, see Section 10.4.
15. Unless practicing true sexual abstinence, WOCBP must agree to practice one highly effective form of contraception during the trial and for 6 months after receiving the last dose of BNT141. WOCBP will also be recommended to use one acceptable method of contraception in addition. For definitions of highly effective and acceptable methods of contraception, see Section 10.4.2.
16. WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the entire trial, until 6 months after the last BNT141 treatment.
17. Men who are sexually active with WOCBP and who have not had a vasectomy must agree to use a barrier method of birth control, during the trial and for 6 months after receiving the last dose of BNT141 (see Section 10.4.2 for information on effective contraceptive methods).
18. Men must agree to not donate sperm during the trial and for 6 months after receiving the last dose of BNT141.

5.2 Exclusion criteria

A patient who meets any of the following criteria will be excluded from trial participation.

Prior and concomitant therapy

1. Receiving: radiotherapy, chemotherapy, or molecularly-targeted agents within 3 weeks or 5 half-lives (whichever is longer) of the start of trial treatment; immunotherapy/monoclonal antibodies within 3 weeks of the start of trial treatment (excluding BNT141); nitrosoureas, antibody-drug conjugates, or radioactive isotopes within 6 weeks of the start of trial treatment. Palliative radiotherapy will be allowed.
2. Receives concurrent systemic (oral or IV) steroid therapy > 10 mg prednisone daily or its equivalent for an underlying condition. Replacement therapy (e.g., thyroxine, insulin,

or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is permitted.

3. Major surgery within the 4 weeks before the first dose of BNT141.
4. Prior treatment with a CLDN18.2 targeting mAb other than BNT141.
5. Ongoing or active infection requiring IV treatment with anti-infective therapy that has been administered less than 2 weeks prior to the first dose of BNT141, including serious COVID-19 infection.
6. Side effects of any prior therapy or procedures for any medical condition not recovered to NCI-CTCAE v.5 Grade ≤ 1, with the exception of anorexia, fatigue, hyperthyroidism, hypothyroidism, and peripheral neuropathy, which must have recovered to ≤ Grade 2. Alopecia of any grade is allowed.
7. Received any live vaccine within 30 days prior to the start of trial treatment.

Medical conditions

8. Current evidence of new or growing brain or leptomeningeal metastases during screening. Patients with known brain or leptomeningeal metastases may be eligible if they have:
    - Radiotherapy, surgery or stereotactic surgery for the brain or leptomeningeal metastases.
    - No neurological symptoms (excluding Grade ≤ 2 neuropathy).
    - Stable brain or leptomeningeal disease on the computer tomography (CT) or MRI scan within 4 weeks before signing the informed consent.
    - Not undergoing acute corticosteroid therapy or steroid taper.

Notes: Patients with central nervous system symptoms should undergo a CT scan or MRI of the brain to exclude new or progressive brain metastases. Spinal bone metastases are allowed, unless imminent fracture with cord compression is anticipated.

9. History of seizures other than isolated febrile seizure during childhood; has a history of a cerebrovascular accident or transient ischemic attack less than 6 months before Screening.
10. Active immunologic disorder requiring immunosuppression with steroids or other immunosuppressive agents (e.g., azathioprine, cyclosporine A).
11. Known history of seropositivity for human immunodeficiency virus with $CD4^+$ T-cell counts < 350 cells/µL and with a history of acquired immunodeficiency syndrome-defining opportunistic infections.
12. Known history/positive serology for hepatitis B requiring active antiviral therapy (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy). Patients with positive serology must have hepatitis B viral load below the limit of quantification.
13. Active hepatitis C virus (HCV) infection; patients who have completed curative antiviral treatment with HCV load below the limit of quantification are allowed.
14. Known hypersensitivity to a component of any trial treatment.

15. Another primary malignancy that has not been in remission for at least 2 years, with the exception of those with a negligible risk of metastasis or death (such as adequately treated carcinoma *in situ* of the cervix, basal or squamous cell skin cancer, localized prostate cancer, or ductal carcinoma *in situ*).

Other comorbidities

16. Abnormal electrocardiograms that are clinically significant, such as Fridericia-corrected QT prolongation > 480 ms.
17. In the opinion of the treating investigator, has any concurrent conditions that could pose an undue medical hazard or interfere with the interpretation of the trial results; these conditions include, but are not limited to:
    - Ongoing or active infection requiring antibiotic/antiviral/antifungal therapy.
    - Concurrent congestive heart failure (New York Heart Association Functional Classification Class III or IV).
    - Concurrent unstable angina.
    - Concurrent cardiac arrhythmia requiring treatment (excluding asymptomatic atrial fibrillation).
    - Acute coronary syndrome within the previous 6 months.
    - Arterial thromboembolic event within the previous 6 months.
    - Significant pulmonary disease (shortness of breath at rest or on mild exertion) for example due concurrent severe obstructive pulmonary disease.
18. Cognitive, psychological or psychosocial impediment that would impair the ability of the patient to receive therapy according to the protocol or adversely affect the ability of the patient to comply with the informed consent process and compliance with the protocol-required visits and procedures.
19. Pregnant or breastfeeding.
20. Concurrent enrolment in another clinical trial, unless it is a non-interventional clinical study.

5.3 Lifestyle considerations

Patients should avoid using drugs of abuse throughout their time of enrolment in the trial unless such drugs are specifically prescribed (e.g., morphine).

5.3.1 Meals and dietary restrictions

There are no meals or dietary restrictions.

5.3.2 Caffeine, alcohol, and tobacco

Patients should refrain from alcohol for a minimum of 24 h prior to each visit. Patients should be able to refrain from tobacco during the in-house period.

5.3.3 Activity restrictions

Patients should refrain from vigorous exercise for 24 h prior to blood chemistry testing.

5.4 Screen failures

Pre-screening failures are patients who consent to have their tumor tissue tested for CLDN18.2-positivity, but do not show the desired expression level of CLDN18.2 antigen per protocol. They will not proceed further to the screening phase as they are not eligible for the trial. Pre-screening failures may be rescreened once, in cases where the tumor CLDN18.2-positivity could not be assessed. Patients must re-sign the pre-screening ICF prior to repeated pre-screening in case an additional biopsy is needed.

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently entered in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Screen failures may be rescreened. Patients who fail their first screening for trial eligibility may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the ICF prior to any re-screening. Rescreened patients will be assigned a new patient number.

6 TRIAL TREATMENTS

Trial treatment is defined as any investigational treatments intended to be administered to a trial patient according to the trial protocol.

6.1 Trial treatments administered

6.1.1 Investigational medicinal product

The IMP in all parts of the trial is BNT141. The IMP is [redacted] for IV administration. Each vial is intended for single use. Detailed information will be given in the Pharmacy Manual.

In Part 1A, BNT141 will be administered IV as monotherapy [redacted] of each 3-week treatment cycle (21 d/Q3W) after all required procedures and assessments before administration have been completed. Trial visits will be performed weekly for the first 4 cycles (Days 1, 8, 15). After the first 4 cycles, trial visits will be performed at Day 1 of each subsequent cycle.

Patients will be administered BNT141 in Part 1A according to dose levels outlined in Table 8. [redacted].

When given in combination with nab-paclitaxel and gemcitabine in Part 1B, BNT141 will be administered as an IV infusion [redacted] for the first two dose levels (0.15 and 0.3 mg/kg) and at a minimum of [redacted] before the first infusion of

cytotoxic therapy. The SRC should decide about the minimal infusion time / maximal infusion speed for further cohorts after careful analysis of collected safety data. BNT141 will be further administered every three weeks and chemotherapy will follow the approved schedule according to local guidelines. Each cycle in Part 1B will be 28 d. Based on Part 1B PK, PD, PK/PD modeling and clinical data, [redacted] The days of administration of BNT141 and nab-paclitaxel and gemcitabine are shown in Table 9.

Table 9: Days of administration of BNT141 and nab-paclitaxel and gemcitabine in Part 1B

[redacted]

For each dose of BNT141, patients will be monitored for at least 4 h post administration. An overnight stay at the trial site [redacted] due to the extensive PK sampling for all patients is recommended, but optional and depends on patient preference (e.g., with regard to travel times to the site), overall health status and foremost decision of the investigator based on any safety concerns. Trial visits will be performed weekly for the first 4 cycles (Days 1, 8, 15, 22). After the first 4 cycles, trial visits will be performed at the days where BNT141 and/or nab-paclitaxel and gemcitabine are administered.

Pre- and post-medications with antipyretics (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs), anti-emetics, histamine type 2 (H2) receptor antagonists or proton-pump inhibitors and anxiolytics per institutional guidelines are allowed. If necessary, patients should be properly pre-hydrated before BNT141 treatment. Corticosteroids should not be used as premedication for BNT141 with the exception of patients who have experienced prior administration related Grade 2 or Grade 3 reactions in the trial. Premedication to prevent IRR in subsequent administrations may be administered at the investigator's discretion according to local guidelines and if considered necessary, patients should receive corticosteroids at a suggested maximum dose of 100 mg prednisone or equivalent.

Further details on the administration of BNT141 in additional cohorts in Part 2 will be provided in a protocol amendment after careful evaluation of all available safety, PK and PD, and efficacy data generated in Parts 1A and 1B by the SRC.

6.1.2 Non-investigational medicinal product

6.1.2.1 Gemcitabine

The recommended dose of gemcitabine for treatment of pancreatic cancer and cholangiocarcinoma is [redacted] over 30 min IV infusion on [redacted] of each 28-day cycle ([redacted]).

Please refer to the US Prescribing Information (USPI) or Summary of Product Characteristics (SmPC) for further information on gemcitabine, including dose modification options.

6.1.2.2 Nab-paclitaxel

The recommended dose of nab-paclitaxel for treatment of pancreatic cancer and cholangiocarcinoma is [redacted] administered as an IV infusion over 30 to 40 min on [redacted] of each 28-day cycle. Gemcitabine should be administered immediately after nab-paclitaxel [redacted] of each 28-day cycle ([redacted]).

Please refer to the USPI or SmPC for further information on nab-paclitaxel, including dose modification options.

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all trial intervention received and any discrepancies are reported and resolved before use of the trial intervention.

Only patients enrolled in the trial may receive trial treatment and only authorized site staff may supply or administer trial intervention. All trial intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, site, or the head of the site (where applicable) is responsible for trial treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused trial treatment are provided in the Pharmacy Manual and/or Clinical Trial Supply Manual.

6.3 Measures to minimize bias: randomization and blinding

This is an open-label, non-randomized trial.

6.4 Trial treatment compliance

Patients will receive trial treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered must be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose

of trial intervention and trial patient identification will be confirmed at the time of dosing by a member of the trial site staff other than the person administering the trial intervention.

6.5 Concomitant therapy

Prior treatments are any medications and non-drug therapies used by the patient up to 21 d before trial treatment initiation [redacted]. All prior anti-cancer treatments need to be collected and documented in the eCRF. Concomitant medications and therapies are any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, or nutritional supplements) used by a patient in addition to protocol-mandated treatment (including prophylactic treatment after BNT141 administration and medications as a result of an AE). Prior/Concomitant medications and non-drug therapies include all anti-cancer pre-treatments and all previous and on-trial COVID-19 vaccinations. All such medications should be reported to the investigator and recorded on the Prior/Concomitant Medications eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

6.5.1 Permitted concomitant medications and therapies

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “prohibited” (Section 6.5.2). Administration of concomitant medications must be reported in the appropriate section of the eCRF.

- Palliative radiotherapy during the trial will be allowed for local pain control provided that each of the following is satisfied:
  - In the opinion of the investigator, the patient does not have progressive disease
  - No more than 10% of the patient’s bone marrow is irradiated
  - The radiation field does not encompass a target lesion
- Granulocyte colony stimulating factor and other hematopoietic growth factors may be used in the management of acute toxicity (such as febrile neutropenia) or prophylactically, when clinically indicated at the investigator’s discretion.
- Blood cell transfusion is allowed if clinically indicated.
- Systemic (oral or IV) steroid therapy ≤ 10 mg prednisone daily or its equivalent for an underlying condition (refer to Section 6.5.2).
- Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency).
- Bisphosphonates (e.g., pamidronate, zoledronic acid, etc.) and denosumab.
- Paracetamol/acetaminophen, or acetylsalicylic acid/aspirin, at doses of less than 2 g/day, is permitted for use at any time during the trial.

- Multivitamins, vitamin D, calcium and supplements in prevention of weight loss.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

See Appendix 1 and Appendix 2 for recommendations on COVID-19 vaccination during trial participation.

6.5.2 Prohibited concomitant therapy

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications and substances are prohibited during the trial:

- Any other investigational therapy.
- Antineoplastic systemic chemotherapy or biological therapy.
- Steroid treatment for any other purpose than to manage emergency situations (according to institutional standards), to modulate symptoms of an IRR, or chronic systemic immunosuppressive corticosteroid doses (i.e., prednisone > 10 mg daily).
- No dietary supplements are allowed during the trial period (except for multivitamins, vitamin D, calcium, and supplements in prevention of weight loss). The use of traditional/herbal medicines is not permitted.

