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Supplementary information

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CLDN18.2–targeting antibody–drug conjugate IBI343 in advanced gastric or gastroesophageal junction adenocarcinoma: a phase 1 trial

In the format provided by the authors and unedited

Clinical Study Protocol

Study Title:	A Phase Ia/Ib, Multicenter, Open-label, First-in-human Study of IBI343 in Subjects with Locally Advanced Unresectable or Metastatic Solid Tumors
Protocol No.:	CIBI343A101
Version date and version number:	May 30, 2024/Version 4.0
Product Name:	Recombinant anti-Claudin18.2 monoclonal antibody-Exatecan conjugate for Injection (R&D code: IBI343)
Study Phase:	Phase Ia/Ib
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, 215213, China
Sponsor Contact:	[redacted]

Sponsor Signature Page

Study Title: A Phase Ia/Ib, Multicenter, Open-label, First-in-human Study of IBI343 in Subjects with Locally Advanced Unresectable or Metastatic Solid Tumors

Protocol No.: CIBI343A101

Title	Name	Signature (Print)	Date
[redacted]	[redacted]		
[redacted]	[redacted]		

Investigator Signature Page

Study Title: A Phase Ia/Ib, Multicenter, Open-label, First-in-human Study of IBI343 in Subjects with Locally Advanced Unresectable or Metastatic Solid Tumors

Protocol No.: CIBI343A101

This protocol is a confidential document of Innovent Biologics (Suzhou) Co., Ltd. I have read through and fully understand this protocol and will conduct this study in accordance with its requirements and Good Clinical Practice. Furthermore, I will abide by the ethics principles in Declaration of Helsinki and GLP and applicable laws and regulations during the study. I promise not to disclose any confidential information in this study to any third party without the written consent of Innovent Biologics (Suzhou) Co., Ltd.

Instructions for Investigators:
Please sign and date this signature page, print the Investigator's name and title, site name/address, and send it back to Innovent Biologics (Suzhou) Co., Ltd. after signing.

I have read all the contents of this study protocol and guarantee to follow it in the study:

Investigator's Signature: _____ Date _____

Printed Name: _____

Investigator Title: _____

Tel.: _____

Site Name/Address: _____

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Synopsis

Note: CIBI343A101 is a Multi-Center Global Phase Ia/Ib Clinical study. The portion that is not applicable to US is indicated likewise in appropriate sections.

<table>
<tr><td>Protocol Number</td><td>CIBI343A101</td></tr>
<tr><td>Sponsor</td><td>Innovent Biologics (Suzhou) Co., Ltd</td></tr>
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<tr><td>Version No./Date</td><td>Version 4.0 /May 30, 2024</td></tr>
<tr><td>Study Objectives and Endpoints</td><td>Objectives and endpoints of the Phase Ia part 1:
<table>
<tr><th>Study Objectives</th><th>Study Endpoints</th></tr>
<tr><td>Primary Objective</td><td>Primary Endpoint</td></tr>
<tr><td>● To assess the safety and tolerability of IBI343 in participants with advanced malignant solid tumors.
● To determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of IBI343.</td><td>● Incidence, severity, and relationship to the study drug of all adverse events, treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs) and serious adverse events (SAEs), etc. Changes in laboratory tests, physical examination, vital signs, etc. after the administration of the study drug.
● Dose-limiting toxicities (DLT).</td></tr>
<tr><td>Secondary Objectives</td><td>Secondary Endpoints</td></tr>
<tr><td>● To assess the pharmacokinetic (PK) profile of IBI343, total anti-tight junction protein 18.2 (CLDN18.2) antibodies, and exatecan.
● To assess the immunogenicity of IBI343.</td><td>● Major PK parameters after single and multiple doses, including but not limited to: area under the curve (AUC), maximum concentration (C_{max}), time to maximum concentration (T_{max}), trough concentration (C_{trough}), clearance</td></tr>
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● To assess the preliminary efficacy of IBI343.	(CL), volume of distribution (V) and half-life ($t_{1/2}$). ● The incidence of anti-drug antibody (ADA). ● Preliminary efficacy: objective response rate (ORR), duration of response (DoR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS) evaluated according to RECIST v1.1, and overall survival (OS).
Exploratory Objectives	Exploratory Endpoints
● To evaluate the correlation between CLDN18.2 expression level in tumor tissue and anti-tumor activities of IBI343.	● Baseline CLDN18.2 expression level and relationship with efficacy.

Objectives and endpoints of the Phase Ia part 2:

Study Objectives	**Study Endpoints**
Primary Objective	Primary Endpoint
● To determine RP2D of IBI343. ● ORR assessed by the investigator based on RECIST version 1.1.	● ORR assessed by the investigator based on RECIST version 1.1. ● Incidence, severity, and relationship to the study drug of all adverse events, TEAEs, AESIs and SAEs, etc. Changes in laboratory tests, physical examination, vital signs, etc. after the administration of the study drug.
Secondary Objectives	Secondary Endpoints

● To assess the preliminary efficacy of IBI343. ● To assess the population pharmacokinetic (PK) profile of IBI343, total anti-CLDN18.2 antibodies, and exatecan. ● To assess the immunogenicity of IBI343.	● Efficacy endpoints: DoR, DCR, TTR, and PFS evaluated according to RECIST v1.1, and OS. ● Major PK parameters, including but not limited to: AUC, C_{max}, T_{max}, C_{trough}, CL, V, and $t_{1/2}$. ● The incidence of ADA.
Exploratory Objectives	Exploratory Endpoints
● To evaluate the correlation between CLDN18.2 expression level in tumor tissue and anti-tumor activities of IBI343.	● Baseline CLDN18.2 expression level and relationship with efficacy.

Objectives and Endpoints of Phase Ib:

Study Objectives	**Study Endpoints**
Primary Objective	Primary Endpoint
● To evaluate the efficacy of IBI343 in participants with advanced gastric/gastroesophageal junction adenocarcinoma.	● ORR as assessed by the Independent Radiological Review Committee (IRRC) according to RECIST v1.1 criteria in Cohort A.
Secondary Objectives	Secondary Endpoints
● To evaluate the efficacy of IBI343 in participants with advanced gastric/gastroesophageal junction adenocarcinoma using other efficacy measures. ● To evaluate the efficacy of IBI343 in participants with advanced pancreatic ductal adenocarcinoma, biliary tract	● ORR as assessed by the investigator per RECIST v1.1 criteria in Cohort A. ● DoR, DCR, TTR, PFS as assessed by IRRC and investigator per RECIST v1.1 in Cohort A. ● ORR, DoR, DCR, TTR, PFS as assessed by the investigator according to RECIST v1.1 in Cohorts B/C/D. ● OS.

	cancer, and other tumor types. ● To assess the safety and tolerability of IBI343 in participants with advanced malignant solid tumors. ● To assess the population PK profile of IBI343, CLDN18.2 antibody, and exatecan. ● To assess the immunogenicity of IBI343.	● Incidence of AE, TEAE, AESI, SAE, etc., and relationship with the study drug; Changes of laboratory tests, physical examination and vital signs after the administration of the study drug. ● Major PK parameters, including but not limited to: AUC, C_{max}, T_{max}, C_{trough}, CL, V, and $t_{1/2}$. ● The incidence of ADA.
Number of Participants	**Part 1 of Phase Ia (not applicable in US)** Dose escalation: approximately 14 to 30 DLT-evaluable participants are planned to be enrolled. Dose expansion: for each tumor type, 2 ~ 4 doses are planned to be expanded, and about 6 ~ 60 participants are planned to be enrolled at each expanded dose, approximately 40 ~ 140 participants are planned in total. **Part 2 of Phase Ia** Dose optimization: Approximately 50-60 participants with G/GEJ AC are planned to be enrolled. Approximately 30-40 participants with PDAC are planned to be enrolled. **Phase Ib (not applicable in US):** Cohort A: Approximately 50 participants are planned to be enrolled. Cohort B: Approximately 50 participants are planned to be enrolled. Cohort C: Approximately 50 participants (including those at the RP2D in the Phase Ia dose expansion phase) are planned to be enrolled. Cohort D: Approximately 50 participants (including those at the RP2D in the Phase Ia dose expansion phase) are planned to be enrolled.	
Study Design	This is a Phase Ia/Ib, multicenter, open-label, first-in-human study to evaluate the safety, tolerability, PK, and efficacy of IBI343 in participants with locally advanced unresectable or metastatic solid tumors. It is planned to be carried out in different countries or regions such as China, Australia and US. There are two parts in phase Ia, part 1 includes dose escalation and expansion phase, and part 2 is designed for dose optimization. **Phase Ia** **<u>Part 1 (not applicable in US)</u>**	