If a patient receives any of these during the trial, the sponsor must be notified for evaluation of whether the patient can continue treatment or not.

6.5.3 Premedication

Pre- and post-medications should be given to mitigate potential reactions to BNT141 or the translated antibody per institutional guidelines and recommendation of the SRC. Medications for consideration for pre- and post-medication:

1. Hydration: 500 mL normal saline IV over 1 hour
2. H1 + H2 antihistamine:
   - IV: Diphenhydramine (Benadryl®) 50 mg + Famotidine 20 mg over 20 min OR
     cetirizine (Quzyttir®) 10 mg + ranitidine 50 mg OR
   - Oral: cetirizine 10 mg + ranitidine 75 mg (3 days, starting 1 day before D1)
3. Antipyretic oral:
   - 2-3 x 1 paracetamol (Tylenol®) 650 mg (max 2 g/day) every 4-6 hours OR
   - Paracetamol 650 mg before the infusion AND 4 hours later
   - Optional 650 mg paracetamol + 300 mg aspirin if temperature > 99.5°F (37.5°C)
4. Antiemetic: as needed
   - IV: palosonetron (Alexi®) 0.25 mg OR

- Oral: ondansetron 8 mg after study drug administration, repeated as needed

5. Proton-pump inhibitor: as needed
   - Omeprazole 20 mg

Corticosteroids should not be used as premedication for BNT141 with the exception of patients who have experienced prior administration related Grade 2 or Grade 3 reactions in the trial. If considered necessary, patients should receive corticosteroids at a suggested maximum dose of 100 mg prednisone or equivalent.

6.6 Dose modifications and safety management guidelines

6.6.1 Dose-limiting toxicity

Serious AEs, non-serious Grade ≥ 3 non-hematological and hematological AEs as defined per DLT criteria and clinically significant abnormal laboratory values Grade ≥ 3 will be collected and considered a DLT if assessed by the investigator to be **at least possibly related** to BNT141 for the Part 1A of the trial, and **at least possibly related** to the combination of BNT141 and nab-paclitaxel and gemcitabine for the Part 1B of the trial. Toxicities clearly not related to BNT141 (e.g., PD, comorbidity, etc.) will not be considered a DLT. The NCI-CTCAE v.5.0 will be used to grade the intensity of Aes.

The DLT period for the BNT141 monotherapy dose escalation in Part 1A will be 21 d. The DLT period for the dose escalation of BNT141 in combination with nab-paclitaxel and gemcitabine will be 28 d.

DLT criteria are defined below:

Hematological

- Grade 4 neutropenia (i.e., ANC < 0.5 × 10^9 cells/L) lasting more than 7 d.
- Any grade febrile neutropenia (i.e., ANC < 1.0 × 10^9 cells/L with a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour).
- Grade 4 thrombocytopenia (≤ 25.0 × 10^9 platelets/L).
- Grade 3 thrombocytopenia with bleeding or requiring platelet transfusion.
- Grade 4 anemia.
- Grade ≥ 3 hematological toxicity lasting more than 7 d.

Exception:

- Grade 3 lymphocytopenia lasting more than 7 d that has no clinical consequence.

Non-hematological

- Any Grade 3 cytokine release syndrome (CRS), as per the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus grading for CRS (Lee et al. 2019), that does not improve to Grade 2 or below within 72 h despite medical management.

- Any Grade 4 CRS.
- Any Grade ≥ 3 non-hematological AE, which occurs during the first BNT141 treatment cycle, excluding:
  - Grade 3 fever (> 40.0°C) for ≤ 24 h.
  - Grade 3 IRRs.
  - Non-hematological laboratory abnormalities that have no clinical consequence and resolve to Grade ≤ 2 within 3 d (this also includes electrolyte abnormalities that respond to medical intervention) (note that if a Grade ≥ 3 non-hematological laboratory abnormality occurs, then a local laboratory assessment should be obtained within 3 d of the occurrence).
  - Grade 3 fatigue when fatigue was present at baseline or that lasts for < 7 d after the last administration of BNT141.
  - Grade 3 anorexia when Grade 2 anorexia was present at baseline or that lasts for < 1 d after the last administration of BNT141.
  - Grade 3 nausea, vomiting or diarrhea that lasts < 48 h, and resolves to Grade ≤ 1 either spontaneously or with conventional medical intervention.

DLT criteria for liver enzyme elevations (transaminases and bilirubin elevations)

Evaluation as to whether the elevation qualifies as a DLT is based on the individual patient's baseline levels as shown in Table 10. Any Grade ≥ 3 liver enzyme elevations (transaminases and bilirubin elevations), at least possibly related to BNT141 and lasting ≥ 7 days, will be considered a DLT.

Table 10: Criteria for liver enzyme elevations

Transaminases at baseline	Bilirubin at baseline	Transaminases on treatment	Bilirubin on treatment	
≤ ULN	≤ ULN	> 5 × ULN	or	> 3 × ULN
> ULN	> ULN	> 5 × Baseline	or	> 3 × Baseline

ULN = upper limit of normal.

In addition, other clinically significant toxicities, including a single event or multiple occurrences of the same event, may be considered as DLTs. AEs occurring after treatment Cycle 1 may be considered DLTs following discussions between the investigators and the sponsor's Medical Monitor.

Dose escalation:

Patients experiencing a DLT (an AE fulfilling the DLT criteria within the DLT period of 21 d) should discontinue trial drug. If requested by the investigator, the sponsor may, after a thorough benefit-risk assessment of the individual patient and endorsement by the SRC, allow a patient with a DLT (apart from anaphylaxis or Grade 4 IRR) to continue in the trial at a reduced dose if the DLT has resolved to Grade ≤ 1.

6.6.2 Dose modification guidance/rules

BNT141

AEs that fulfill the DLT criteria after the DLT period has ended in the dose escalation part of the trial (i.e., from Cycle 2 Day 1 and beyond) or during the expansion (i.e., from Cycle 1 Day 1 and beyond) should be handled as shown in the Figure 7.

First occurrence of AE fulfilling DLT criteria Grade ≥ 3:

- As a first measure, administration of BNT141 needs to be held.
- Investigator must contact the sponsor to discuss whether the patient should be withdrawn from BNT141 treatment or if the next dose should be delayed.

CCI [redacted]

Second occurrence of an identical AE Grade ≥ 3 after re-exposure to BNT141:

- As a first measure, administration of BNT141 needs to be held.

CCI [redacted]

- Re-treatment may be considered on a case-by-case basis after review by the SRC. Intermediate dose levels defined in the protocol may be considered.

Third occurrence of an identical AE Grade ≥ 2 after re-exposure to BNT141:

- As a first measure, administration of BNT141 needs to be held.

[redacted]

Please note:

[redacted]

- BNT141 must be permanently discontinued if the patient experiences an AE fulfilling the DLT criteria (after the DLT period has ended for the dose escalation or during the expansion) that fails to resolve to Grade ≤ 1 within 21 d after the planned dosing date unless otherwise approved by the sponsor Medical Monitor.
[redacted]
- BNT141 must be permanently discontinued in case of a dose delay of more than 21 d due to toxicity possibly related to BNT141 unless otherwise approved by the sponsor Medical Monitor.

The investigators are encouraged to contact sponsor in case of any safety concern that needs thorough discussion and evaluation.

For AEs occurring in Part 1B and Part 2 (BNT141 in combination with nab-paclitaxel and gemcitabine) which are considered clearly related to the chemotherapy regimen and require delay or discontinuation of the chemotherapy regimen, continuation of BNT141 administration as monotherapy is permitted at the same dose level after the AE has resolved to Grade ≤ 1 or baseline.

Nab-paclitaxel and gemcitabine

Nab-paclitaxel and gemcitabine should be dose modified as per the USPI or the SmPC.

Recommended dosage modifications for gemcitabine for myelosuppression are described in Table 11.

Table 11: Recommended dosage modifications for gemcitabine for myelosuppression

Absolute neutrophil count (x 10^6/L)	Platelet count (x 10^6/L)		Dosage modification
Greater than or equal to 1000	And	Greater than or equal to 100,000	None
500 to 999	Or	50,000 to 99,999	75% of full dose
Less than 500	Or	Less than 50,000	Hold

Permanently discontinue gemcitabine for any of the following:

- Unexplained dyspnea or evidence of severe pulmonary toxicity
- Hemolytic uremic syndrome or severe renal impairment
- Severe hepatic toxicity
- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

Withhold gemcitabine or reduce dose by 50% for other Grade 3 or 4 non-hematological adverse reactions until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

Dose level reductions of nab-paclitaxel in combination with gemcitabine are provided in Table 12.

Table 12: Dose level reductions of nab-paclitaxel in combination with gemcitabine

Dose level	Nab-paclitaxel ([redacted])	Gemcitabine ([redacted])
Full dose	[redacted]	[redacted]
1st dose reduction	[redacted]	[redacted]
2nd dose reduction	[redacted]	[redacted]
If additional dose reduction required	Discontinue	Discontinue

Recommended dose modifications of nab-paclitaxel in combination with gemcitabine for neutropenia and thrombocytopenia are provided in Table 13.

Table 13: Recommended dose modifications of nab-paclitaxel in combination with gemcitabine for neutropenia and thrombocytopenia

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	Nab-paclitaxel/Gemcitabine
[redacted]	< 1500	OR	< 100,000	Delay doses until recovery
[redacted]	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
[redacted]				
500 to < 1000	OR		50,000 to < 75,000	Reduce 1 dose level from [redacted]

Cycle Day	ANC (cells/mm^3)	Platelet count (cells/mm^3)	Nab-paclitaxel/Gemcitabine
< 500	OR	< 50,000	Withhold doses
[redacted]	CCI		
≥ 1000	OR	≥ 75,000	Reduce 1 dose level from CCI
500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from CCI
< 500	OR	< 50,000	Withhold doses

ANC = absolute neutrophil count.

Recommended dose modifications of nab-paclitaxel in combination with gemcitabine for other adverse drug reactions in patients are provided in Table 14.

Table 14: Recommended dose modifications of nab-paclitaxel in combination with gemcitabine for other adverse drug reactions

Adverse drug reaction	Nab-paclitaxel	Gemcitabine
Febrile neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

ANC = absolute neutrophil count.

6.6.3 Mitigation plans for specific AEs

6.6.3.1 Injection/infusion-related reactions

IRRs are a general risk to be considered for any new compound administered IV irrelevant of its mechanism of action. An IRR is typically of immediate onset during or after the compound's administration. The risk of IRR cannot be excluded due to the given limited experience with BNT141.

All patients should be pre-medicated. Premedication to prevent IRR may be administered at the investigator's discretion according to local guidelines and recommendation of the SRC, see Section 6.5.3.

The following treatment guidelines are provided below for patients who experience an IRR associated with administration of BNT141 treatment (Table 15).

Table 15: Treatment guidelines for patients who experience an IRR

	NCI-CTCAE (v5.0)	Recommendation	Next administration
Grade 1	Mild transient reaction; infusion interruption not indicated; intervention not indicated	The administration does not need to be interrupted and can be continued at the investigator's discretion at half the infusion rate under close medical supervision.	To be performed per protocol.
Grade 2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	The administration should be interrupted and appropriate medical management instituted. The administration may be re-started at the investigator's discretion at half the administration rate under close medical supervision if symptoms have resolved within an hour.	To be performed per protocol.
Grade 3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	The administration should be stopped and appropriate medical management instituted.	If considered necessary, patients could receive corticosteroids at a suggested maximum dose of 100 mg prednisone or equivalent.
Grade 4	Life-threatening consequences; urgent intervention indicated	If anaphylaxis or a Grade 4 IRR occurs, administration of BNT141 should be discontinued immediately and permanently, and appropriate medical therapy should be administered.	Next administration of BNT141 is not allowed.

Source: National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
IRR = infusion-related reactions; NCI = national cancer institute; IV = intravenous; NSAIDs = non-steroidal anti-inflammatory drugs.

Please note:

- At all times during BNT141 administration, medication must be available for immediate emergency treatment of an anaphylactic reaction according to institutional standards. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.
- All premedication must be reported on the Prior/Concomitant Medication eCRF.
- IRR grade ≥ 3 is an AESI (see Section 8.2.8).

6.6.3.2 Cytokine release syndrome

The following guidelines should serve as recommendations to trial physicians to monitor and manage a potential case of CRS. The guidelines should not replace any clinical decisions made by the physicians based on their sound clinical judgment depending on an individual patient's situation. In any given situation, all measures must be taken by the trial physicians to ensure the optimal clinical management is delivered to the patients based on the diagnosis.

For assessment and treatment recommendations for the management of CRS, the following guidelines are adapted based on the ASTCT Consensus Grading for Cytokine Release Syndrome.

The definition of CRS according to the ASTCT consensus is: a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction.

The CRS consensus grading of ASTCT (previously known as American Society for Bone Marrow Transplant) is given in Table 16 (Lee et al. 2019).

If tocilizumab is not available, the following alternative agents could be considered: siltuximab, anakinra, cyclophosphamide, or anti-thymocyte globulin (rabbit).

Table 16: American Society for Transplantation and Cellular Therapy CRS consensus grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever [1]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
with				
Hypotension	None	Not requiring vasopressors	Requiring vasopressor with or without vasopressin	Requiring vasopressors (excluding vasopressin)
and/or [2]				
Hypoxia	None	Requiring low-flow nasal cannula [3] or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

1 Fever is defined as temperature ≥ 38°C not attributable to any other cause. If patients who have CRS then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

2 CRS grade is determined by the more severe event: Hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring one vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

3 Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/min. Low-flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min.

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = common terminology criteria for adverse events.

Organ toxicities associated with CRS may be graded according to NCI-CTCAE v5.0 but they do not influence CRS grading.

For the management of CRS, the guidelines in Table 17 should apply:

Table 17: Guidelines for management of CRS

ASTCT CRS Grade	Management
Grade 1	• Antipyretics and IV hydration • Diagnostic work-up to rule out infection • Consider growth factors and antibiotics if neutropenic
Grade 2	• Supportive care as in Grade 1 • IV fluid boluses and/or supplemental oxygen • Tocilizumab +/- dexamethasone or its equivalent of methylprednisolone
Grade 3	• Supportive care as in Grade 1 • Consider monitoring in ICU • Vasopressor support and/or supplemental oxygen • Tocilizumab + dexamethasone 10 to 20 mg IV Q6H or its equivalent of methylprednisolone
Grade 4	• Supportive care as in Grade 1 • Monitoring in ICU • Vasopressor support and/or supplemental oxygen via positive pressure ventilation • Tocilizumab + methylprednisolone 1000 mg/d

ASTCT = American Society for Transplantation and Cellular Therapy (previously known as: ASBMT, American Society for Bone Marrow Transplant); CRS = cytokine release syndrome; ICU = intensive care unit; IV = intravenous; Q6H = every 6 hours.
Source: Neelapu 2019.

6.6.4 Safety stopping criteria

In individual patients, treatment with BNT141 should be discontinued due to safety concerns under the following conditions:

- Patients experiencing a DLT (an AE fulfilling the DLT criteria within the DLT period of 21 d) should discontinue trial drug. If requested by the investigator, the sponsor may, after a thorough benefit-risk assessment of the individual patient and endorsement by the SRC, allow a patient with a DLT (apart from anaphylaxis or Grade 4 IRR) to CCI [redacted].

Treatment with BNT141 must be discontinued due to safety concerns:

- if the patient experiences an AE fulfilling the DLT criteria (after the DLT period has ended for the dose escalation or during the expansion) that fails to resolve to

Grade ≤ 1 within 21 d after the planned dosing date unless otherwise approved by the sponsor Medical Monitor.

- CCI [redacted]
- in case of a dose delay of more than 21 d due to toxicity possibly related to BNT141 unless otherwise approved by the sponsor Medical Monitor.
- second occurrence of an IRR of Grade ≥ 3 despite premedication prior to second administration.
- first occurrence of anaphylaxis or Grade 4 IRR.

Please note: Patients should, whenever possible, irrespective of the reason for discontinuation, be examined as soon as possible after they have withdrawn.

Trial stopping rules

If any of the below-listed events occurs, a prompt cumulative review of safety data will be conducted by the SRC to determine whether the trial will be discontinued permanently.

1. If, at any time, all dose levels are considered unsafe as defined by the SRC.
2. Any safety finding assessed as related to BNT141 that, in the opinion of the SRC, contraindicates further dosing of trial patients.
3. Any death possibly related to the IMP occurring within 30 d of receiving IMP.
4. The occurrence of two Grade ≥ 4 DLTs in two trial participants.
5. At any time during repeat treatment, if more than 33% of trial participants develop AEs meeting DLT criteria, regardless if it is within or outside of the defined DLT evaluation window, the trial cohort shall be paused pending a safety evaluation by the SRC and sponsor.

For each individual patient who has already received BNT141 and is currently in the trial at the time the trial stopping criteria are met, the risk/benefit whether to stop or continue treatment will be assessed. To allow continuation of treatment, SRC consultation will be considered. All patients exposed to BNT141 should continue to be followed by the investigator for safety.

Where applicable, regulatory authorities and independent ethics committees (IECs)/institutional review board (IRBs) will be notified of any significant actions taken with the trial.

6.7 Treatment after the end of the trial

The Investigator together with the sponsor will decide on and ensure post-trial treatment for ongoing trial participants with a potential treatment benefit.

7 DISCONTINUATION OF TRIAL TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of trial treatment

Patients will receive BNT141 treatment until one of the pre-defined discontinuation of treatment criteria has been met:

- Radiographic disease progression per RECIST 1.1 (see Imaging Manual). If the investigator assesses that the patient has clinical benefit from continuation of the trial drug and after discussion with the sponsor, treatment can continue beyond progression provided that the patient is tolerating the trial drug and treatment beyond progression will not delay an imminent intervention to prevent serious complications for PD (e.g., CNS metastases requiring immediate treatment).
- Death.
- Unacceptable AEs requiring BNT141 discontinuation (refer to safety stopping criteria Section 6.6.4).
- Investigator believes that it is in the best interest of the patient to stop BNT141 treatment.
- Withdrawal of consent.
- Pregnancy.
- Lost to follow-up.
- Trial termination by the sponsor.

If trial treatment is definitively discontinued, the patient will remain in the trial to be evaluated for safety and survival follow-up.

Patients who discontinue treatment for reasons other than radiographic disease progression (e.g., toxicity) will continue scheduled tumor assessments at the same frequency as would have been followed if the patient had remained on trial treatment.

Patients should, whenever possible, irrespective of the reason for discontinuation, be examined as soon as possible after withdrawal.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary discontinuation

See section on safety stopping criteria (Section 6.6.4).

7.2 Patient discontinuation/withdrawal from the trial

Patients will be withdrawn from the trial (dose escalation or expansion phases [Part 1A or Part 1B]) for the following reasons:

- A patient may withdraw from the trial at any time at his or her own request

- At the discretion of the investigator for safety, behavioral, compliance or administrative reasons
- Lost to follow-up
- Patient died
- Trial closure

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the trial, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

The sponsor will make any effort to ensure patients are followed up for completion of safety assessment in the trial. Refer to the SoA in Section 1.3 for the data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed.

When a patient withdraws consent, the reason for withdrawal is to be documented in the eCRF and in the source document. The trial drug assigned to the withdrawn patient may not be assigned to another patient.

7.3 Lost to follow-up

A patient will be considered lost to follow-up if they fail to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a patient fails to return to the clinic for a required trial visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the trial.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record. Any knowledge of the patient status (progressive disease, death, etc.) also requires documentation in the patient's files.

8 TRIAL ASSESSMENTS AND PROCEDURES

See the SoA (Section 1.3) for all planned time points for assessments.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue trial treatment.

Adherence to the trial design requirements, including those specified in the SoA, is essential and required for trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the informed consent may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

8.1 Safety assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.1.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded and body surface area calculated using the equation:

  BSA (m^2) = √((height [cm] x weight [kg])/3600).
- A symptom-directed examination will be based upon the symptoms displayed.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Depending on timing (before or after signing the ICF) clinically significant abnormalities observed at screening will be recorded on the general Medical History page or on the AE page of the eCRF. At subsequent visits, examination will be performed and new or worsened clinically significant abnormalities will be recorded in the AE page of the eCRF.

8.1.2 Vital signs

- Temperature, blood pressure (systolic and diastolic), heart rate, oxygen saturation and respiratory rate will be assessed.
- Blood pressure and heart rate will be assessed with the patients in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs assessment should be preceded by at least 5 min of rest for the patient in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be assessed at the following times, in relation to the start of BNT141 dosing:
  - Pre-dose (up to 30 min pre-dose);

  - 15 min (± 5 min);
  - 30 min (± 5 min);
  - 60 min (± 10 min);
  - 90 min (± 10 min);
  - 120 min (± 15 min);
  - If the infusion lasts longer than 120 min then vital signs should be performed every 30 min (± 5 min) until end of infusion; and
  - Vital signs should be monitored closely after IMP infusion until the patient leaves the site.
- Single readings will be performed on all other days.

8.1.3 Electrocardiograms

- Triplicate 12-lead ECGs will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc (according to Frederica) intervals. Patients should be resting in a supine position for at least 10 min prior to ECG recording. Triplicate ECGs should be performed in accordance with institutional guidance, with a time difference between the ECGs of ≥ 2 mins.

8.1.4 Clinical safety laboratory assessments

- See Table 3 and Table 6 for the list, timing and frequency of clinical laboratory tests to be performed. Additional safety laboratory assessments can be performed at any time point when clinically indicated and can include assessments as indicated.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the trial or within 21 d after the last dose of trial intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
  - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the Laboratory Manual and the SoA.

- If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

Routine clinical laboratory safety tests (e.g., blood chemistry, hematology, etc.) will be performed in a local laboratory at the site.

All other tests and blood biomarker panel analyses will be performed by central laboratories.

A Laboratory Manual will be provided to sites which specifies the procedures for collection, processing, storage and shipment of samples, as well as central laboratory contact information, specific to this clinical research trial.

8.2 Adverse events and serious adverse events

AEs will be reported by the patient (or, whenever appropriate by a caregiver, or the patient's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs and SAEs.

8.2.1 Time period and frequency for collecting AE and SAE information

All AEs will be collected from the signing of the trial-specific ICF until the second Safety Follow-up Visit at the time points specified in the SoA (Section 1.3). During pre-screening no AEs/SAEs will be reported, with the exception of AEs/SAEs related to the procedure of collection of a fresh biopsy.

All SAEs (initial and follow-up reports) will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 h after becoming aware of the event, as indicated in Section 10.3.1.10.

Investigators are not obligated to actively seek AE or SAE after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the trial, and he/she considers the event to be reasonably related to the trial treatment or trial participation, the investigator must promptly notify the sponsor.

8.2.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE or SAE occurrences.

8.2.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs, SAEs and DLTs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.1.7.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a patient dies during participation in the trial or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post mortem findings including histopathology if available.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to the sponsor within 24 h of receipt of the information as described in Section 10.3.1.7.

All ongoing AEs/SAEs will be followed until resolution, considered by the investigator to be stable or chronic (resolved with sequelae), the patient is lost to follow-up or the patient withdraws consent, or second safety follow-up is reached. If no final status is reached at second Safety Follow-up Visit, the investigator must confirm the unavailability of a final status.

8.2.4 Regulatory reporting requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a trial treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. The execution of expedited reporting to the different entities may be delegated as detailed in the trial-specific Safety Management Plan.

Safety reports will be prepared for suspected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

For the IMPs, it is the sponsor’s or delegate’s responsibility to perform SUSAR reporting to the regulatory authority, the IRB/IEC and the other investigators as required by national law and applicable guidelines.

All AEs suspected to be related to any NIMP should be sent by the investigator to the national competent authority in the country where it occurred (according to the national

legislation) or to the marketing authorization holder of the NIMP, but not to both to avoid duplicate submissions (ENTR/CT-3, good pharmacovigilance practices [GVP] Module VI EMA/873138/2011 Rev 2).

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor should review it and then file it together with the investigator's brochure. If required by local requirements, the investigator will notify the relevant IRB/IEC.

8.2.5 Pregnancy

Details of all pregnancies in female patients and, female partners of male patients will be collected after the start of trial intervention and until 60 d after the last dose of IMP for pregnant female patients and 28 d for pregnant partners of male patients.

If a pregnancy is reported, the investigator should inform the sponsor within 24 h of learning of the pregnancy and should follow the procedures outlined in Section 10.4.3.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.2.6 Cardiovascular and death events

8.2.6.1 Cardiovascular

Where the cardiovascular event meets one of the conditions outlined in Section 6.6 then the patient should be discontinued from treatment. All clinically significant cardiovascular events should be reported as AEs or SAEs depending on the criteria they meet.

8.2.6.2 Deaths

Any death that occurs within the observation period will be reported as an SAE. Exemptions to the SAE definition as defined in Section 10.3.1.4 do also apply for fatal cases. A copy of an autopsy report should be submitted if available upon request. Date and cause of death will be recorded.

Deaths clearly related to the progression of the disease will not be documented as AEs,

nor reported as SAEs. These deaths must be collected on the death page of the eCRF.

In case of a fatal event, the event term should not be "death" but the underlying event which led to death (death = outcome). If there is more than one AE in a fatal case, only for the AE leading to death the outcome "fatal" should be selected. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be documented as event term.

In addition to reporting as SAE, the death page of the eCRF needs to be completed.

8.2.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

The progression of underlying disease (e.g., new metastases) and symptoms related to disease progression during trial participation is not considered as AE.

Because disease progression is common for patients with cancer, it will not be reported according to the standard process for expedited reporting of an SAE even though the event may meet the definition of a SAE. These events will be recorded on the corresponding eCRF page in the patient's eCRF.

The recorded disease-related events will be monitored by an SRC on a routine basis, for details see Section 9.6.