	Dose Escalation Phase The phase Ia dose escalation phase will enroll participants with advanced malignant solid tumors who have failed or were intolerant to standard treatment or have no standard treatment, mainly focusing on participants with gastric/gastro-esophageal junction adenocarcinoma (G/GEJ AC) or pancreatic ductal adenocarcinoma (PDAC). The dose escalation will use accelerated titration combined with classical "3 +3" design. The 5 dose groups intended for dose escalation are 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg, respectively. The accelerated titration will be used for 0.3 mg/kg and 1 mg/kg dose groups, and the classical "3 +3" dose escalation design will be used for subsequent dose groups. IBI343 will be administered intravenously (IV) Q3W on Day 1 of every 3 weeks (21 days). The DLT observation period is 21 days after the first dose. After all participants receiving the current highest dose will have been observed for at least 21 days, the decision on whether to continue dose escalation will be made based on the safety data obtained during the DLT observation period. In the accelerated titration phase, 1 participant will be enrolled and treated with IBI343 0.3 mg/kg firstly. If no ≥ Grade 2 treatment-related adverse event (TRAE) occurs during the DLT observation period, 1 participant will be enrolled and treated with 1 mg/kg. If no ≥ Grade 2 TRAE occurs during the DLT observation period, subsequent dose levels (3 mg/kg, 6 mg/kg and 10 mg/kg) will follow the classical "3 +3" dose escalation design; If a participant in the accelerated titration phase experienced ≥ Grade 2 TRAE during the DLT observation period, the classical "3 +3" dose escalation will start at that dose level. The classic "3 +3" dose escalation design is as follows: 3 participants will be enrolled in each dose group first, and if none of these 3 participants experience DLT during the DLT observation period, the next higher dose group will be administered. If 1 of the first 3 participants experiences DLT, another 3 participants will be included in the same dose group; If no DLT occurs in the additional 3 participants, the administration of the next higher dose group will be started; If DLT occurs in ≥ 1 of the additional 3 participants or ≥ 2 of the total 6 participants, or ≥ 2 of the first 3 participants, the dose is defined as intolerable, and no further dose escalation will be allowed; At the same time, the former lower dose group will be supplemented to 6 participants until the MTD is determined. It is allowed to explore the intermediate dose between the intolerable dose and the previous lower dose according to the "3 +3" design to determine the MTD more precisely. For example, if > 1 participant in the 6 mg/kg dose group experiences a DLT during the DLT observation period, 4.5 mg/kg will be explored according to the "3 +3" design; If > 1 participant in the 10 mg/kg dose group experiences a DLT during the DLT

	observation period, the 8 mg/kg dose group will be explored according to "3 +3". If ≤ 1 participant in the anticipated highest dose of 10 mg/kg experienced a DLT, a higher dose was allowed to be further explored to determine the MTD after adequate discussion of the safety, toxicity, and PK data between the sponsor and the investigator. No intra-participant dose escalation will be allowed throughout the dose escalation Phase. After completion of the DLT observation period and confirmation of safety, participants will continue treatment with the current IBI343 dose group regimen until disease progression, intolerable toxicity, withdrawal of consent, other reason for discontinuation of study treatment, or 24 months of treatment, whichever occurs first. After discontinuation of treatment, participants will be followed for safety and survival. After the DLT observation period, participants will continue to be observed for safety and tolerability. During the study, the investigator and the sponsor will jointly review and evaluate the safety, PK and efficacy data to decide whether to explore the next dose group and whether to adjust the dose escalation scheme (e.g., dose level, number of dose groups, dosing cycle, etc.). In the Phase Ia dose escalation phase, countries will compete for enrollment. **Dose Expansion Phase** If participants in a dose group in the dose escalation phase have completed the DLT observation period and confirmed safety and tolerability, the sponsor may request that this dose and/or doses below this dose level (4.5 mg/kg Q3W if the dose is 6 mg/kg Q3W and above; 8 mg/kg Q3W if the dose is 10 mg/kg Q3W) be allowed to expand enrollment based on safety, efficacy and/or PK data to further characterize the safety, PK profile and preliminary efficacy of IBI343 and to determine the RP2D. The dose expansion phase will include participants with CLDN18.2-positive advanced malignant tumors who have failed or were intolerant to the following standard therapies or for whom no standard therapies are available: G/GEJ AC: preferentially enroll participants with moderate to high CLDN18.2 expression (Claudin18.2 immunohistochemical membrane staining intensity ≥ 2 + in ≥ 40% of tumor cells); PDAC, preferentially enroll participants with moderate to high expression of CLDN18.2 (Claudin18.2 immunohistochemical membrane staining intensity ≥ 2 + in ≥ 40% of tumor cells); CLDN18.2-positive Biliary Tract Cancer or other solid tumors. For each tumor type, it is planned to select 2 ~ 4 doses for expansion, and about 6

	~ 60 participants are planned to be enrolled at each expanded dose. The tumor type, dose, timing, and region to initiate dose expansion will be determined by the sponsor, and the CLDN18.2 expression level of enrolled participants will be adjusted according to the study progress. Real-time safety monitoring will be performed for each dose group in the dose expansion phase using the Bayesian toxicity monitoring method. The parameters of the Bayesian toxicity monitoring method are set as follows: the maximum probability of significant adverse events of interest to the sponsor in each dose group is not more than 20%, the Bayesian prior distribution is (1, 1), the minimum sample size at the time of implementation of the monitoring method is 6 cases, and the Bayesian posterior probability is > 80%. Significant adverse events of interest to the sponsor are defined as adverse events related to the study drug that meet the 5 categories of DLT specified in the protocol. During the course of the study, the investigator and the sponsor will discuss together to determine the dose and number of participants enrolled in the dose expansion phase. Participants will continue treatment with IBI343 until disease progression, intolerable toxicity, withdrawal of consent, other reason for discontinuation of study treatment, or 24 months of treatment, whichever occurs first. In the Phase Ia dose expansion phase, participants will be allowed to receive higher than the starting dose of IBI343 from the second cycle based on the safety, tolerability and preliminary efficacy observed in the study after communication between the investigator and the sponsor, but this dose must be the safe dose assessed for DLT in the dose escalation phase. After discontinuation of treatment, participants will be followed for safety and survival. **Part 2:** **Dose Optimization Phase** The dose optimization phase may be initiated under comprehensive discussion between Sponsor and Investigator. Randomized, parallel cohorts may be designed to determine the optimal dose for further parts if needed. The study will be conducted in advanced G/GEJ AC and PDAC participants with CLDN18.2 expression. Approximately 50-60 participants with G/GEJ AC from China and 30-40 participants with PDAC are planned to be enrolled in China, US and Australia. For each tumor type, participants will be randomized in a 1:1 ratio to 2 different dose groups：4.5mg/kg and 6mg/kg, which will be selected by the sponsor based on the emerging clinical data. ***G/GEJ AC (not applicable in US)*** Preferentially enroll participants with high CLDN18.2 expression (Claudin18.2

	immunohistochemical membrane staining intensity ≥ 2 + in ≥ 75% of tumor cells). The randomization stratification factor is history of prior gastrectomy (Yes vs No). ***PDAC (If applicable)*** Preferentially enroll participants with moderate to high expression of CLDN18.2 (Claudin18.2 immunohistochemical membrane staining intensity ≥ 2 + in ≥ 40% of tumor cells). The randomization stratification factors include: prior anti-cancer therapy line (1L vs. 2L+), prior irinotecan therapy (Yes vs. No), CLDN18.2 expression level (<75% vs. ≥75%) and region (China vs. other). Participants will continue treatment with IBI343 until disease progression, intolerable toxicity, withdrawal of consent, other reason for discontinuation of study treatment, or 24 months of treatment, whichever occurs first. After discontinuation of treatment, participants will be followed for safety and survival. **Phase Ib (not applicable in US)** After the RP2D and preliminary efficacy have been determined by the investigator and the sponsor based on the results of the Phase Ia study, a Phase Ib study to evaluate the efficacy and safety of IBI343 monotherapy in participants with advanced malignant solid tumors will be initiated at the request of the sponsor. The timing of initiation of each study cohort in Phase Ib will be determined after joint discussion between the sponsor and the investigator. The following cohorts are planned for Phase Ib，**sponsor will submit a protocol amendment should the sample size increase beyond the number specified in each of the cohorts below:** Cohort A: Approximately 50 participants with advanced G/GEJ AC with high CLDN18.2 expression (Claudin18.2 immunohistochemical membrane staining intensity ≥ 2 + in ≥ 75% of tumor cells) who have received at least 2 prior lines of systemic therapy and have progressed are planned to be enrolled. Cohort B: Approximately 50 participants with CLDN18.2-positive advanced G/GEJ AC who have failed first-line standard therapy are planned to be enrolled. Cohort C: Participants with advanced PDAC who have received at least one systemic therapy and have progressed, and approximately 50 participants are planned to be enrolled (including the number of participants who received the RP2D in the dose expansion phase of phase Ia). Cohort D: Approximately 50 participants with CLDN18.2-positive advanced BTC who have failed at least one systemic therapy (including the number of participants who received the RP2D in dose expansion phase of phase Ia) are planned to be enrolled. Participants will continue treatment with IBI343 until disease progression,

	intolerable toxicity, withdrawal of consent, other reason for discontinuation of study treatment, or 24 months of treatment, whichever occurs first. After discontinuation of study treatment, participants will be followed for safety and survival. During the course of the study, participants in Phase Ib Cohort A will undergo radiological assessment by IRRC and investigator according to RECIST v1.1; Participants in Phase Ia and Phase Ib B/C/D cohorts will undergo radiographic assessments by the investigator according to RECIST v1.1.
Dose Limiting Toxicity	Toxicity evaluation will be performed according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. DLT is defined as any of the following AEs (unless clearly attributable to underlying disease or an extraneous event) within 21 days after the first dose in the dose escalation phase of Phase Ia: **1. <u>Hematologic Toxicity</u>** • Grade 4 neutrophil count decreased lasting > 7 days • Grade ≥ 3 febrile neutropenia [absolute neutrophil count (ANC) < 1 × 10^9/L and a single temperature > 38.3 ℃ or a sustained temperature ≥ 38.0 ℃ for more than 1 hour] • Grade 4 anemia that cannot be explained by underlying disease • Grade 4 platelet count decreased • ≥ Grade 3 decreased platelet count lasting > 7 days • ≥ Grade 3 platelet count decreased with bleeding • Grade 4 lymphocyte count decreased lasting ≥ 14 days **2. <u>Hepatotoxicity</u>** • Grade 4 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation • AST or ALT > 5 × upper limit of normal (ULN), if accompanied by ≥ Grade 2 elevated total bilirubin (TBIL) • In participants without liver metastases, AST or ALT > 5 × ULN lasting > 7 days following optimal therapy • In participants with liver metastases, AST or ALT > 5 × ULN lasting > 7 days following optimal therapy, if baseline ≤ 3 × ULN • In participants with liver metastases, AST or ALT > 8 × ULN lasting > 7 days following optimal therapy if baseline > 3 × ULN **3. <u>Non-hematological, non-hepatotoxic</u>** 1） Any Grade ≥ 3 non-hematologic, non-major hepatotoxicity (other than laboratory abnormalities) with the following exceptions: • Grade 3 arthralgia

	• Grade 3 myalgia • Grade 3 rash • Grade 3 alopecia • Grade 3 fatigue/asthenia • Grade 3 hypertension or hypotension • Grade 3 nausea, vomiting, diarrhea, or anorexia that resolves to ≤ Grade 2 within 3 days with best supportive care 2） Any Grade ≥ 3 non-hematologic, non-major hepatotoxicity laboratory abnormality that requires treatment or results in hospitalization, with the following exceptions: • Grade 3 Electrolyte Abnormalities • Grade 3 gamma-glutamyl transferase (GGT) increased • Asymptomatic laboratory abnormalities including Grade 3/4 alkaline phosphatase increased, hyperuricemia, serum amylase increased, and lipase increased **4. <u>Any Grade 5 AE</u>** **5. <u>Other AE determined to be DLT after discussion between the investigator and the sponsor</u>** **Notes:** • Grade 3 or 4 infusion related reaction (IRR) is not considered as DLT. However, in the event of a Grade 3 or 4 IRR, the participant will be discontinued from study treatment and replaced with a new participant. If ≥ 2 participants in a dose group experience a Grade 3 or 4 IRR, enrollment must be suspended, and the sponsor will need to review the safety data of the study to determine whether to continue enrollment. • The above criteria will be used to make individual participant determinations regarding dose delays or discontinuation throughout the course of the trial. However, only those DLTs occurring during the DLT observation period after the first dose will determine dose escalation and tolerability. • If any of the above toxicities occur during the DLT observation period, whether or not the toxicity is regarded as a DLT will be determined based on consultation between the investigator and the sponsor. In addition, for other toxicities affecting study drug treatment, the determination of whether or not the toxicity is regarded as a DLT will be determined based on the consultation between the investigator and the sponsor. • “Adverse events are lasting >7 days following optimal therapy” means

	"despite optimal therapeutic intervention, the adverse events are lasting > 7 days".
Study Drug Strength and Method of Administration	IBI343 Dosage form: Lyophilized preparation for injection Strength: 100 mg/vial Method of Administration: Intravenous (IV) infusion
Inclusion Criteria	Participants must meet all of the following criteria to participate in the study: **Enrollment criteria to be met for both Phase Ia and Phase Ib:** 1. Has signed written Informed Consent Form (ICF), willing and able to comply with protocol-specified visits and related procedures. 2. Phase Ia dose escalation phase: Has at least 1 evaluable lesion according to RECIST v1.1; Phase Ia dose expansion and dose optimization phase, Phase Ib: Has at least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors RECIST v1.1. 3. Age ≥ 18 years, of either sex. 4. Has an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. 5. Has an expected survival ≥ 12 weeks. 6. Has adequate bone marrow and organ function. Defined as: • Hematology: ANC ≥ 1.5 × 10^9/L; Platelet count ≥ 100 × 10^9/L; Hemoglobin ≥ 9.0 g/dL, participants must not have received transfusion of blood products (including red blood cell suspension, apheresis platelets, cryoprecipitate, etc.), erythropoietin (EPO), G-colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) within 7 days prior to blood sample collection; • Hepatic function: TBIL ≤ 1.5 × ULN (TBIL ≤ 3 × ULN is allowed for participants with Gilbert's syndrome); ALT and AST ≤ 2.5 × ULN for participants without liver metastasis and ≤ 5 × ULN for participants with liver metastasis; Albumin ≥ 28 g/L; • Renal function: creatinine clearance ≥ 60 mL/min (using the Cockcroft-Gault formula). • Coagulation function: international normalized ratio (INR) ≤ 1.5 and activated partial thromboplastin time (APTT) ≤ 1.5 × ULN (participants receiving anticoagulant therapy with coagulation function within the above range are allowed). 7. Female participants of childbearing potential or male participants whose partners are female of childbearing potential are required to use effective

	contraceptive measures throughout the treatment period and for 6 months after the final treatment period. **Inclusion Criteria for Phase Ia Dose Escalation:** 1. Participants with histopathologically confirmed unresectable locally advanced or metastatic malignant solid tumors that have failed or were intolerant to standard therapy or for whom no standard therapy is available. **Inclusion Criteria for Phase Ia Dose Expansion and Dose Optimization:** 1. Participants with histopathologically confirmed unresectable locally advanced or metastatic G/GEJ AC, PDAC, BTC, or other solid tumors who have failed or were intolerant to standard therapy or for which no standard therapy is available. 2. * CLDN18. 2 positive confirmed by pathological examination (in dose expansion phase, G/GEJ AC and PDAC preferentially enrolled *** moderate to high expression of CLDN18. 2; in dose optimization phase, G/GEJ AC preferentially enrolled **high expression of CLDN18.2 and PDAC preferentially enrolled moderate to high expression of CLDN18.2). **Enrollment Criteria for Phase Ib Cohort A:** 1. Histopathologically confirmed unresectable locally advanced or metastatic G/GEJ AC. 2. Have received at least 2 lines of systemic therapy [anti-PD-(L) 1 + platinum, fluoropyrimidines, paclitaxel/docetaxel, or irinotecan; participants with HER2 overexpression (defined as 3 + or 2 + by immunohistochemistry and ISH +) must have received anti-HER2 therapy, and participants who have not received prior anti-PD-(L) 1 or anti-HER2 therapy must have had a contraindication or reasonable reason for no benefit] and have had disease progression. 3. High expression of **CLDN18. 2 was confirmed by pathological examination. **Enrollment Criteria for Phase Ib Cohort B:** 1. Histopathologically confirmed unresectable locally advanced or metastatic G/GEJ AC. 2. Disease progression after first-line standard therapy (HER2-overexpressing participants must have received prior anti-HER2 therapy unless contraindicated or justified non-benefit). 3. Confirmed * CLDN18. 2 positive by histopathological examination. **Enrollment Criteria for Phase Ib Cohort C:** 1. Histopathologically confirmed unresectable locally advanced or metastatic PDAC. 2. Disease progression after at least one prior systemic therapy. **Enrollment Criteria for Phase Ib Cohort D:**

	1. Histopathologically confirmed unresectable locally advanced or metastatic BTC. 2. Disease progression after at least one prior systemic therapy. 3. Confirmed * CLDN18. 2 positive by histopathological examination. **Notes:** * CLDN18.2-positive: defined as ≥ 1% of tumor cells with membranous staining of any intensity in tumor tissue by immunohistochemistry, when tested previously, at the study site, or at the central laboratory. ** High expression of CLDN18. 2: Claudin18.2 immunohistochemical membrane staining intensity ≥ 2 + in ≥ 75% of tumor cells. *** Moderate to high expression of CLDN18.2: Claudin18.2 immunohistochemical membrane staining intensity ≥ 2 + in ≥ 40% of tumor cells.
Exclusion Criteria	Participants will not be enrolled in the study if any of the following criteria are met: **Exclusion criteria common to Phases Ia and Ib:** 1. Is participating in another interventional clinical study other than an observational (non-interventional) clinical study or is in the survival follow-up phase of an interventional study. 2. Has received the last dose of antineoplastic therapy within 4 weeks or 5 half-lives of an antineoplastic therapy (whichever is shorter) prior to the first dose of study drug. 3. Plans to receive other anti-tumor therapy during treatment with the study drug [palliative radiotherapy for symptomatic relief (e.g., pain) that does not affect response assessment is allowed]. 4. Has received a strong cytochrome P450 3A4 (CYP3A4) inhibitor within 2 weeks or 5 half-lives (whichever is longer) prior to the first dose of study drug. 5. Has received live vaccine within 4 weeks prior to the first dose of study drug or plans to during the study. 6. Toxicities due to prior therapy that have not recovered to Grade 0 or 1 per NCI CTCAE v5.0 prior to the first dose of study drug (excluding alopecia, asthenia, hyperpigmentation, and other conditions with no safety risk per the judgment of the investigator). 7. Has undergo major surgical procedure (craniotomy, thoracotomy, laparotomy or others per the investigator, excluding needle biopsy) or has unhealed wounds, ulcers, or bone fracture within 4 weeks prior to the first dose of study drug; Or plans to undergo major surgery during the study period; Note: Local surgical treatment of isolated lesions for palliative purposes is acceptable. 8. Has received whole pelvic radiotherapy. 9. Has gastric pyloric obstruction and/or persistent recurrent vomiting (≥ 3