8.2.8 Adverse events of special interest

- Infusion-related reactions Grade ≥ 3.
- Grade ≥ 3 AST or ALT elevation lasting ≥ 7 days, at least possibly related to BNT141.
- Grade ≥ 3 bilirubin elevation lasting ≥ 7 days, at least possibly related to BNT141.

8.3 Treatment of overdose

For this trial, an overdose is defined as a patients receiving a 15% excess of the intended dose of BNT141 specified in this protocol.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities (at least 21 d).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.4 Pharmacokinetics

Planned time points for PK sampling are provided in the SoA (Section 1.3). The actual date and time (24-h clock time) of each sample should be recorded. Blood samples for PK analysis should be collected, handled, frozen and shipped as outlined in the Laboratory Manual.

- PK samples will be analyzed by a central laboratory. All collection and storage tubes will be provided in laboratory sampling kits.
- Intact RiboMab[redacted] (full-length and fully assembled antibody) PK samples will be collected and analyzed to enable characterization of PK profile.
- Lipid PK samples will be drawn to enable potential further exploratory PK assessments. Refer to Table 2 and Table 5.

8.5 Efficacy assessments

Planned time points for efficacy assessments are provided in the SoA (Section 1.3). There will be no central reading of CT and/or MRI images in this trial. The assessments will be done at site by a qualified radiologist experienced in RECIST 1.1 criteria according to an Imaging Manual where all assessments will be described.

8.5.1 Computer tomography/magnetic resonance imaging scans

- Patients will undergo CT and/or MRI scans in order to provide images which will be assessed by an experienced radiologist applying RECIST 1.1 criteria.
- The MRI scans will be performed using a 3-tesla whole body instrument. The same machine should be used for all scans for an individual patient.
- The CT scans should be performed using the same machine for an individual patient throughout the trial.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and throughout the trial.
- The following criteria will be used when evaluating lesions:
  - Complete response: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
  - Partial response: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
  - Progressive disease: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
  - Stable disease: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on trial.
- Monitoring of the liver and the spleen size will be performed as described in the Imaging Manual.
- Guidelines on the RECIST 1.1 criteria should be followed (Eisenhauer et al. 2009).

8.5.2 Tumor marker CA 19-9

- CA 19-9 measurements will be taken to follow disease, according to the SoA (Section 1.3).

8.5.3 Eastern Cooperative Oncology Group Performance Status

The ECOG PS should be assessed by the investigator or suitably qualified designee using Table 18.

Table 18: Eastern Cooperative Oncology Group Performance Status grading

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

8.5.4 New anti-cancer treatments and survival follow-up

New anti-cancer treatments will be documented, following end of treatment, at the visits outlined in the SoA (Section 1.3). Following the second Safety Follow-up Visit site staff will make contact with the patient every 12 weeks until the patient is lost to follow-up or dies to determine survival status and if they have taken any new anti-cancer treatments. This contact may be by telephone, e-mail or other form of communication but must be documented in the source notes.

8.6 Pharmacodynamics

Planned time points for PD sampling are provided in the SoA (Section 1.3). Exploratory PD markers include cytokines/chemokines, antibody-dependent cellular cytotoxicity (ADCC) from serum as well as complement-dependent cytotoxicity (CDC) from serum. CDC assessments will only be performed depending on total blood volume.

- Blood samples for PD analysis should be collected, handled, frozen and shipped as outlined in the Laboratory Manual.
- PD samples will be analyzed by a central laboratory. All collection and storage tubes will be provided in laboratory sampling kits.

8.7 Genetics

No genetic testing will be performed during the study. However, cancer related somatic genomic alterations and germline status will be collected as cancer related medical history.

8.8 Biomarkers

Planned time points for biomarker sampling are provided in the SoA (Section 1.3).

Biomarker assessments will include (but will not be limited to) blood sampling for cytokine analysis and for exploratory functional assays (see Section 8.6). The list of planned assessments may change, i.e., listed assessments may be deleted or added, depending on the results obtained. The exploratory biomarker data generated will be used in support of the defined clinical trial objectives. The exploratory biomarker data generated used in support of the defined clinical trial objectives will be reported in suitable biomarker reports and reported in accordance with the requirements of applicable regulations and laws. Details on the collection, processing, shipment and storage of samples will be provided in separate documents (e.g., sample handling sheets or lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.

8.8.1 Tumor biomarkers

- Tumor samples should be sent during pre-screening, Cycle 1 Day 1 and during treatment (Section 1.3). Testing of pre-treatment archival or fresh tumor tissue as well as on-treatment tumor biopsy includes but is not limited to CLDN18.2 expression.
- An on-treatment biopsy, preferred on Cycle 2 Day 8 (± 1 d), but can be performed at any time during the study treatment if feasible/without a risk of complications for the patient.
- Fresh tissue samples should be collected according to local procedures under either local or general anesthetic (depending on location), if feasible.
- Some additional tumor tissue (preferably 10 µm thick curls) will be taken from the FFPE block for further exploratory research on CLDN18-ARHGAP fusion for all patients enrolled in the trial. Transcripts of CLDN18-ARHGAP6/26 fusion results in better accessibility of CLDN18.2 molecules for targeted antibody therapies by increasing the aberrant allocation of CLDN18.2 from the tight junction to the cell surface.
- Some additional tumor tissue may be stored with an external vendor for future research, where this is agreed by the patient in the ICF.
- Tumor tissue should be handled according to the Laboratory Manual.

8.9 Immunogenicity assessments

Immunogenicity samples will be collected from all patients. Planned time points for immunogenicity sampling (anti-RiboMab CCI antibodies and anti- CCI lipid antibodies) are provided in the SoA (Section 1.3). Samples will also be collected at the final visit from patients who discontinued trial treatment or were withdrawn from the trial.

An extra sample for further analysis will be taken which can be used either for re-testing or future analysis if required.

All samples that were not analyzed during the trial, will be stored for up to 15 years after the end of the trial and then destroyed.

- Blood samples for immunogenicity analysis should be collected, handled, frozen and shipped as outlined in the Laboratory Manual.
- Immunogenicity samples will be analyzed by a central laboratory. All collection and storage tubes will be provided in laboratory sampling kits.

8.10 Blood lipids

Blood lipids (total cholesterol, LDL, VLDL, HDL, triglycerides and Apolipoprotein E) will be assessed at time points provided in the SoA (Section 1.3).

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

There is no formal statistical hypothesis being tested in this FIH trial.

9.2 Sample size determination

The sample size for trial Part 1A and 1B is driven by the classical 3+3 trial design and will range from 2 to 6 DLT-evaluable patients per cohort depending on the occurrence of DLTs. In both trial Parts 1A and 1B, the sample size will be up to 48 DLT-evaluable patients in each part depending on the DLTs, which may occur. Non-DLT-evaluable patients will be replaced.

Once the MTD is reached, up to 10 additional patients with CLDN18.2 expressing pancreatic and biliary tract cancers will be enrolled at the MTD level in Parts 1A and up to 10 additional patients with CLDN18.2 expressing pancreatic adenocarcinoma and cholangiocarcinoma in Part 1B respectively, to obtain additional data on safety, PK and PD. Based on this sample size the probability to observe a particular AE with incidence of 15% would be 80.3%.

The sample size determination for Part 2 will be provided in a protocol amendment.

9.3 Analysis sets

The analyses sets are defined in Table 19:

Table 19: Analysis set definitions

Analysis set	Description
Screened Set	All patients who signed informed consent form.
Treated Set	All patients who received IMP (i.e., at least one dose of BNT141).
Efficacy Evaluable Set	All patients who are assigned to IMP and have a baseline and at least one on-treatment/post-treatment tumor response assessment. This analysis set may only be used in Part 2 of the trial.
Safety Set	All patients who received IMP (i.e., at least one dose of BNT141).

Analysis set	Description
DLT Evaluation Set	All patients from the Safety Set who either have completed the DLT evaluation period and meet the minimum exposure criterion or have experienced a DLT during the DLT evaluation period (21 d for Part 1A, 28 d for Part 1B). Patients who do not experience any DLT during the DLT observation period are considered to be evaluable if they have been observed for minimum 21 d for Part 1A, 28 d for Part 1B following the first target dose and are considered to have sufficient safety data to conclude that a DLT did not occur. A patient is considered to have met the minimum exposure criterion in Part 1A if the relative dose intensity of BNT141 in Cycle 1 is at least 80%. A patient is considered to have met the minimum exposure criterion in Part 1B if the relative dose intensity of BNT141, nab-paclitaxel, and gemcitabine in Cycle 1 is at least 90%. Patients who are excluded from the DLT Evaluation Set will be replaced. This analysis set may only be used in Part 1 of the trial.
PD Set	All patients with baseline and at least one valid on-treatment/post-treatment PD assessment.
PK Set	All patients with baseline and at least one valid on-treatment/post-treatment PK assessment.

DLT = dose-limiting toxicity; IMP = investigational medicinal product; PD = pharmacodynamics; PK = pharmacokinetics.

The DLT Evaluation Set will be used for the evaluation of DLTs in order to assess the MTD and RP2D. The Safety Set will be used for all other safety analyses. The Treated set and Efficacy Evaluable Set will be used for efficacy analyses.

9.4 Statistical analyses

Statistical analyses will be performed by the BioNTech or a designated contract research organization (CRO). All statistical analyses will be carried out using Statistical Analysis System (SAS)®, Version 9.4 or higher, and/or other statistical software as required.

The Statistical Analysis Plan (SAP) will be finalized prior to database snapshot for the primary analysis and it will include a more technical and detailed description of the statistical analyses described in this section. Any deviations from the planned analyses described in the final SAP will be described and justified in the clinical trial report. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General considerations

In general, data will be analyzed by cohort and/or combined across cohorts as appropriate.

Continuous variables will be summarized by cohort using the following descriptive statistics: number of patients (n), mean, standard deviation, median, minimum and maximum.

Categorical variables will be summarized by cohort presenting absolute and relative frequencies (n and %) of patients in each category.

Time-to-event-endpoints will be analyzed using Kaplan-Meier methodology by cohort and censored in accordance with the FDA Guidance: Clinical Trial Endpoints for the Approval

of Cancer Drugs and Biologics and the EMA Guideline on the evaluation of anti-cancer medicinal products in man. Censoring rules will be defined in the SAP.

The median survival time (including 95% confidence limits according to Brookmeyer and Crowley) and the first and third quartile will be presented. Survival rates (including 95% confidence intervals (CIs) based on Greenwood's formula) as well as the number and percentage of patients with events, censored and under risk will be displayed for selected time points (e.g., at 3, 6, 12 months).

Baseline is defined as last available value prior to first dose of IMP.

9.4.2 Primary endpoints

The primary analyses of primary safety endpoints (i.e., AEs, adverse event of special interest [AESI], SAEs and DLTs) will be performed using the Safety Set (for AEs), and DLT Evaluation Set (for DLTs), respectively, and are described in Section 9.4.5.

9.4.3 Secondary endpoints

PK profile of the intact BNT141-encoded protein RiboMab[redacted]

The analyses of PK parameters will be performed using the PK analysis set. Individual and mean (± standard deviation) serum and plasma concentration data will be tabulated and plotted over time by dose level. The PK parameters will be estimated from the serum concentration data using a non-compartmental analysis method and will include (but are not limited to): C_{max}, t_{max}, $t_{1/2}$, Vd, AUC, and CL, and C_{trough}. These parameters will be listed by individual patient and summarized using descriptive statistics (means, medians, ranges, standard deviations, and coefficient of variation as appropriate) by cohort, as appropriate.

Population PK modeling approaches may be also considered and will be reported separately.

Objective response rate

Objective response rate is defined as the proportion of patients in whom a CR or PR is confirmed as best overall response. Patients not meeting the criteria for CR or PR, including those without any post-baseline tumor assessments, will be considered as non-responders.

Objective response rate will be summarized with absolute and relative frequencies along with 2-sided Clopper-Pearson 95% CIs. For Part 1B, a sensitivity analysis will be performed using the Efficacy Evaluable Set.

Disease control rate

Disease control rate is defined as the proportion of patients in whom a CR or PR or SD (SD assessed at least 6 weeks after first dose) is observed as best overall response.

Disease control rate will be summarized with absolute and relative frequencies along with 2-sided Clopper-Pearson 95% CIs.

Duration of response

Duration of response is defined as the time from first objective response (CR or PR) to first occurrence of objective tumor progression, or death from any cause, whichever occurs first. Only patients in whom a CR or PR is confirmed will be analyzed for DOR.

Duration of response will be analyzed using Kaplan-Meier methodology. Patients alive and without disease progression at data cut-off date or patients lost to follow-up will be censored at the day of their last tumor assessment. Additional censoring rules will be defined in the SAP.

9.4.4 Tertiary/exploratory endpoints

Exploratory endpoints include but not limited to: efficacy endpoints (PFS and OS), potential biomarkers (CLDN18.2 expression level, cytokine concentrations, chemokine concentrations), ADAs (anti-CCI lipid and anti-RiboMabCCI), PK of plasma lipids, and pre-treatment lipid levels (total cholesterol, LDL, VLDL, HDL, triglycerides, Apolipoprotein E).