	episodes in 24 hours). 10. Has a history of gastrointestinal perforation and/or fistula within 6 months that has not resolved surgically prior to the first dose of study drug. 11. Has symptomatic central nervous system metastases. Participants with asymptomatic brain metastases (i.e., no neurological symptoms, no need for glucocorticoid treatment, all brain metastasis ≤ 1. 5 cm) or stable symptoms after treatment of brain metastases must meet all of the following criteria to participate in the study: no metastasis in the midbrain, pons, cerebellum, meninges, medulla oblongata or spinal cord; Stable clinical status for at least 4 weeks with definitive clinical evidence of no new or enlarging brain metastasis and discontinuation of corticosteroids and anticonvulsants for at least 2 weeks prior to the first dose of study drug. Note: lesions of the central nervous system will not be considered as a target lesion. 12. Has a history of pneumonitis requiring corticosteroids therapy, or a history of interstitial lung disease, non-infectious pneumonitis, severely impaired lung function or uncontrolled lung disease, such as pulmonary fibrosis, severe radiation pneumonitis, acute lung injury, or suspected of having the above diseases during the screening period. 13. Has uncontrolled medical conditions, such as: • Active or clinically uncontrolled serious infection requiring treatment with systemic anti-infectives (antibiotics, antivirals, or antifungals) within 1 week prior to the first dose of study drug, including but not limited to the infection of respiratory tract, urinary system, biliary tract infection, etc. • Participants infected with human immunodeficiency virus (HIV) (HIV 1/2 antibody positive). • Acute or chronic active hepatitis B (defined as hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibody positive (HBcAb) with hepatitis B virus DNA copies ≥ 10^4 copies/mL or ≥ 2000 IU/mL or above the lower limit of detection) or acute or chronic active hepatitis C [hepatitis C virus antibody (HCVAb) positive with HCV RNA > 10^3 copies/mL]. Participants whose test results are below the above criteria after receiving antiviral therapy with nucleotides, or participants with positive serology but negative HCV-RNA test result are eligible. • Has active COVID-19 infection. • Has active pulmonary tuberculosis, is being treated with anti-tuberculosis therapy or having received anti-tuberculosis therapy within 1 year prior to the first dose of study drug.

	• Has active syphilis or latent syphilis requiring treatment. • Has symptomatic congestive heart failure (New York Heart Association classification NYHA class II-IV), symptomatic or uncontrolled arrhythmia, QTc interval > 480 ms, or personal or family history of congenital long/short QT syndrome. • Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) by standard treatment. 14. Has one or more arterial thromboembolic event, including myocardial infarction, unstable angina, cerebrovascular accident, transient ischemic attack, etc., within 6 months prior to the first dose of study drug. 15. Has tumor invasion of surrounding vital structures or organs (e.g., great vessels, trachea, etc.) or risk of gastrointestinal/respiratory fistula. 16. Has received stent implantation in tracheal or digestive tract. 17. Has symptomatic pleural, ascites, or pericardial effusion requiring intervention (e.g., drainage, peritoneal shunt, or cell-free and concentrated ascites reinfusion therapy [CART]). Asymptomatic participants with a small amount of pleural effusion, ascites or pericardial effusion on imaging are allowed. (Drainage and CART are not allowed within 2 weeks prior to screening assessment). 18. Has esophageal or gastric varices that require immediate intervention (e.g., ligature or sclerotherapy) or are considered to be at high risk for bleeding in the opinion of the investigator or consulting gastroenterologist or hepatologist. Participants with evidence of portal hypertension (including splenomegaly on imaging) or a history of prior variceal bleeding must undergo endoscopic evaluation within 3 months prior to the first dose of study drug. 19. Has one or more life-threatening bleeding event or Grade 3 or 4 gastrointestinal/variceal bleeding requiring blood transfusion, endoscopic or surgical treatment within 3 months prior to the first dose of study drug. 20. Has a history of deep vein thrombosis, pulmonary embolism, or any other serious venous thromboembolism within 3 months prior to the first dose of study drug (implantable venous access port or catheter-derived thrombosis, or superficial vein thrombosis is not considered "serious" venous thromboembolism). 21. Has hepatic encephalopathy, hepatorenal syndrome, or Child-Pugh B or more severe cirrhosis. 22. Has complete or incomplete intestinal or bowel obstruction at the time of screening or a history of complete or incomplete intestinal or bowel

	obstruction within 3 months prior to first dose, or is at risk of intestinal perforation (including but not limited to acute diverticulitis, history of intra-abdominal abscess), or a history of any of the following disease: inflammatory bowel disease or extensive bowel resection (partial colectomy or extensive small bowel resection with concurrent chronic diarrhea), Crohn's disease, ulcerative colitis, and chronic diarrhea. 23. Has significant malnutrition (loss of more than 5% of body weight within 1 month or more than 15% of body weight within 3 months, or loss of more than 50% or more food intake within 1 week, if intravenous nutrition is required). Participants with malnutrition corrected over 4 weeks before the first dose of study drug are allowed. 24. Has other acute or chronic disease or laboratory abnormality that may result in increased risk associated with study participation or study drug administration, or interfere with the interpretation of study results, and is considered unfit for this study per the Investigator's judgement. 25. Is under neurological, psychiatric illness or social situation that affects compliance with study requirements, significantly increases the risk of AE, or affects the participant's ability to provide written ICF. 26. Has a history of other primary malignancies, with the following exceptions: • Curatively treated malignancy with no known active disease for ≥ 2 years prior to study enrollment and is at minimal risk of recurrence; • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease recurrence; • Adequately treated carcinoma in situ with no evidence of disease recurrence. 27. Has a known history of immunodeficiency. 28. Has a history of allogeneic organ transplantation and history of allogeneic hematopoietic stem cell transplantation. 29. Has a history of severe allergic reaction to other monoclonal antibodies and/or hypersensitivity to any of the formulation components of IBI343. 30. Female participants who are pregnant or lactating. 31. Has other conditions considered not eligible to participate in this study per the Investigator's judgement.
Evaluation Parameters	**Safety Assessments** ● Incidence, relationship to study drug, and severity of all TEAE, AESI, SAE. ● Changes in vital signs, physical examination, and laboratory test results after treatment with study drug.

	● Immunogenicity: All participants will be tested for ADA and, if necessary, for neutralizing antibody (NAb) in ADA-positive serum samples. **PK assessment** ● To characterize the single-and multiple-dose PK of the drug in humans and determine key PK parameters, including but not limited to: AUC, T_{max}, C_{trough}, C_{max}, CL, V and $t_{1/2}$. **Efficacy Assessments** ● Response in solid tumors will be evaluated according to RECIST v1.1, and the evaluation parameters included: ORR, DoR, DCR, TTR and PFS. ● OS. **Biomarker Assessments** ● To evaluate the relationship between baseline CLDN18.2 expression level in tumor tissue and efficacy.
Statistical Methods	**Sample Size** Part 1 of phase Ia (not applicable in US): Dose escalation: approximately 14 to 30 DLT evaluable participants are planned to be enrolled to accurately assess the MTD. Dose expansion: for each tumor type, 2 ~ 4 doses are planned to be expanded, and about 6 ~ 60 participants are planned to be enrolled at each expanded dose, approximately 40 ~ 140 participants are planned in total. Part 2 of phase Ia: Dose optimization: Approximately 50-60 participants with G/GEJ AC are planned to be enrolled. Approximately 30-40 participants with PDAC are planned to be enrolled. Phase Ib (not applicable in US): Approximately 200 participants are planned to be enrolled. Cohort A: Approximately 50 participants are planned to be enrolled to evaluate the efficacy of IBI343 monotherapy. Cohort B: Approximately 50 participants are planned to be enrolled to evaluate the efficacy of IBI343 monotherapy. Cohorts C and D: Approximately 50 participants per cohort (including participants at the RP2D in the Phase Ia dose expansion phase) are planned to be enrolled to evaluate the efficacy of IBI343 monotherapy. **Statistical Methods** ● Descriptive statistics will be used to summarize all safety, PK, immunogenicity, and efficacy data. Descriptive statistics (including

	number, mean, standard deviation, median, minimum, and maximum for continuous variables, and geometric mean and geometric coefficient of variation for PK variables) will be used to summarize; Frequency and percentage will be provided for category variables. ● Anti-tumor efficacy endpoints include: - Best overall response [complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD)] - ORR (CR + PR) and DCR (CR + PR + SD) - DoR or TTR - PFS - OS ● ORR and DCR and their 95% CIs will be provided if applicable, the proportion of participants with best overall response of CR, PR, SD or PD will also be provided, the median time of DoR, TTR, PFS and OS and their 95% CIs will be estimated using Kaplan-Meier method, and the survival rate and their 95% CIs at specified time points (if applicable, eg, Months 6, 12 and every 6 months thereafter) will be provided.

Schedule of Activities

Table 1. Schedule of activities (Phase Ia Dose Escalation)

Stage	**Screening**	**Treatment**						**End of Treatment / Safety Follow-up [17]**	**Survival Follow-up [18]**
		Cycle 1 The DLT observation period is 21 days					**Cycle 2 and beyond (21 days/cycle)**		
Window (days)	**-28 ~-1**	**1**	**2**	**3**	**8 (± 1)**	**15 (± 1)**	**Day 1 of each cycle (± 3)**	**± 7**	**Every 90 days (± 7)**
General Study Procedures									
Informed consent[1]	X								
Inclusion/Exclusion Criteria	X								
Demographics/Medical history/Prior therapy[2]	X								
Vital signs[3]	X	X	X	X	X	X	X	X	
Weight/Height[4]	X	X					X	X	
Physical examination	X						X	X	
ECOG PS score	X						X	X	
12-lead ECG[5]	X	X					X	X	
Laboratory Tests									
Hematology/Serum chemistry[6]	X			X	X	X	X	X	
Urinalysis [7]	X				X	X	X	X	