The presence and concentration of ADAs will be reviewed to evaluate the immunogenicity of BNT141. Number of positive/negative cases by dose level for each cycle will be reported, and the PK parameters between ADA positive and negative patients will be compared. This approach will be applied to both anti-CCI lipid antibodies and anti-RiboMabCCI antibodies.

The analysis for the exploratory endpoints and the potential association with clinical response and/or exposure to trial treatment (measured by BNT141-encoded protein RiboMabCCI level) will be described in the corresponding statistical analysis plan(s).

9.4.5 Safety analyses

Safety data that will be summarized includes AEs, clinical laboratory parameters, vital signs and ECGs. All safety analyses will be based on the Safety Set and will be summarized descriptively by cohort unless otherwise stated.

AEs

AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA®) coding system to get a System Organ Class and Preferred Term (PT) for each AE and graded for severity using NCI-CTCAE v5.0.

A TEAE is defined as any AE with an onset date on or after the first administration of IMP (if the AE was absent before the first administration of IMP) or worsened after the first administration of IMP (if the AE was present before the first administration of IMP). AEs with an onset date more than 60 d after the last administration of IMP will be considered as treatment-emergent only if assessed as related to IMP by the investigator. TEAEs will be summarized overall and by cohort.

The number and percentage of patients reporting at least one TEAE will be summarized by PT nested within the System Organ Class for each of the following AE types:

- Any AE
- Related AE

- Grade ≥ 3 AE
- Related Grade ≥ 3 AE
- Any AESI
- Any SAE
- Related SAE
- Serious AE leading to death
- AEs leading to dose reduction
- AEs leading to dose delay
- AEs leading to permanent discontinuation of treatment
- DLTs

Moreover, the number and percentage of patients with any AE will be summarized by worst NCI-CTCAE grade by PT nested within System Organ Class.

DLTs will be presented in terms of listings presenting the reported term and MedDRA PT and System Organ Class term, its time of onset, duration, and outcome, relationship, NCI-CTCAE grade, and seriousness including dose exposure data.

Laboratory parameters

Clinical laboratory assessments to be summarized include hematology, blood chemistry, and urinalysis. The clinical laboratory parameters and the scheduled time points for assessment are tabulated in Section 1.3.

Clinical laboratory parameters at each time point and change from baseline to each post-baseline time point will be summarized using descriptive summary statistics for each parameter by cohort.

Clinical laboratory results will be classified according to the most recent version of NCI-CTCAE. Shift tables from baseline to worst grade on treatment will be provided for each laboratory parameter by cohort.

Additionally, the occurrence of clinically significant abnormal laboratory results within a patient will be analyzed using descriptive summary statistics for each parameter and visit by cohort.

Laboratory results will be listed along with the normal ranges and NCI-CTCAE grade. Laboratory values that are below or above the normal ranges will be flagged.

Vital signs

Vital sign parameters and the scheduled time points for assessment are presented in Section 1.3 and 8.1.2.

Vital sign parameters at each time point and change from baseline to each post-baseline time point will be summarized using descriptive summary statistics for each parameter by cohort.

Additionally, the occurrence of abnormal vital sign results within a patient will be analyzed using descriptive summary statistics for each parameter and visit by cohort.

Electrocardiogram

Electrocardiogram parameters and the scheduled time points for assessment are presented in Section 1.3.

Electrocardiograms will be judged by the investigator as clinically significant (yes/no). The number and percentage of patients with clinically significant ECG findings will be summarized by cohort for each visit.

9.4.6 Other analyses

Treatment exposure

The following dose exposure variables will be derived and analyzed for each compound using the DLT Evaluation Set for Part 1 limited to the DLT evaluation period (21 d) as well as using the Safety Set for the full treatment period:

- Number of cycles.
- Treatment Duration (weeks) defined as follows: (Date of last administration - Date of first administration + Planned Duration) / 7, whereas the Planned Duration (days) is defined as the planned time between two consecutive administrations.
- Cumulative Dose (µg) defined as sum of all administered doses.
- Dose Intensity defined as Cumulative Dose (µg) / Treatment Duration (weeks).
- Relative Dose Intensity (RDI) defined as follows:

$$\text{RDI (\%)} = \frac{\text{Actual Dose Intensity } \left(\frac{\mu g}{week}\right)}{\text{Planned Dose Intensity } \left(\frac{\mu g}{week}\right)} \text{ x } 100 = \text{DI x TI x } 100$$

Whereas

$$\text{(Actual) Dose Intensity} \left(\frac{\mu g}{week}\right) = \frac{\text{(Actual) Cumulative Dose (µg)}}{\text{(Actual) Treatment Duration (week)}}$$

$$\text{Planned Dose Intensity } \left(\frac{\mu g}{week}\right) = \frac{\text{Planned Cumulative Dose (µg)}}{\text{Planned Treatment Duration (week)}}$$

$$\text{Dose Index (DI)} = \frac{\text{Total Administered Dose (µg)}}{\text{Total Planned Dose (µg)}}$$

$$\text{Time Index (TI)} = \frac{\text{Planned Treatment Duration (week)}}{\text{Actual Treatment Duration (week)}}$$

9.5 Interim analyses

A formal interim statistical analysis is not planned.

A final analysis will be performed when the last patient discontinued from the trial.

9.6 Safety Review Committee

For details on the SRC, see Section 10.1.5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, ethical, and trial oversight considerations

This trial will be conducted according to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, GCP, and applicable regulatory requirements.

10.1.1 Regulatory and ethical considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Conference on Harmonisation (of technical requirements for registration of pharmaceuticals for human use [ICH]) GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 (US) Code of Federal Regulations [CFR], ICH guidelines, the IRB/IEC, European regulation 536/2014 (if applicable), and all other applicable local regulations.

The principal investigator, any investigator(s), the sponsor, or personnel at other establishments, must cooperate with any inspection of the documents, facilities, records, and other resources deemed appropriate by the inspecting authorities to be related to the trial and that may be located at the trial site, at the sponsor, or at other establishments.

The sponsor must be notified as soon as possible about any upcoming regulatory authority inspection.

10.1.2 Financial disclosure

All investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3 Informed consent process

The investigator or his/her representative will explain the nature of the trial to the patient.

Patients must be informed that their participation is voluntary and must be given adequate time for making the decision to participate in the trial. Patients will be required to sign a statement of informed consent that meets the requirements of local regulations (e.g., 21 CFR 50), ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or trial site.

The medical record must include a statement that written informed consent was obtained using the sponsor ICF before the patient was enrolled in the trial and the date and the time the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF during their participation in the trial.

A copy of the signed ICF(s) must be provided to the patient.

Separate ICFs will be used in this trial:

- Trial-specific ICF for trial participation
- Pregnant partner ICF
- Progression ICF
- Additional ICFs will be used if required by local regulations

10.1.4 Pre-screening ICF data protection

Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.

The patient must be informed that his/her medical records may be examined by sponsor Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees structure – SRC

An SRC will be established to review the ongoing efficacy and safety results. The SRC will act according to its own written standard operating procedures described in a charter, and will prepare written minutes of its meetings.

10.1.6 Dissemination of clinical trial data

A final report integrating all trial results will be prepared by the sponsor.

This trial will be registered on publicly accessible trial registries and trials results publicly disclosed on trial registries (e.g., ClinicalTrials.gov) in accordance with the applicable regulations.

Clinical trial data and documentation will be disseminated as required per applicable laws and regulations, e.g., the European Union (EU) Regulation No 536/2014, EU Regulation 1049/2001, and the US Final Rule, which implements Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801). Clinical documents under such laws includes protocols and protocol amendments, SAPs, ICH E3 clinical study reports.

If this clinical trial is used to support marketing authorization packages/submissions, the sponsor will comply with the EU Policy 0070, the proactive publication of clinical data on the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, ICH E3 clinical study reports, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. under Phase 2 of this policy, “clinical data” includes the publishing of individual patient data.

Even if not required by applicable laws and regulations, this trial will be registered, and trial results be publicly posted on ClinicalTrials.gov. In addition, expert summaries of the outcomes for all primary and secondary outcome measures (irrespective of outcome) and lay summaries, will be posted on a publicly accessible website.

The results for all primary and secondary outcome measures, irrespective of outcome, will be submitted for publication in academic journals (for further details, see Section 10.1.10).

10.1.7 Data quality assurance

All patient data relating to the trial will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The sponsor assumes accountability for actions delegated to other parties (e.g., CRO).

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for 25 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

Definition of what constitutes source data can be found in the source data agreement at each site.

10.1.9 Trial and site start and closure

The trial start date is the date on which the clinical trial starts recruitment of patients.

The first act of recruitment is the first site open and will be the trial start date.

The sponsor designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further trial treatment development

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.1.10 Publication policy

The results of this trial may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-site trials only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Clinical laboratory tests

The parameters and day/time at which they will be analyzed are listed in Table 3 and Table 6.

10.3 Adverse events: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1 Definition of an AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical trial patient, administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- A TEAE is defined as any AE with an onset date on or after the first administration of IMP (if the AE was absent before the first administration of IMP) or worsened after the first administration of IMP (if the AE was present before the first

administration of IMP). AEs with an onset date more than 60 d after the last administration of IMP will be considered as treatment-emergent only if assessed as related to IMP by the investigator.

10.3.1.1 Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions or worsening of pre-existing conditions detected or diagnosed after signing the ICF.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE.

10.3.1.2 Events not meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.
- Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are further specified in Section 8.2.7.

10.3.1.3 Suspected adverse reaction (suspected AR)

- All untoward and unintended responses to an IMP related to any dose administered.
- The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

- The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

10.3.1.4 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under trial, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  - The term “life-threatening” in the definition of “serious” 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, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - Hospitalization signifies that the patient has been admitted (at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
  - Hospitalization for signs/symptoms of the disease under trial including worsening of the disease under trial and hospice admission for palliative care is not considered an AE.
- Results in persistent disability/incapacity
  - The term disability means a substantial disruption of a person’s ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Other medically important conditions:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical treatment to

prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.1.5 Definition SUSAR

Any suspected serious adverse reaction (SUSAR) that is classified as unexpected by the sponsor.

A suspected serious adverse reaction is classified as unexpected when the nature or severity is not consistent with the applicable product information (reference safety information [RSI], i.e., the investigator's brochure for an unauthorized investigational product or SmPC for an authorized product).

The expectedness of a suspected serious adverse reaction is determined by the sponsor according to the RSI. This should be done from the perspective of events previously observed, not based on what might be anticipated from the pharmacological properties of a medicinal product.

If the RSI is contained in the investigator's brochure, the investigator's brochure should contain a clearly identified section to expected serious adverse reactions.

10.3.1.6 Use of the terms "severe" and "serious"

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI-CTCAE; see Section 10.3.1.7 for guidance on the assessment of intensity; the event itself may be of relatively minor medical significance [such as severe headache without any further findings]).

Severity and seriousness need to be assessed independently for each AE recorded on the eCRF.

SAEs must be reported by the investigator to the sponsor immediately (i.e., no more than 24 h after learning of the event; see Section 10.3.1.10 for reporting instructions).

10.3.1.7 Recording and follow-up of AE and/or SAE

Adverse event and SAE recording

The investigator needs to assess and document any AE regardless of association with the use of the trial treatment during the period of observation (starting from the ICF being signed until the second Safety Follow-up Visit).

- Data pertaining to AEs will be collected during each trial visit, either based on the patient's spontaneous description or investigator's inquiry or discovered in the course of examinations done during the visit, clinical significance of any sign or symptom needs to be evaluated by the investigator.

- Clinically significant findings need to be documented as AEs in the source data and eCRF. Findings that are evaluated and documented in the source data as not clinically significant (e.g., an abnormal laboratory value without any clinical manifestation), should not be documented as AE.
- The investigator will then record all relevant AE information in the eCRF and perform an assessment on:
  - intensity according to NCI-CTCAE v5.0;
  - seriousness;
  - outcome;
  - causal relationship of the AE to the trial treatment; and
  - any trial treatment action and/or any other action taken.
- All assessments as well as AE term (diagnosis/description), start date and time of onset, end date and time need to be documented in the eCRF.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the sponsor.
- To avoid colloquial expressions, the AE should be reported in standard medical terminology. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded.

Assessment of intensity

The intensity of an AE (i.e., severity of organ toxicity) will be graded according to the NCI-CTCAE v 5.0. AEs that are not listed in NCI-CTCAE v 5.0 should be classified according to the investigator's discretion as close as possible to NCI-CTCAE v 5.0, based on the comparison with the most severe case encountered in past training and clinical experience.

The investigator will make an assessment of intensity for each AE and SAE reported during the trial and assign it to one of the following categories:

- Grade 1 - Mild
- Grade 2 - Moderate
- Grade 3 - Severe
- Grade 4 - Life-threatening consequences; urgent intervention indicated
- Grade 5 - Death related to AE

With regards to the intensity of an AE the following needs to be documented:

- Initial intensity of the AE

- For each change of intensity:
  - New grade of intensity
  - Date of change (= start of new grade of intensity)
  - Time of change (only if relevant)

A change of intensity only needs to be documented if there is a clearly definable change in grading of the AE (e.g., a laboratory result change from severe to moderate according to NCI-CTCAE criteria).

- An event is defined as “serious” when it meets at least one of the pre-defined seriousness criteria as described in the definition of an SAE, NOT when it is rated as severe.

Actions taken by the investigator

Actions taken by the investigator as a result of an AE have to be documented.

Action(s) taken with trial treatment (IMPs) by the investigator:

- Dose not changed (= continuation of trial treatment administration according to the trial protocol)
- Dose reduced (= reduction of the trial treatment dosage *)
- Drug interrupted, e.g.:
  - Delayed administration of IMP within one treatment cycle
  - Delayed start of the next treatment cycle
  - Cancellation of administration at a given visit
  - Interruption of IMP administration during a given visit
- Drug withdrawn
- Unknown (e.g., in case the patient is lost to follow-up)
- Not applicable (e.g., in case treatment with trial treatment has not yet started or event starts after last trial treatment administration)

Other action(s) that may be taken by the investigator include:

- None
- Initiation of a concomitant medication for the treatment of the AE
- Initiation/termination of a non-drug therapy for the treatment of the AE

Outcome

The investigator has to assess the outcome of an AE (and not the patient’s outcome) at the time of documentation based on the following criteria:

- Recovered/resolved* (= complete resolution of the AE)

- Recovering/resolving (= AEs which are improving but not yet resolved completely, e.g., decrease in an intensity grade)
- Not recovered/not resolved (= AEs which are ongoing without improving or still present when the patient deceases due to another cause)
- Recovered/resolved with sequelae* (= patient recuperated but retained pathological conditions resulting from the AE; the sequelae should be indicated)
- Fatal** (= death due to the AE)
- Unknown (e.g., in case the patient is lost to follow-up)

* Generally, an AE is defined as recovered/resolved if all symptoms have ceased, no medication for treatment of the event is taken anymore and no other measures (e.g., hospitalization) are ongoing.

If the patient has developed permanent or chronic symptoms or if the event requires long-term medication(s), the AE is defined as recovered/resolved with sequelae as soon as no changes of symptoms and/or medication(s) are expected anymore.

An AE that is documented as a worsening of a medical condition already known at baseline, is defined as recovered as soon as the medical condition has returned to baseline status.

** In case of a fatal event, the event term should not be “death” but the underlying event which led to death (death = outcome). If there is more than one AE in a fatal case, only the AE leading to death will be attributed with the outcome “fatal”. All other AEs ongoing at the time of death will be attributed with the outcome “not recovered/not resolved”. A copy of an autopsy report should be submitted if available.

Assessment of causality

The investigator is obligated to assess the relationship between trial treatment/trial procedure and each occurrence of each AE/SAE.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.

It is sufficient to document the causality in the source data and eCRF as:

- Related (= there is a reasonable possibility of a causal relationship) or
- Not related (= there is no reasonable possibility of a causal relationship)

Relationship to trial treatment

- The relationship or association of an AE or SAE to a trial treatment (either BNT141 or in BNT141 combination with nab-paclitaxel and gemcitabine) will be made by the investigator after having evaluated all accessible data and, if necessary, he/she will re-evaluate the case as new information becomes available.

- Events caused by the procedure of trial treatment administration should be differentiated from events caused by the trial treatment itself. Only events suspected to be caused by the IMPs itself should be documented as suspected ARs but not events caused by the NIMP or the procedure of trial treatment administration.

Relationship to trial procedures

- In this trial, it cannot be excluded that during the course of the trial some procedures give rise to AEs which are related to the trial procedure and not to the trial treatment. Procedure related AE can occur at the site of injection of the trial treatment e.g., redness, swelling, hematoma or itching or during or after trial-specific procedure, e.g., discomfort after blood drawing. These events have to be reported in the eCRF on Adverse Event pages as “related to trial procedure” with the causing procedure specified. The intensity of these AEs will be characterized according to the NCI-CTCAE v 5.0.

Applicable for all categories

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the trial or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 h of receipt of the information.

10.3.1.8 SAE exemptions

In general, SAEs are defined according to ICH Topic E2A (CPMP/ICH/377/95), EU Directive 2001/20/EC and ENTR/CT-3 (see Section 10.3.1.4). In the present trial, some events are excluded from the SAE definition. The following events do not need to be reported as SAEs:

- AEs and SAEs occurring later than the second Safety Follow-up Visit must only be reported by the investigator to the sponsor if a relationship to trial treatment or trial procedure is suspected.
- Hospitalizations for respite care will not be considered as reportable SAE.
- Hospitalizations solely for coordination of care, including hospice arrangements, will not be considered as reportable SAE.
- Hospitalizations that were necessary solely because of patient requirement for outpatient care outside of normal outpatient clinic operating hours will not be considered as reportable SAE.
- Planned hospitalizations required by the protocol (e.g., for trial treatment administration or insertion of access device for trial treatment administration) will not be considered as reportable SAE.
- Hospitalizations for procedures or interventions of a pre-existing condition of the patient (elective surgery = planned, non-emergency surgical procedure) will not be considered as a reportable SAE (unless the intervention/procedure is not caused by an acute worsening of the pre-existing condition during the time trial participation).
  - If it was planned and documented in patient record before the trial-specific patient informed consent was signed (ICF for trial participation, see Section 10.1.3, or
  - If it was scheduled during the trial when elective surgery became necessary and the patient has not experienced an AE.

Nevertheless, this kind of hospitalization should be avoided during trial treatment.

- The progression of underlying disease (e.g., new metastases) during trial participation is not considered as AE.
- Routine treatment or monitoring of the underlying disease not associated with any deterioration in the patient’s condition.

10.3.1.9 Documentation of particular situations

AEs that are secondary to other events:

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be documented as an independent AE in source data and eCRF. For example:

If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be documented as AE.

If vomiting results in severe dehydration, both events should be documented as AEs separately.

Abnormal laboratory results and vital signs values:

Not every laboratory or vital signs abnormality needs to be documented as AE. For clinically significant laboratory/vital signs abnormalities the following definitions and documentation rules apply:

If a laboratory/vital signs abnormality is a sign of a disease or syndrome, the laboratory/vital signs abnormality is clinically significant and only the diagnosis of the causing disease or syndrome needs to be documented as AE.

If a laboratory/vital signs abnormality results in specific symptoms but no diagnosis of a disease or syndrome can be made, the laboratory/vital signs abnormality is clinically significant and only the symptoms need to be documented as AEs.

If a laboratory/vital signs abnormality is not a sign of a disease or syndrome and does not result in specific symptoms but leads to a change in trial treatment or in a medical intervention, the laboratory/vital signs abnormality is clinically significant and must be documented as AE.

AEs associated with an overdose or error in drug administration:

An overdose is the accidental or intentional use of a drug in an amount (per administration or cumulatively) higher than the dose being studied (for the trial treatment) or higher than the maximum recommended dose according to the authorized product information (for approved concomitant medications). An overdose or incorrect administration of a drug is not itself an AE, but it may result in an AE.

All AEs associated with an overdose or incorrect administration should be documented as AE in source data and eCRF and reported as SAE if applicable.

10.3.1.10 Reporting of SAEs

All SAEs which occur in a patient during the observation period, and do not meet any of the above listed SAE exemptions, whether considered to be associated with trial medication or not, must be reported by the investigator to the sponsor within 24 h following knowledge of the event.

All SAEs occurring after the end of the period of observation only have to be reported to the sponsor if the investigator suspects a relationship to trial medication or the trial procedure.

SAE reporting to the sponsor via paper SAE Form

For the period of observation please refer to Section 8.2.1.

A paper SAE Form needs to be completed and forwarded to the sponsor for all SAE that do not meet any of the above defined AE or SAE exemptions, and all DLTs regardless if serious or not.

The investigator needs to complete the paper Serious Adverse Event Form which must be sent to the sponsor via one of the following reporting lines:

- Safety Report Fax No.: [redacted]
- Safety Report E-Mail Address: [redacted]

Information for final description and evaluation of a case report may not be available within the required time frames for reporting. Nevertheless, for regulatory purposes, initial reports should be submitted if the following minimal information is available:

- An identifiable patient (patient number)
- A suspected medicinal product
- An identifiable reporting source (investigator/trial site identification)
- An event or outcome that can be identified as serious

SAE follow-up information should be sent to the sponsor (indicating that this is a “follow-up” report using the SAE Form or the Additional Information and Follow-Up Form) without delay as described above and accompanied by appropriate anonymous supporting documentation (e.g., discharge letters, medical reports or death certificates), until a final outcome and date are available. All confidential information (name, address, full day of birth) needs to be blackened before sending. In addition to a medical record, the investigator should complete an Additional Information and Follow-Up Form, which contains the SAE term and patient number.

A copy of the submitted SAE report must be retained on file by the investigator. If explicitly required according to national legislation, the investigator must submit copies of the SAEs to the IRB/IEC or authority and retain documentation of these submissions in the Investigator Site File.

In case an investigator or any other trial team member has questions on safety reporting the sponsor may be contacted via:

- E-Mail: [redacted]

For medical questions, the Medical Monitor for this trial should be contacted.

10.4 Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

Woman of childbearing potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea after chemotherapy) and a menstrual cycle cannot be confirmed before first dose of trial treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
   - Documented bilateral tubal ligation or occlusion

For patients with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining trial entry.

Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.

Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrolment.

10.4.2 Contraception guidance

The investigator or delegate should advise the patient how to achieve highly effective contraception.

The following birth control methods may be considered as highly effective:

- Combined estrogen and progestogen-based hormonal contraception associated with inhibition of ovulation [1] (oral, intravaginal, or transdermal)
- Progesterone-only contraception associated with inhibition of ovulation [1], (oral, injected, implanted) [2]
- Intrauterine device / hormone-releasing system. [2]
- Bilateral tubal ligation / occlusion. [2]
- Vasectomy (for a male patient or male partner of a female patient). [2, 3]
- Sexual abstinence. [4]

1 Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

2 Contraception methods that in the context of this guidance are considered to have low user dependency.

3 Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
4 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

The following birth control methods may be considered as acceptable but potentially not highly effective methods:

- Male or female condom with a spermicidal agent; both female and male condom should not be used together.
- Cap diaphragm or sponge with a spermicidal agent.

A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

10.4.3 Collection of pregnancy information

Pregnancy information will only be collected after obtaining written informed consent from the pregnant female patient (or if a male patients' partner becomes pregnant, written informed consent from both).

Pregnancy information will be collected for pregnancies that occurred after the start of trial intervention and until 60 d after the last dose.

The initial and follow-up information must be documented on the paper-based Pregnancy Reporting Form and submitted to the sponsor within 24 h of learning of a patient's pregnancy/partner's pregnancy. The completed form needs to be sent to the Safety Report Fax number or e-mail detailed in Section 10.3.1.10. Completed pregnancy forms must be signed by an investigator before faxing/mailing them to the sponsor. Blank reporting forms are provided to the investigator during the site initiation visit and are filed in the investigator's site file (ISF).

The investigator will collect follow-up information on the patient/patient's partner and the neonate and the information will be forwarded to the sponsor. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications and their presumed relation to the IMP. Generally, the follow-up will be of a duration determined in consultation with the pediatrician.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

A spontaneous abortion is always considered to be a SAE and will be reported as such. Any post-trial pregnancy related SAE considered reasonably related to the trial intervention by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former trial patients, he or she may learn of an SAE through spontaneous reporting.

10.5 Liver safety: Suggested actions and follow-up assessments

Section 6.6.1 specifies which liver events will be treated as DLTs and how treatment should be adjusted. If liver events which do not meet the criteria of a DLT occur, then the investigator should treat them according to their best judgment.

10.6 Investigators and trial administrative structure

10.6.1 Investigators and trial site personnel

There must be an investigator at each trial site.

If the trial is conducted by a team of individuals at the trial site, the investigator leading and responsible for the team is called the principal investigator.

All persons assigned responsibility as principal investigator must sign a declaration of their responsibilities and their agreement to this protocol before any trial-related procedure is performed.

Curriculum vitae and/or other relevant documents confirming the current qualification of the investigators must be provided to the sponsor. This should include any previous training in the principles of GCP, experience obtained from work with clinical trials, and experience with patient care.

Documentation of all involved investigators must be maintained according to GCP and applicable regulatory requirements.

10.6.2 Trial site personnel assigned trial-related duties

The principal investigator may define appropriately qualified personnel at a trial site to perform significant trial-related procedures and/or to make trial-related decisions under his/her supervision. In this case, the principal investigator must maintain a signed list of the persons to whom they delegate significant trial-related duties/responsibilities; the delegated trial-related duties/responsibilities must be specified in the list.

When personnel or responsibility changes are made, the principal investigator must ensure that the relevant documentation is updated before any trial-related activities are performed.

Documentation of all involved trial site personnel performing significant trial-related procedures and/or making trial-related decisions must be maintained according to GCP and applicable regulatory requirements.

10.6.3 Contract research organizations

Documentation of all involved CRO must be maintained according to GCP and applicable regulatory requirements. This includes documentation of any delegation of responsibilities to CROs.