Stage	**Screening**	**Treatment**						**End of Treatment / Safety Follow-up [17]**	**Survival Follow-up [18]**
		Cycle 1 The DLT observation period is 21 days					**Cycle 2 and beyond (21 days/cycle)**		
Window (days)	**-28 ~-1**	**1**	**2**	**3**	**8 (± 1)**	**15 (± 1)**	**Day 1 of each cycle (± 3)**	**± 7**	**Every 90 days (± 7)**
Fecal analysis[8]	X								
Myocardial enzyme and Troponin [9]	X					X	X	X	
Coagulation test [10]	X					X	X	X	
Pregnancy test[11]	X							X	
HIV/HBV/HCV/Treponema test[12]	X								
Immunogenicity	See Table 3 for details								
PK	See Table 3 for details								
Safety Assessments									
Assessment of AE [13]	X								
DLT Assessment[14]		X							
Concomitant medications	X	X	X	X	X	X	X	X	
Survival		X							
Subsequent antineoplastic therapy								X	X
Efficacy Assessments									
Tumor Assessment[15]	X							X	

Stage	**Screening**	**Treatment**						**End of Treatment / Safety Follow-up [17]**	**Survival Follow-up [18]**
		Cycle 1 The DLT observation period is 21 days					**Cycle 2 and beyond (21 days/cycle)**		
Window (days)	**-28 ~-1**	**1**	**2**	**3**	**8 (± 1)**	**15 (± 1)**	**Day 1 of each cycle (± 3)**	**± 7**	**Every 90 days (± 7)**
Administration of Study Drug									
IBI343[14]		X					X		
Biomarkers									
Tumor tissue samples[16]	X								

Notes:

1. Signature of the informed consent form (ICF) during the screening period should be performed prior to any protocol-specified procedures. The results of laboratory tests and imaging examinations conducted at the study center before signing the informed consent form, which meet the time window and technical requirements during the screening period, are acceptable in order to minimize the psychological and physical trauma caused by repeated blood sampling or examination.
2. Medical history includes all active diseases, as well as any conditions diagnosed within the past 10 years and considered clinically significant by the investigator, including but not limited to hypertension, diabetes, smoking/drinking history, surgery history, drug allergy history, etc. Relevant information regarding study disease should be recorded, including disease stage (AJCC 8th edition), date of diagnosis and previous treatments, including chemotherapy, radiotherapy, surgical treatment, targeted drugs, immunotherapy, etc. The date of last administration should be recorded (oral drugs need to be recorded until the date of last administration). Other concomitant medications will be recorded within 30 days prior to the first dose of study drug.
3. Vital signs include: temperature, pulse, respiratory rate, and blood pressure. Vital signs should be recorded within 15 minutes prior to dosing, immediately after the end of infusion (+15 min), and 2 hours (± 1 h) after the end of infusion, and at the end-of-treatment visit. During the infusion, vital signs will be assessed and monitored as clinically indicated.
4. Height measurements will be performed at screening only. Body weight will be measured during the study before or on the day before each dose of study drug, at the End-of-Treatment Visit, and at the Safety Follow-up Visit. If the participant's weight changes less than ± 10% from baseline (at the time of the first dose of study treatment), the dose will be calculated using the baseline weight, otherwise the actual dose will be calculated based on the weight on the scheduled day of dosing or the day before dosing.

5. 12-lead ECG: within 7 days before the first dose in screening period, between 2.5 h and 5.5 h after the end of infusion in Cycle 1 and Cycle 4, within 3 days before administration in each cycle from Cycle 2, at the end of treatment visit, at the safety follow-up visit, and as clinically indicated. Inspections will be performed at each study site.
6. Hematology includes: red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), white blood cell count (WBC), platelet count (PLT), white blood cell differential (lymphocyte count, neutrophil count). Blood chemistry includes: liver function [total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (γ-GGT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), lactate dehydrogenase (LDH)], renal function [urea (UREA) or BUN, creatinine (Cr)], blood electrolytes (Na, K, Cl, Mg, Ca, P), amylase, lipase and fasting blood glucose (FBG). Hematology and Serum chemistry will be performed within 7 days prior to the first dose in the screening period, on Days 3 and 8/15 (± 1) of Cycle 1, within 3 days prior to dosing in each cycle from Cycle 2 onwards, at the End of Treatment Visit, Safety Follow-up Visit, and as clinically indicated. Tests will be performed at each study site.
7. Urinalysis includes: pH value (PH), specific gravity, urine white blood cells (UWBC), urine protein (UPRO), urine red blood cells (URBC), urine occult blood or occult blood (UBLD), urine glucose (UGLU). For participants with urine protein ≥ 2 + in urine routine at screening, 24-hour proteinuria test should be performed. Urinalysis will be performed within 7 days prior to the first dose in the screening period, on Day 8/15 (± 1) of Cycle 1, within 3 days prior to each dose from Cycle 2 onwards, at the End of Treatment Visit, Safety Follow-up Visit, and as clinically indicated. Tests will be performed at each study site.
8. Fecal analysis included: occult blood (OB). Stool analysis will be performed within 7 days prior to the first dose in the screening period and as clinically indicated. Tests will be performed at each study site.
9. Myocardial enzyme and Troponin: creatine kinase (CK), creatine kinase isoenzyme (CK-MB), troponin (troponin T or troponin I, this test should be consistent for the same participant during the study as far as possible). To be performed within 7 days prior to the first dose in the screening period, on Day 15 (± 1) of Cycle 1, within 3 days prior to each dose from Cycle 2 onwards, at the End of Treatment Visit, at the Safety Follow-up Visit, and as clinically indicated. For clinically significant ECG abnormalities or relevant medical history, symptoms and signs, other myocardial-related indicators, such as B-type natriuretic peptide, can be added according to the investigator's judgment. Tests will be performed at each study site.
10. Coagulation tests includes: activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), fibrinogen (Fbg), D-dimer, to be performed within 7 days prior to the first dose at screening, on Day 15 (± 1) of Cycle 1, within 3 days prior to each dose from Cycle 2 onwards, at the End of Treatment Visit, at the Safety Follow-up Visit, and as clinically indicated. Tests will be performed at each study site.
11. Women of childbearing potential will have a serum pregnancy test performed within 7 days prior to the first dose in the screening period, at the End of Treatment Visit, and at the Safety Follow-up Visit. Tests will be performed at each study site.
12. Tests for hepatitis B (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) will be performed at screening. If HBsAg and/or HBcAb are positive, HBV DNA will be further tested. HCV antibody test will be performed at screening, and if HCV antibody is positive, HCV RNA will be further tested. HIV antibody and treponema pallidum-specific antibody tests will be performed at screening. Tests will be performed at the study site within 28 days prior to the first dose of study drug during the screening period and as clinically indicated. For hepatitis B carriers, it is recommended to refer to local guidelines for prophylactic antiviral therapy and to monitor viral activity regularly during

the study.

13. Safety assessments of AEs and laboratory tests will be performed according to NCI CTCAE v5.0.
14. IBI343 will be administered IV Q3W on Day 1 of every 3 weeks (21 days). The DLT observation period will be 21 days after the first dose of study drug in the dose escalation phase of Phase Ia. Participants will receive IBI343 until disease progression, intolerable toxicity, withdrawal of consent, other reason for discontinuation of study treatment, or 24 months of treatment, whichever occurs first. In case of holidays, the corresponding visit window for study drug administration may extend to up to 7 days.
15. Response evaluation of solid tumors will be performed according to RECIST v1.1. Imaging methods include enhanced CT or MRI, including chest, abdomen and pelvic cavity. The investigator will assess the response. The same imaging technique should be used during the study for the same participant. Baseline assessments will be performed within 28 days prior to the first dose. Tumor imaging assessment will be performed every 6 weeks (± 7 days) from the first dose; After 48 weeks, tumor imaging assessments will be performed every 12 weeks (± 7 days) until initiation of new antineoplastic therapy, disease progression, withdrawal of consent, study termination, lost to follow-up, or death, whichever occurs first. Participants who discontinue study drug for reasons other than radiographic PD should undergo radiographic assessments at the End of Treatment Visit and continue to undergo radiographic assessments at the protocol-specified cycles after discontinuation.
16. Tumor tissue samples (optional): Participants provide archival or fresh baseline tumor tissue samples (5 to 10 unstained slides/participant) for central laboratory test of CLDN18.2 expression.
17. End-of-treatment visit should be performed within ± 7 days after confirmation of end of treatment. If the participant has undergone relevant examinations within 7 days prior to the end of treatment visit and does not receive any treatment drugs, it is at the discretion of the investigator whether to repeat the examinations. Imaging for confirmation of treatment discontinuation is not mandatory if the previous imaging is no more than 4 weeks away from treatment discontinuation. The Safety Follow-up Visit should be performed 30 (± 7) days after the last dose or before the initiation of new antineoplastic therapy. If the end-of-treatment visit window and the safety follow-up visit window overlap, only the end-of-treatment visit and relevant examinations should be performed, but all the examinations required for safety visit (such as immunogenicity) should be supplemented.
18. Survival Follow-up: every 90 days (± 7 days) after the Safety Follow-up Visit, telephone calls are acceptable. If safety follow-up is not performed, survival follow-up will be performed 30 days (± 7 days) after the last dose and every 90 days (± 7 days) thereafter.