10.6.4 The sponsor and sponsor's personnel

The trial sponsor listed on the title page accepts the responsibilities of the sponsor according to GCP and applicable regulatory requirements.

The sponsor must designate appropriately qualified personnel to advise on trial-related topics. The trial site will be provided with contact details for these personnel before any trial-related procedure is performed.

A list of key sponsor personnel involved in the preparation of this protocol and the conduct of the trial, including their full names, titles, roles, and responsibilities, must be maintained.

10.7 Country-specific requirements

There are no country-specific requirements at this time.

10.8 Other standard abbreviations and definitions

For trial-specific abbreviations, see the list of trial-specific abbreviations.

For definitions related to safety, see Section 10.3.

Abbreviation	Explanation
AE	Adverse event
AUC	Area-under-the-concentration-time curve in the dosing interval
C_{max}	Maximum observed concentration
CR	Complete response
CRF	Case report form
CRO	Contract Research Organization
CT	Computerized tomography
C_{trough}	Concentration prior to next dose
d	Day
DCR	Disease control rate
dCTP	Deoxycytidine triphosphate
DLT	Dose-limiting toxicity
DNA	Deoxyriboucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FDA	(United States) Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
h	Hour(s)
ICF	Informed consent form
ICH	International Conference on Harmonisation (of technical requirements for registration of pharmaceuticals for human use)
IEC	Independent ethics committee

Abbreviation	Explanation
IMP	Investigational medicinal product
IRB	Institutional review board
IRR	Injection/infusion-related reaction(s)
ISF	Investigator's site file
IV	Intravenous
MAD	Maximally administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	Non-investigational medicinal product(s)
ORR	Objective response rates
OS	Overall survival
PD	Pharmacodynamic(s)
PFS	Progression-free survival
PGDE	Pharmacologically-guided dose escalation
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
PS	Performance status
Q3W	Once every three weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SmPC	Summary of Product Characteristics
SoA	Schedule of activities
SOC	Standard of care
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reactions
$t_{½}$	Half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time of maximum observed concentration
ULN	Upper limit of normal
US	United States (of America)
USPI	United States Prescribing Information
Vd	Volume of distribution
WBC	White blood cell
WOCBP	Woman of childbearing potential

10.9 Protocol amendments

10.9.1 Protocol amendment 01

Amendment rationale

The protocol was amended from v1.0 to v2.0 following feedback from the FDA (23 and 25 February 2021).

This update will be issued before any trial subjects have been enrolled into the trial. This change has no impact on the planned trial objectives or trial conduct.

Detailed description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

Formerly read	Now reads
Section 1.3, Table 1 and 2 heading: *Cycle X* redefined	Table 1: *Cycle 3 and beyond* Table 2: *Cycle 4 and beyond*
Section 1.3, Tables 3 and 4 heading revised to clarify that there may be more than 21 cycles	*"etc." added to list of cycles*
Section 2.3.1 sentence added. Change also reflected in **Section 4.1, Section 4.1.4.1**, and **Section 4.1.4.2**	*To further augment patient safety, there will be a minimum of 14 d between the first, second and third subject enrolled in the first dosing cohort in each of the monotherapy (Part 1A) and the combination (Part 1B) escalation parts of the trial*
Section 4.1 sentence added. Change also reflected in **Section 4.1.4.2**	*The MTD of BNT141 in combination with nab-paclitaxel and gemcitabine in Part 1B will not exceed the monotherapy BNT141 MTD determined in Part 1A.*
Section 5.1 clarification added to inclusion criterion. Changes are reflected in **Section 1.1**	• *CLDN18.2-positive tumor sample defined as moderate-to-strong CLDN18.2 protein expression defined as intermediate (2+) to strong (3+) staining intensity in ≥ 50% of tumor cells as assessed by central testing using a CLIA validated immunohistochemistry assay in FFPE neoplastic tissues. New biopsies and archival bio-samples are allowed. If archival tissue samples from several points of time are available, the most recent one is preferred. Patients with a lower expression level or with CLDN18.2-negative cancers are not eligible.*
Section 5.1 clarification added to inclusion criterion. Changes are reflected in **Section 1.1**, **Section 1.2, Section 4.1**	• *Patients must have received all available standard therapies and failed at least first-line SOC therapy prior to enrolment.*
Section 6.6.1 added to DLT definitions	***Non-hematological***

Formerly read	Now reads
	• *Any Grade 3 cytokine release syndrome (CRS), as per the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus grading for cytokine release syndrome (CRS) (Lee et al. 2019), that does not improve to Grade 2 or below within 72 h despite medical management.* • *Any Grade 4 CRS* ***DLT criteria for liver enzyme elevations.*** *Any Grade ≥ 3 liver enzyme elevations (transaminases and bilirubin elevations), at least possibly related to study agents and lasting ≥ 7 days, will be considered a DLT.*
Section 6.6.2 *Sponsor and investigator will discuss any safety concerns in order to decide whether the next dose of BNT141 should be administered at same dose level* CCI .	CCI
Section 6.6.2 *The next dose of BNT141 should be administered* CCI	*Re-treatment may be considered on a case-by-case basis after review by the SRC.*
Section 6.6.3.2 management plan for CRS added	*Management plan for CRS added*
Section 6.6.4 (Change also reflected in **Section 6.6.1**) *Patients experiencing a DLT (an AE fulfilling the DLT criteria within the DLT period of 21 d). If requested by the investigator, the sponsor may allow a patient with a DLT to continue in the trial* CCI *. For this decision, a thorough benefit-risk assessment of the individual patient is required and consultation with the SRC needs to be considered.*	*Patients experiencing a DLT (an AE fulfilling the DLT criteria within the DLT period of 21 d) should discontinue trial drug. If requested by the investigator, the sponsor may, after a thorough benefit-risk assessment of the individual patient and endorsement by the SRC, allow a patient with a DLT (apart from anaphylaxis or Grade 4 IRR) to continue in the trial* CCI
Section 6.6.4 Trial stopping rules added	*3. Any death possibly related to the IMP occurring within 30 days of receiving IMP.* *4. The occurrence of two Grade ≥ 4 DLTs in 2 study participants.* *5. At any time during repeat treatment, if more than 33% of study subjects develop adverse events meeting DLT criteria, regardless if it is within or outside of the defined DLT evaluation window, the study cohort shall be paused pending a safety evaluation by the SRC and sponsor*
Section 8.2.8 Adverse event of special interest added	*Liver injury*

10.9.2 Protocol amendment 02

Amendment rationale

The protocol was amended from v2.0 to v3.0 to specify unique identifiers to the inclusion criteria, to correct an error in the implementation of the change to DLT definitions in Section 6.6.1, and minor administrative changes.

This update will be issued before any trial subjects have been enrolled into the trial. This change has no impact on the planned trial objectives or trial conduct.

Detailed description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

Formerly read	Now reads
Section 1.1 and 3, Secondary endpoint *Objective response rate (ORR) is defined as … observed as best overall response*	*Objective response rate (ORR) is defined as … confirmed as best overall response*
Section 1.3 Table 1 / Table 3. Updates for clarity in the footnotes. *1 Trial visits will be performed weekly for the first 4 cycles (Days 1, 8 and 15). After the first 4 cycles, trial visits will be performed at Day 1 of each subsequent cycle.* *13 If no tumor blocks/archival tissue is available, then a fresh tumor biopsy sample must be taken. Further biopsy at Cycle 2 Day 8 (± 3 d) during treatment will be performed in the same patients where the target C_{trough} of [redacted] is reached and if feasible/without a risk of complications for the patient. Some fresh tumor tissue may also be used for further exploratory assays on Claudin 18.2 mRNA expression. It may also be stored for future research, where this is agreed by the patient in the informed consent form.* *16 Includes temperature, blood pressure, and heart rate. During treatment cycles vital signs need to be collected as outlined in Section 8.1.2.* New footnote added to "Local Lab assessments": *24* (Table 1) */ 25* (Table 3) *… differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils, basophils, other cells)….*	*1 Trial visits will be performed weekly for the first 4 cycles (Days 1, 8 and 15). After the first 4 cycles, trial visits will be performed at Day 1 of each subsequent cycle. Treatment will continue until disease progression and until protocol-defined treatment discontinuation criteria are met.* *13 If no tumor blocks/archival tissue is available, then a fresh tumor biopsy sample will be taken. Further biopsy at Cycle 2 Day 8 (± 3 d) during treatment will be performed in the same patients where the target C_{trough} of [redacted] is reached and if feasible/without a risk of complications for the patient.* *16 Includes temperature, blood pressure (systolic and diastolic), heart rate, oxygen saturation and respiratory rate. During treatment cycles vital signs need to be collected as outlined in Section 8.1.2.* *24* (Table 1) */ 25* (Table 3) *Local laboratory assessments can take place one day prior to patient visit apart from Cycle 2 Day 1.* *25* (Table 1) */ 26* (Table 3)*… differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)….*
Section 1.3 Table 1 / 3	Fresh biopsy timepoint for collection on Cycle 2 Day 8 added to table for easier visualization.

Formerly read	Now reads
Section 1.3 Table 2, footnote 2 updated and footnote 4 added / Table 4, footnote 1 updated and footnote 3 added, to clarify start of visit windows. *2* (Table 2) */1* (Table 4) *Time 0 is defined as the start of infusion. EOI is end of infusion and flushing of line.*	*2* (Table 2) */1* (Table 4) *EOI is end of infusion and flushing of line.* *4* (Table 2) */3* (Table 4) *Pre-dose visit window is measured from SOI. All subsequent visit windows are measured from the EOI. Investigators should adhere to the given time points. However, due to possible time deviations that may occur in clinical practice, those will not be reported as protocol deviations.*
Section 4.1 *Efficacy assessments will continue until disease progression is assessed by the investigator, withdrawal of consent, trial termination by the sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.*	*Efficacy assessments will continue until disease progression is assessed by the investigator, withdrawal of consent, trial termination by the sponsor, or death, whichever occurs first*
Section 4.1.2 *Where archived FFPE neoplastic tissue of sufficient quality and quantity (refer to the Laboratory Manual) is not available, a fresh biopsy can be taken.*	*Where archived FFPE neoplastic tissue of sufficient quality and quantity (refer to the Laboratory Manual) is not available, a fresh biopsy will be taken.*
Section 4.1.4.2 A definition of DLT eligibility, and replacement of non-DLT-evaluable patients, for Part 1B has been added	*To be eligible for DLT assessment, patients should receive:* • *two administrations of BNT141,* CCI *during Cycle 1 (DLT assessment period)* CCI *and* • CCI *Patients who will not be able to fulfill the criteria for the DLT assessment will be replaced (this only applies to patients who do not experience a DLT). Replaced patients can continue with BNT141 treatment and follow the same trial procedures except for DLT assessment until they meet the protocol-defined treatment discontinuation criteria.*
Section 5.1 Inclusion criteria have been given unique number identifiers	
Section 5.4 *Individuals who do not meet the criteria for participation in this trial (screen failure) will not be rescreened.*	*Screen failures may be rescreened. Patients who fail their first screening for trial eligibility may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the ICF prior to*

Formerly read	Now reads
	any re-screening. Rescreened patients will be assigned a new patient number.
Section 6.6.1 Correction such that DLT definitions not listed under DLT exclusions	
Section 6.6.2 Figure 7 aligned with text [redacted] CCI	[redacted] CCI
Section 8.1.2 Clarification of vital signs • *Vital signs (blood pressure, heart rate and breathing rate)…* • *Vital signs readings will be performed at the following times, in relation to the start of BNT141 dosing.*	• *Vital signs blood pressure (systolic and diastolic), heart rate, oxygen saturation and respiratory rate…* • *Vital signs will be assessed at the following times, in relation to the start of BNT141 dosing*
Section 8.1.3 Clarification of triplicate ECG criteria	Triplicate ECGs should be performed in accordance with institutional guidance, with a time difference between the ECGs of ≥ 2 mins.
Section 8.8.1 Exploratory CLDN18.2 expression clarified *Testing of pre-treatment archival tissue or fresh tumor tissue as well as on-treatment tumor biopsy is exploratory and may include but is not limited to CLDN18.2 expression via immunohistochemistry.*	*Testing of pre-treatment archival tissue or fresh tumor tissue as well as on-treatment tumor biopsy is exploratory and may include but is not limited to CLDN18.2 expression.*
Section 9.3 Definition of analysis sets updated. Per protocol set removed, mITT set renamed as Efficacy Evaluable Set, Treated Set added and definition of DLT Evaluation Set for Part 1B clarified.	*Treated Set: All patients who received IMP (i.e., at least one dose of BNT141).* *DLT Evaluation Set: … the DLT evaluation period (21 d for Part 1A, 28 d for Part 1B). Patients who do not experience any DLT during the DLT observation period are considered to be evaluable if they have been observed for minimum 21 d for Part 1A, 28 d for Part 1B following the first target dose.… A patient is considered to have met the minimum exposure criterion in Part 1A if the relative dose intensity of BNT141 in Cycle 1 is at least 80%. A patient is considered to have met the minimum exposure criterion in Part 1B if the relative dose intensity of BNT141, nab-paclitaxel, and gemcitabine in Cycle 1 is at least 90%...*
Section 9.4.3 Definitions updated *The secondary analyses will be performed using the safety and/or mITT set as appropriate.* ***Objective response rate*** *Objective response rate is defined as the proportion of patients in whom a confirmed CR or PR is observed as best overall response. Patients not meeting the criteria for CR or PR, including those without any post-baseline tumor assessments, will be considered as non-responders.* *Objective response rate will be summarized with absolute and relative frequencies along with 2-sided Clopper-Pearson 95% CIs.*	(sentence deleted) ***Objective response rate*** *Objective response rate is defined as the proportion of patients in whom a CR or PR is confirmed as best overall response. Patients not meeting the criteria for CR or PR, including those without any post-baseline tumor assessments, will be considered as non-responders.* *Objective response rate will be summarized with absolute and relative frequencies along with 2-sided Clopper-Pearson 95% CIs. For Part 1B, a sensitivity*

Formerly read	Now reads
Disease control rate *Disease control rate is defined as the proportion of patients in whom a CR or PR or SD (SD assessed at least 6 weeks after first dose) is observed as best overall response. Patients not meeting the criteria for CR or PR or SD, including those without any post-baseline tumor assessments, will be considered as non-responders.* *Disease control rate will be summarized with absolute and relative frequencies along with 2-sided Clopper-Pearson 95% CIs.* ***Duration of response*** *Duration of response is defined as the time from first objective response (CR or PR) to first occurrence of objective tumor progression, or death from any cause, whichever occurs first. Only patients in whom a CR or PR is observed will be analyzed for DOR.*	*analysis will be performed using the Efficacy Evaluable Set.* ***Disease control rate*** *Disease control rate is defined as the proportion of patients in whom a CR or PR or SD (SD assessed at least 6 weeks after first dose) is observed as best overall response.* *Disease control rate will be summarized with absolute and relative frequencies along with 2-sided Clopper-Pearson 95% CIs.* ***Duration of response*** *Duration of response is defined as the time from first objective response (CR or PR) to first occurrence of objective tumor progression, or death from any cause, whichever occurs first. Only patients in whom a CR or PR is confirmed will be analyzed for DOR.*
Section 9.4.5 *The number and percentage of patients reporting at least one AE will be summarized by PT nested within the system organ class for each of the following AE types:*	*The number and percentage of patients reporting at least one TEAE will be summarized by PT nested within the system organ class for each of the following AE types:*
Section 10.2, Table 17 *WBC count (neutrophils, lymphocytes, monocytes, eosinophils, basophils, other cells)*	*WBC count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)*
Section 10.3.1.7 *Other action(s) that may be taken by the investigator include:* • *None* • *Initiation of a concomitant medication for the treatment of the AE* • *Termination of a concomitant medication (e.g., if this might be the cause of the AE)* • *Change of the dose of a concomitant medication* • *Hospitalization or prolongation of hospitalization (please complete SAE Form)* • *Initiation/termination of a non-drug therapy*	*Other action(s) that may be taken by the investigator include:* • *None* • *Initiation of a concomitant medication for the treatment of the AE* • *Initiation/termination of a non-drug therapy for the treatment of the AE*
Change throughout the CTP, to reflect current practice guidelines: *SOC nab-paclitaxel and gemcitabine*	*Nab-paclitaxel and gemcitabine*

10.9.3 Protocol amendment 03

Amendment rationale

The protocol was amended from v3.0 to v4.0.

A comparison of every new sponsor approved protocol version with the next approved version is filed together with the protocol in the TMF.

Description of changes

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

See the table for a summary of the reasons for major changes compared to the previous version.

Section	Reason for change
Brief title	Updated to include indications
1.1, 3	Clarification of PK secondary endpoints, move of ADA endpoint to exploratory objective, removal of ADCC as exploratory endpoint, and addition of exploratory endpoint on pre-dose lipids
1.1, 4, 5	Update of eligible indications to include patients with specific tumors [redacted CCI]
1.1, 4.1.2, 5	Clarification of details and timepoint of biopsy collection
1.1, 5	Amendment of inclusion and exclusion criteria related to AEs, contraception guidance, receipt of live vaccine prior to start of trial, handling of COVID-19 infection, glomerular filtration rate, previous receipt of BNT141
1.3, 4.1.3, 8.1.4, 8.7, 8.10	Schedules of activities simplified, inconsistencies removed, PK C1D5 timepoint removed, pre-dose lipid testing added, additional safety labs added, Part 1B, additional timepoints for ECGs added, additional PD sample collection added
4	Inclusion of 48 h safety window between second and third patient in each dose cohort to account for any acute safety signals in each new dose level
1.1, 4.4	Update of end of trial and patient completion definitions
6.5.1	Added that granulocyte colony stimulating factor and other hematopoietic growth factors may be used prophylactically
6.5.3	Detailed recommendations for premedication added
6.6.3	Update of treatment guidelines for IRRs
6.7	Update of terms under which treatment will be made available after the end of the trial
8.1.2	Additional information on vital signs monitoring added
8.2.1	Alignment with SoAs that AEs/SAEs during pre-screening will not be reported except those related with the procedure of collection of a fresh biopsy.
6.6.3.1, 8.2.8	AESI will include IRRs grade ≥ 3 instead of grade ≥ 2
8.8	Clarification of collection timepoints for tumor samples and biomarker measurements
9.4.4	Tertiary/exploratory endpoints listed
10.1.6	Further information on dissemination of trial data included
10.3.1.4	Definition of SAE regarding inpatient hospitalization or prolongation of existing hospitalization updated
10.4.2	Contraception guidance updated
Appendix 1-3	Additional guidance for COVID-19 vaccination and infection during the trial

10.10 Data collection and management

The trial documentation must be adequate for the reconstruction of the trial.

10.10.1 Case report forms

CRFs will be completed through use of an electronic data capture system, i.e., will be electronic (eCRF). Trial site personnel will receive training and have access to a manual for appropriate CRF completion. The CRFs will be submitted electronically to the sponsor via the system and should be handled in accordance with instructions from the sponsor.

The CRF is set up in accordance to the SoA, reviewed, and tested via user acceptance test before it is pushed to production. Different roles/accounts with different access rights will be set up during this process.

All CRFs should be completed by designated, trained trial site personnel. CRFs should be reviewed, verified, and then electronically signed and dated by the investigator or a designee.

At the end of the trial, the investigator will receive trial patient data for his/her trial site in a readable format that must be kept with the trial records. Acknowledgment of receipt and readability of the trial patient data will be required.

10.10.2 Patient reported outcomes

There will be no patient reported outcome measures planned in this trial.

10.10.3 Data management

The sponsor or designee is responsible for the data management of this trial. Data management will be performed in accordance to the respective data management plan.

The sponsor or designee is responsible for eCRF design and development, data imports from external data sources (e.g., central laboratory), data reconciliations, data cleaning, data coding, data exports and database lock.

Data cleaning includes quality checking the data for completeness and consistency, in accordance with an edit check specifications document, via programmed or manual review checks. In case of discrepancies, queries will be generated accordingly in the eCRF as appropriate. Additional reviews by the qualified team (e.g., medical review, SAE reconciliation, etc.) may also lead to queries. All discrepancies and queries need to be resolved prior database lock.

Medical conditions, AEs and non-drug therapies, will be coded using MedDRA® throughout the trial.

Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Product group/level codes will be assigned according to the anatomical, therapeutic, and chemical classification system.

Investigator's site file and the trial master file

The principal investigator is responsible for the filing of all essential documents in an ISF. The sponsor is responsible for the timely filing of all essential documents in the trial master file. As applicable, these files must be available at monitoring visits and during audits or regulatory inspections.

After trial completion, the principal investigator must ensure that all source data/documentation related to the trial is recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. The principal investigator must take measures to prevent accidental or premature destruction of these documents.

The principal investigator must keep the ISF, the source data/documentation arising from the trial according to the prescribed record retention period in the country and/or according to the hospital/investigational site's policy, but at least until informed by the sponsor that the trial-related records are no longer required.

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Appendix 1: Recommendation for COVID-19 vaccination during trial participation

BioNTech as the sponsor of the BNT141-01 trial recommends that patients and their physicians discuss on an individual basis the risks and benefits of COVID-19 vaccination in the context of the BNT oncology trials, considering also guidelines from the FDA, EMA, CDC, ASCO, ESMO and local agencies. COVID-19 vaccination may be performed in accordance with the most current guidelines. As of May 2021, these are:

- Patients with prior COVID-19 vaccination may be allowed to enter the trial with a wash-out period of at least 7 days since the last COVID-19 vaccine dose.
- For patients already enrolled in the clinical trial and still receiving trial treatment, COVID-19 vaccination may be allowed if at least 7 days between individual dose of COVID-19 vaccine and trial treatment dose are ensured.
- COVID-19 vaccination during DLT evaluation period in dose escalation trial or parts of the trial should be avoided to circumvent any confounding effect of the vaccination on the DLT evaluation. However, as the data in dose escalation are accumulating, the decision to vaccinate should be made by the treating oncologist, and any decision should be discussed with the sponsor's Medical Monitor.
- Administration of COVID-19 vaccine during participation in BNT141-01 trial should be documented as a concomitant medication.
- Previous administration of COVID-19 vaccine should be documented on the prior and concomitant medication form. Past confirmed infection of COVID-19 by RT-PCR before enrolment in the BNT141-01 trial should be documented in the medical history.

Appendix 2: Risk-benefit assessment of COVID-19 vaccination in BNT141-01 trial

BNT141 encodes the antibody RiboMab[redacted] directed against CLDN18.2. The specific RiboMab[redacted] binding to CLDN18.2 on the cell surface of tumor cells mediates cell death through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). BNT141 is entering early clinical development, and the safety profile in humans has not been characterized.

At this time, there are three COVID-19 vaccines authorized and recommended in the United States: the Pfizer-BioNTech, Moderna, and Johnson & Johnson/Janssen vaccines. These vaccines are described on the US Center for Disease Control's vaccine page. In the EU, the same vaccines are authorized and recommended with the addition of the COVID-19 vaccine by AstraZeneca. The Pfizer-BioNTech and Moderna vaccines are mRNA vaccines, whereas both Johnson & Johnson/Janssen and AstraZeneca are viral vector vaccines. None of the vaccines are a live virus vaccine mentioned by the protocol as per exclusion criterion 7 (i.e., received any live vaccine within 30 days prior to the start of trial treatment).

The COVID-19 pandemic is an ongoing pandemic with different stages and impacts at any one time across the whole world. The governments of the countries involved in this trial have started a nationwide vaccination program including vaccination for oncology patients. All prominent regulatory, government and professional bodies have recommended for COVID-19 vaccination even in oncology patients under active treatment. As to this date, there is no clear or specific guidance for patients enrolled in interventional oncology clinical trials and should be taken on a case-by-case basis.

Recently results of short-term safety of the Pfizer-BioNTech mRNA COVID-19 vaccine in oncology patients treated with immune checkpoint inhibitors were published (Waissengrin et al. 2021). Considering the high mortality due to COVID-19 in patients with cancer who are being treated, data supports current guidelines and call for vaccination of patients being treated with immune checkpoint inhibitors, especially during pandemic surges.

The interactions of BNT141 with all the vaccines approved in the US and EU are not known. However, the sponsor assesses the risk of significant side effects of BNT141 in combination with COVID-19 vaccine to be low. The National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) recommend for the COVID-19 vaccine to be administered on the same day as oncology therapy, including immunotherapy. However, since no clinical data are available for BNT141 as no clinical trials have been performed, the protocol would recommend at least seven days interval between COVID-19 vaccine and administration of BNT141 as a precaution.

However, a longer interval may be necessary during the DLT observation period. The oncologist should always assess the situation on an individual basis and discuss with the sponsor. Considering the high morbidity and mortality from COVID-19 in patients with cancer, the benefits of vaccination are likely to far outweigh the risks of vaccine-related AE in patients enrolled in clinical trials (Desai et al. 2021).

Appendix 3: Recommendation for COVID-19 infection in BNT141-01 trial

There is no clear or specific guidance for patients enrolled in interventional oncology clinical trials who have COVID-19 infection. The decision should be taken on a case-by-case basis taking into consideration the institutional guidelines and the patient's symptoms, comorbidities, age, presence of lung tumor or metastasis, COVID-19-vaccination status, etc. and should be discussed with the sponsor.

Patients who have not been enrolled:

Patients with serious COVID-19 infection are not eligible for the trial.

Patients with asymptomatic or mild COVID-19 infection should not receive their first trial treatment until symptom resolution and a negative SARS-CoV-2 test (antigen or PCR).

Patients with ongoing trial treatment:

The oncologist should always assess the situation individually and discuss it with the sponsor.

For asymptomatic, vaccinated patients, trial treatment continuation can be discussed.

For symptomatic patients, trial treatment interruption should be discussed. If trial treatment is interrupted, a negative SARS-CoV-2 test (antigen or PCR) is recommended after symptom resolution to continue the trial treatment.