Table 2. Schedule of activities (Phase Ia Dose Expansion Phase, Dose Optimization Phase and Phase Ib Study)

Stage	**Pre-screening**	**Screening**	**Treatment**			**End of Treatment / Safety Follow-up [17]**	**Survival Follow-up [18]**
			Cycle 1 (21 days/cycle)		**Cycle 2 and beyond (21 days/cycle)**		
Window (days)		**-28 ~-1**	**1**	**15 (± 1)**	**Day 1 of each cycle (± 3)**	**± 7**	**Every 90 days (± 7)**
General Study Procedures							
Informed consent[1]	X	X					
Inclusion/Exclusion Criteria		X					
Demographics/Medical history/Prior therapy[2]		X					
Vital signs[3]		X	X		X	X	
Weight/Height[4]		X	X		X	X	
Physical examination		X			X	X	
ECOG PS score		X			X	X	
12-lead ECG[5]		X	X		X	X	
Laboratory Tests							
Hematology/Serum chemistry[6]		X		X	X	X	
Urinalysis [7]		X		X	X	X	

Stage	**Pre-screening**	**Screening**	**Treatment**			**End of Treatment / Safety Follow-up [17]**	**Survival Follow-up [18]**
			Cycle 1 (21 days/cycle)		**Cycle 2 and beyond (21 days/cycle)**		
Window (days)		**-28 ~-1**	**1**	**15 (± 1)**	**Day 1 of each cycle (± 3)**	**± 7**	**Every 90 days (± 7)**
Fecal analysis[8]		X					
Myocardial enzyme and Troponin [9]		X		X	X	X	
Coagulation test [10]		X		X	X	X	
Pregnancy Test[11]		X				X	
HIV/HBV/HCV/Treponema test[12]		X					
Immunogenicity		See Table 3for details					
PK		See Table 3 for details					
Safety Assessments							
Assessment of AE [13]		X					
Concomitant Medications		X	X	X	X	X	
Survival			X				
Subsequent antineoplastic therapy						X	X
Efficacy Assessments							
Tumor Assessment[15]		X				X	

Stage	**Pre-screening**	**Screening**	**Treatment**			**End of Treatment / Safety Follow-up [17]**	**Survival Follow-up [18]**
			Cycle 1 (21 days/cycle)		**Cycle 2 and beyond (21 days/cycle)**		
Window (days)		**-28 ~-1**	**1**	**15 (± 1)**	**Day 1 of each cycle (± 3)**	**± 7**	**Every 90 days (± 7)**
Administration of Study Drug							
IBI343[14]			X		X		
Biomarkers							
Tumor tissue samples[16]	X	X					

Notes:

1. Pre-screening for participants who do not have a previous report of CLDN18.2 expression in tumor tissue in the Phase Ia dose expansion, dose optimization and Phase Ib cohorts. Participants must sign the prescreening informed consent to allow CLDN18.2 expression in tumor tissue to be tested outside the 28-day screening period. Signature of the informed consent form (ICF) during the screening period should be performed prior to any protocol-specified procedures. The results of laboratory tests and imaging examinations conducted at the study center before signing the informed consent form, which meet the time window and technical requirements during the screening period, are acceptable in order to minimize the psychological and physical trauma caused by repeated blood sampling or examination.
2. Medical history includes all active diseases, as well as any conditions diagnosed within the past 10 years and considered clinically significant by the investigator, including but not limited to hypertension, diabetes, smoking/drinking history, surgery history, drug allergy history, etc. Detailed disease information of the participant's tumor will be recorded separately. Tumor history includes disease stage (AJCC Version 8), date of diagnosis and previous treatments, including chemotherapy, radiotherapy, surgical treatment, targeted drugs, immunotherapy, etc., and the date of last administration should be recorded (oral drugs need to be recorded until the date of last administration). Other concomitant medications will be recorded within 30 days prior to the first dose of study drug.
3. Vital signs include: temperature, pulse, respiratory rate, and blood pressure. Vital signs should be recorded within 15 minutes prior to dosing, immediately after the end of infusion (+15 min), and 2 hours (± 1 h) after the end of infusion, and at the end-of-treatment visit. During the infusion vital signs will be assessed and monitored as clinically indicated.

4. Height measurements will be performed at screening only. Body weight will be measured during the study before or on the day before each dose of study drug, at the End-of-Treatment Visit, and at the Safety Follow-up Visit. If the participant's weight changes less than ± 10% from baseline (at the time of the first dose of study treatment), the dose will be calculated using the baseline weight, otherwise the actual dose will be calculated based on the weight on the scheduled day of dosing or the day before dosing.
5. 12-lead ECG: within 7 days before the first dose in screening period, between 6 h and 48 h after the end of infusion in Cycle 1 and Cycle 4, within 3 days before administration in each cycle from Cycle 2, at the end of treatment visit, at the safety follow-up visit, and as clinically indicated. Inspections will be performed at each study site.
6. Hematology includes: red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), white blood cell count (WBC), platelet count (PLT), white blood cell differential (lymphocyte count, neutrophil count). Blood chemistry includes: liver function [total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyl transferase (γ -GGT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), lactate dehydrogenase (LDH)], renal function [urea (UREA) or BUN, creatinine (Cr)], blood electrolytes (Na, K, Cl, Mg, Ca, P), amylase, lipase and fasting blood glucose (FBG). Hematology and Serum chemistry will be performed within 7 days prior to the first dose in the screening period, on Day 15 (± 1) of Cycle 1, within 3 days prior to dosing in each cycle starting from Cycle 2, at the End of Treatment Visit, Safety Follow-up Visit, and as clinically indicated. Tests will be performed at each study site.
7. Urinalysis includes: pH value (PH), specific gravity, urine white blood cells (UWBC), urine protein (UPRO), urine red blood cells (URBC), urine occult blood or occult blood (UBLD), urine glucose (UGLU). For participants with urine protein ≥ 2 + in urine routine at screening, 24-hour proteinuria test should be performed. Urinalysis will be performed within 7 days prior to the first dose in the screening period, on Day 15 (± 1) of Cycle 1, within 3 days prior to each dose from Cycle 2 onwards, at the End of Treatment Visit, Safety Follow-up Visit, and as clinically indicated. Tests will be performed at each study site.
8. Fecal analysis included: occult blood (OB). Stool analysis will be performed within 7 days prior to the first dose in the screening period and as clinically indicated. Tests will be performed at each study site.
9. Myocardial enzyme and Troponin: creatine kinase (CK), creatine kinase isoenzyme (CK-MB), troponin (troponin T or troponin I, this test should be consistent for the same participant during the study as far as possible). To be performed within 7 days prior to the first dose in the screening period, on Day 15 (± 1) of Cycle 1, within 3 days prior to each dose from Cycle 2 onwards, at the End of Treatment Visit, at the Safety Follow-up Visit, and as clinically indicated. For clinically significant ECG abnormalities or relevant medical history, symptoms and signs, other myocardial-related indicators, such as B-type natriuretic peptide, can be added according to the investigator's judgment. Inspections will be performed at each study site.
10. Coagulation tests includes: activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), fibrinogen (Fbg), D-dimer, to be performed within 7 days prior to the first dose at screening, on Day 15 (± 1) of Cycle 1, within 3 days prior to each dose from Cycle 2 onwards, at the End of Treatment Visit, at the Safety Follow-up Visit, and as clinically indicated. Tests will be performed at each study site.
11. Women of childbearing potential will have a serum pregnancy test performed within 7 days prior to the first dose in the screening period, at the End of Treatment Visit, and at the Safety Follow-up Visit. Tests will be performed at each study site.

12. Tests for hepatitis B (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) will be performed at screening. If HBsAg and/or HBcAb are positive, HBV DNA will be further tested. HCV antibody test will be performed at screening, and if HCV antibody is positive, HCV RNA will be further tested. HIV antibody and treponema pallidum-specific antibody tests will be performed at screening. Tests will be performed at the study site within 28 days prior to the first dose of study drug during the screening period and as clinically indicated. For hepatitis B carriers, it is recommended to refer to local guidelines for prophylactic antiviral therapy and to monitor viral activity regularly during the study.
13. Safety assessments of AEs and laboratory tests will be performed according to NCI CTCAE v5.0.
14. IBI343 will be administered IV Q3W on Day 1 of every 3 weeks (21 days). Participants will receive IBI343 until disease progression, intolerable toxicity, withdrawal of consent, other reason for discontinuation of study treatment, or 24 months of treatment, whichever occurs first. In case of holidays, the corresponding visit window for study drug administration may extend to up to 7 days.
15. Response evaluation of solid tumors will be performed according to RECIST v1.1. Imaging methods include enhanced CT or MRI, including chest, abdomen and pelvic cavity. The investigator will assess the response. The same imaging technique should be used during the study for the same participant. Baseline assessments will be performed within 28 days prior to the first dose. Tumor imaging assessment will be performed every 6 weeks (± 7 days) from the first dose; After 48 weeks, tumor imaging assessments will be performed every 12 weeks (± 7 days) until initiation of new antineoplastic therapy, disease progression, withdrawal of consent, study termination, lost to follow-up, or death, whichever occurs first. Participants who discontinue study drug for reasons other than radiographic PD should undergo radiographic assessments at the End of Treatment Visit and continue to undergo radiographic assessments at the protocol-specified cycles after discontinuation.
16. Tumor tissue samples (mandatory): Participants are required to provide archival or fresh baseline tumor tissue samples (5 to 10 unstained slides/participant) during pre-screening/screening period for central laboratory test of CLDN18.2 expression. Participants enrolled with results from historical tests or from the study site may provide baseline tumor tissue samples (5 to 10 unstained slides/participant) at pre-screening/screening/post-enrollment for central laboratory test of CLDN18.2 expression.
17. End-of-treatment visit should be performed within ± 7 days after confirmation of end of treatment. If the participant has undergone relevant examinations within 7 days prior to the end of treatment visit and does not receive any treatment drugs, it is at the discretion of the investigator whether to repeat the examinations. Imaging for confirmation of treatment discontinuation is not mandatory if the previous imaging is no more than 4 weeks away from treatment discontinuation. The Safety Follow-up Visit should be performed 30 (± 7) days after the last dose or before the initiation of new antineoplastic therapy. If the end-of-treatment visit window and the safety follow-up visit window overlap, only the end-of-treatment visit and relevant examinations should be performed, but all the examinations required for safety visit (such as immunogenicity) should be supplemented.
18. Survival Follow-up: every 90 days (± 7 days) after the Safety Follow-up Visit, telephone calls are acceptable. If safety follow-up is not performed, survival follow-up will be performed 30 days (± 7 days) after the last dose and every 90 days (± 7 days) thereafter.

Table 3. Phase Ia, Ib PK/Immunogenicity Sampling Schedule

Stage	**Screening**	**Treatment**														**Safety Follow-up**
Days	**-28 ~ -1**	**Dose escalation phase Cycle 1/4**										**Sparse sampling period**				**Last dose +30 days**
		D1					**D2**	**D3**	**D8**	**D15**	**D22**	**D1**			**D1-3**	
Sampling time [1]		**-1 h**	**Infusion Period**	**Infusion End**	**1h**	**6h**	**24 h**	**48 h**	**168 h**	**336 h**	**504 h**	**-1 h**	**Infusion Period**	**Infusion End**	**6-48 h**	**± 7 days**
Sampling time window				**+5 min**	**± 5 min**	**± 15 min**	**± 1 h**	**± 2 h**	**± 8 h**	**± 12 h**	**± 24 h**			**+5 min**		
IBI343			X										X			
PK[2]		X		X	X	X	X	X	X	X	X	X		X	X	
ADA[3]		X										X				X

Notes:

1. Post-infusion flushing is required, flushing time should be included in the calculation of EOI; collect EOI blood samples from side opposite to the infusion location of the IBI343.
2. PK sampling design:

   Dose escalation phase in Ia part 1:

   In Cycle 1, blood samples will be collected within 1 h before the start of infusion of IBI343, immediately after the end of infusion (+5 min), 1 h ± 5 min after the end of infusion, and 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15) after the start of infusion.

   In Cycles 2 and 3, samples will be collected within 1 h before the start of infusion, immediately after the end of infusion (+5 min).

   In Cycle 4, blood samples will be collected within 1 h before the start of infusion, immediately after the end of infusion (+5 min), 1 h ± 5 min after the end of infusion, 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15), 504 h ± 24 h (Day 22) after the start of infusion.

   In Cycles 6 and 8: Blood samples will be collected within 1 h before the start of the IBI343 infusion, immediately after the end of the infusion (+5 min).

   Dose expansion phase in Ia part 1, dose optimization phase in Ia part 2, phase Ib:

In Cycle 1, blood samples will be collected immediately (+5 min) after the end of IBI343 infusion, 6-48 h after the start of infusion.
In Cycle 2, blood samples will be collected within 1 h before the start of infusion;
In Cycle 4, blood samples will be collected within 1 h before the start of infusion, immediately after the end of infusion (+5 min), 6-48 h after the start of infusion.
In Cycle 8, 12, 18, blood samples will be collected within 1 h before the start of infusion.

3. ADA sampling design:
   Blood samples will be collected within 1 h prior to the start of IBI343 infusion in Cycles 1, 2, 4, 8, 12, and 18, and at the Safety Follow-up Visit.

Study Design

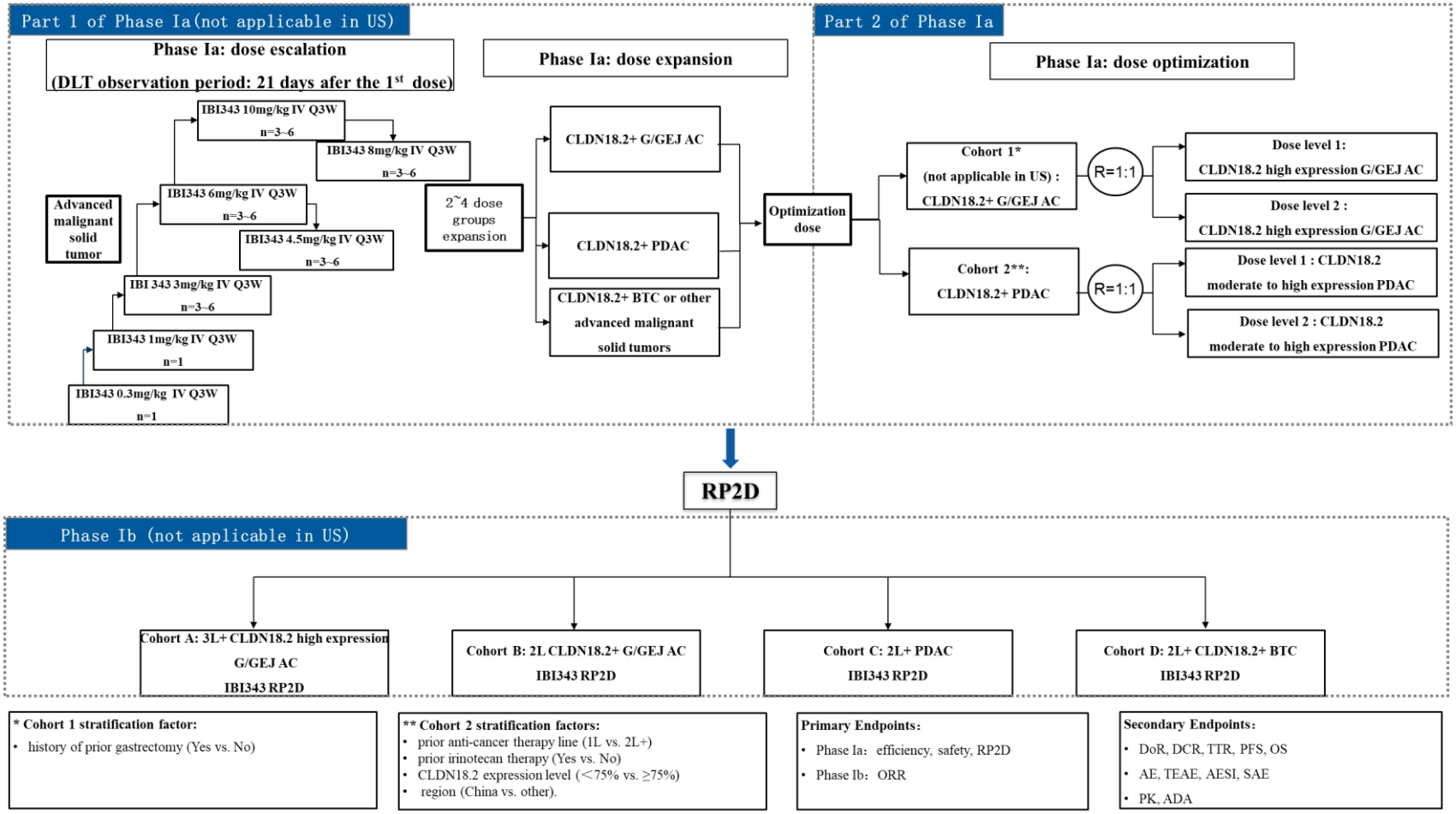

Figure 1. Study Design

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List of Abbreviations and Definitions of Terms

Abbreviations	Definition
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADCC	antibody dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
AST	aspartate aminotransferase
AUC	Area under curve
CDC	Complement dependent cytotoxicity
CI	Confidence interval
CR	complete response
CRA	clinical research association
CRO	contract research organization
CSR	Clinical study report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose limiting toxicity
DoR	Duration of response
EC	ethics committee
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EDC	electronic data capture
EEP	efficiency evaluable population
FDA	Food and Drug Administration
FIH	first in human
GCP	Good clinical practice
G/GEJ AC	Gastro/gastro-esophageal junction adenocarcinoma
HBV	Hepatitis B virus

Abbreviations	**Definition**
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
ICF	Informed consent form
INR	international normalized ratio
IRR	infusion related reaction
IV	intravenously
MAD	maximum ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAb	neutralizing antibody
NSAID	Non-steroidal anti-inflammatory drug
ORR	Overall response rate
OS	Overall survival
PAD	pharmacologically active dose
PD	progressive disease
PDAC	pancreatic ductal adenocarcinoma
PFS	Progression free survival
PK	pharmacokinetics
PR	partial response
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	stable disease
SP	Safety population
TEAE	Treatment emergency adverse event
TGI	Tumor growth inhibition
TRAE	Treatment related adverse event
TTR	Time to response
ULN	upper limit of normal value

1 Introduction

1.1 Study Background

1.1.1 Disease Background

Gastric cancer is one of the most common malignant tumors in the world and one of the deadliest cancers worldwide[1]. According to the data of GLOBOCAN [2], the incidence and mortality of gastric cancer ranked fifth and fourth respectively in 2020, and the 5-year survival rate of participants with metastatic gastric cancer was less than 5% [3]. At present, surgical resection remains the only curative treatment for gastric cancer, and chemotherapy with a combination of fluoropyrimidine and platinum is the standard treatment for participants with advanced metastatic gastric cancer. Treatment options for gastric cancer have increased with the advent of immunotherapy and targeted therapies such as trastuzumab and ramucirumab. However, the efficacy of systemic therapy for advanced gastric cancer is limited, and the median survival of participants is only about 1 year [4]. In terms of immunotherapy, based on the results of the ATTRACTION-02 study [5], nivolumab is approved in Japan for advanced gastric and gastroesophageal junction cancer after failure of at least two systemic therapies. In April 2021, based on the results of the CheckMate-649 study [6], FDA approved nivolumab in combination with fluoropyrimidine and platinum-based chemotherapy as first-line treatment for advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma, which is also the first FDA-approved first-line immunotherapy for gastric cancer. Despite the encouraging results of these studies, new therapies are needed to reach more participants with gastric cancer.

Pancreatic cancer is one of the most common malignant digestive system tumors. In 2020, there were 496,000 new cases and 466,000 deaths of pancreatic cancer worldwide, ranking the seventh among all malignancies [7]. Pancreatic cancer is often diagnosed at an advanced stage, with poor prognosis. According to the statistics of SEER (Surveillance, Epidemiology and End Results) database of National Cancer Institute, the 5-year survival rate of pancreatic cancer is only 8%, and only 28.6% participants survive over 1 year after initial diagnosis [8]. In addition, because of the high grade of malignancy, participants with pancreatic cancer often relapse despite surgical intervention, and the 5-year survival rate of participants with pancreatic cancer after radical resection is only 18-27% [9]. Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer, accounting for more than 90% of pancreatic cancer cases. Although traditional therapies such as chemotherapy, surgery and radiotherapy have been applied, no significant improvement in survival has been found. Surgical resection and chemotherapy (gemcitabine in combination with nab-paclitaxel and FOLFIRINOX) have been shown to improve survival in participants with early-stage pancreatic cancer, but these are not sufficient to treat participants with advanced pancreatic cancer [10].

Biliary tract cancer is divided into cholangiocarcinoma and gallbladder cancer. According to the anatomy, cholangiocarcinoma is divided into extrahepatic cholangiocarcinoma and intrahepatic cholangiocarcinoma. The incidence of cholangiocarcinoma is extremely low in Western countries. However, liver fluke and other parasitic infections have led to a substantial increase in cholangiocarcinoma incidence in parts of Southeast Asia and China. At the same time, recent epidemiological studies have shown that the incidence and mortality of intrahepatic cholangiocarcinoma are increasing [11]. Cholangiocarcinoma is aggressive and is usually diagnosed at an advanced stage. Most participants with cholangiocarcinoma have unresectable disease at the time of initial diagnosis, while in the few participants who are able to undergo radical surgery, the recurrence rate is very high. The 5-year survival rate for American Joint Committee on Cancer stages I, II, III, and IV is 50%, 30%, 10%, and 0%, respectively[12]. Palliative chemotherapy is the only treatment option for most participants with cholangiocarcinoma. The first-line standard treatment for participants with unresectable and metastatic biliary tract cancer is gemcitabine in combination with cisplatin. Studies of this combination regimen have shown an objective response rate of 19.5% to 26.1%, a median PFS of 5.8 to 8.0 months, and a median OS of 11.2 to 11.7 months [13][14]. There is currently no approved standard of care for participants with biliary tract cancer who have progressed after first-line systemic therapy. Pembrolizumab is approved for the treatment of MSI-H/dMMR solid tumors that have progressed after prior therapy, but because MSI-H/dMMR is rare in advanced cholangiocarcinoma, most participants are not eligible for this treatment[15].

In conclusion, gastric cancer, pancreatic cancer and biliary tract cancer are highly malignant and have poor prognosis. Systemic chemotherapy and checkpoint inhibitors have very limited efficacy and benefit in advanced gastric, pancreatic, and biliary cancers, and there is an urgent need to explore and develop new therapeutic targets and combination therapies.

1.1.2 CLDN18.2 Target Drug Development Background

Claudin, a member of the tight junction family, is a key structural and functional component of epithelial tight junctions, which can regulate cell permeability, maintain ion homeostasis, and maintain tight junctions and polarity between cells. In mammals, at least 27 Claudins (CLDNs) have been reported to exhibit different tissue-specific expression, with CLDN18 having two splice forms, CLDN18.1 and CLDN18.2. CLDN18.1 is predominantly expressed in the lung, and CLDN18.2 is predominantly expressed in differentiated epithelial cells of the gastric mucosa, and in most primary and metastatic lesions of gastric, pancreatic, and esophageal cancers [16]. CLDN18.2 is normally buried in the gastric mucosa, but the development of malignancy results in disruption of tight junctions and exposure of CLDN18.2 epitopes on the surface of tumor cells [17].

CLDN18.2 is highly expressed in gastric and pancreatic cancer tissues, the expression rate of gastric cancer participants reached 80% [18]; In pancreatic cancer, positive expression accounted for about 60%, and medium-high expression accounted for 54.6% [19]. It has been reported in the literature that the positive rate of CLDN18 in extrahepatic cholangiocarcinoma can reach 90%, and in intrahepatic cholangiocarcinoma can also reach 43% [20]. Thus, CLDN18.2 may be a potentially effective target for the treatment of CLDN18.2-positive tumors and also make CLDN18.2 a competitive target for numerous innovator drug companies. Nearly 20 pharmaceutical companies at home and abroad have begun to develop CLDN18.2 targeted drugs, including monoclonal antibodies, CAR-T therapy, antibody-drug conjugate (ADC) and bispecific antibodies.

Some targeting CLDN18.2 drugs have started clinical studies and showed good efficacy and safety. Zolbetuximab (IMAB362, claudixmab, Astellas), the first drug to be developed against the CLDN18.2 target, is a chimeric IgG1 monoclonal antibody that specifically binds to CLDN18.2 on the surface of tumor cells and causes antibody dependent cell-mediated cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), apoptosis, and inhibition of cell proliferation. Subsequently, several clinical trials have also evaluated its efficacy and safety in participants with gastroesophageal cancer.

A Phase IIa trial (NCT01197885, MONO [21]) evaluated the efficacy and safety of zolbetuximab as a single agent in 54 participants with relapsed or refractory advanced adenocarcinoma of the stomach or lower esophagus who had moderate or high CLDN18.2 expression in ≥ 50% of tumor cells. The study showed that among 43 evaluable participants, 10 participants had clinical benefit, of which 4 participants achieved partial response (PR) [objective response rate (ORR) 9%] and 6 participants (14%) achieved stable disease (SD). The median duration of response (DoR) for participants who responded to zolbetuximab was 24.6 weeks (range: 13.1 to 156.1 weeks). Of the 10 participants who achieved clinical benefit [complete response (CR) + PR + SD], 9 participants (90%) had moderate or high CLDN18.2 expression in ≥ 70% of tumor cells. Subgroup analysis of these 9 participants showed that 4 participants (14%) achieved PR and 5 participants (17%) achieved SD. Among all participants, 52 participants (96%) experienced treatment-emergent adverse events (TEAE), most of which were Grade 1 or 2. TEAE that occurred in ≥ 30% of participants included nausea (63%), vomiting (57%), fatigue (43%), and decreased appetite (30%). Grade 3 vomiting was reported in 12 participants (22%) and Grade 3 nausea was reported in 8 participants (15%). Two participants had Grade 4 TEAE: dyspnea and diarrhea (1 participant each). Treatment-related adverse events (TRAE) occurred in 44 participants (82%), with nausea, vomiting, fatigue, and decreased appetite occurring in ≥ 10% of participants. Only 5 participants experienced serious TRAE. Grade 3 and 2 TEAE (nausea and vomiting) each occurred in 1 participant, Grade 2 hematemesis in 1 participant, and Grade 3 vomiting in 2 participants. All serious TRAE occurred in participants who received the 600 mg/m2 dose,

except for 1 participant who experienced Grade 3 vomiting. These TEAE could be resolved by withholding or slowing the zolbetuximab infusion. Participants without prior gastrectomy were more likely to report nausea and vomiting. The incidence of these TEAE decreased over time as participants received repeated zolbetuximab infusions.

Another Phase II trial (NCT01630083, FAST) evaluating the efficacy and safety of zolbetuximab plus EOX versus EOX in the first-line treatment of CLDN18.2-positive advanced gastric/gastro-esophageal junction adenocarcinoma (G/GEJ AC) showed that median progression-free survival (PFS) improved from 5.3 months to 7.5 months [hazard ratio (HR), 0.44; 95% CI, 0.29-0.67; P < 0.0005]; Median overall survival (OS) increased from 8.3 months to 13.0 months (HR, 0.55; 95% CI, 0.39-0.77; P < 0.0005) [22]. The most frequently reported TEAE in the zolbetuximab plus EOX arm were nausea (81.8%) and vomiting (67.5%), with a low incidence of vomiting in participants with prior gastrectomy and a dose-dependent relationship between the incidence and severity of vomiting and zolbetuximab. The most frequently reported serious AE (SAE) in the zolbetuximab plus EOX arm were malignant neoplasm (3.9%), pneumonia (2.6%) and febrile neutropenia (2.6%), and the most frequently reported SAE in the EOX arm were malignant neoplasm (8.3%), gastric haemorrhage (3.6%) and nausea, renal failure, pulmonary embolism and febrile neutropenia (2.4% each) [22][23]. Two ongoing Phase 3 studies (NCT03504397/NCT03653507) evaluating zolbetuximab in combination with different chemotherapy regimens (mFOLFOX6 or CAPOX) versus placebo in combination with chemotherapy for the first-line treatment of CLDN18.2-positive and HER2-negative locally advanced unresectable or metastatic G/GEJ AC provide safety and efficacy data for agents that target CLDN18.2.

1.2 Study Rationale

IBI343 is a recombinant human anti-CLDN18.2 ADC composed of an IgG1 monoclonal antibody conjugated to the topoisomerase I inhibitor exatecan at the N-linked glycosylation site via a cleavable linker. Upon binding of IBI343 to CLDN18.2-expressing tumor cells, CLDN18.2-dependent internalization of the ADC occurs, followed by degradation of the cleavable linker, resulting in DNA damage by the released drug, leading to tumor cell apoptosis. The free drug can also diffuse through the plasma membrane to reach and kill neighboring cells, so IBI343 also has a bystander effect. In preclinical pharmacodynamic studies, CB17-SCID mice bearing DAN-G-Claudin18.2 tumors showed a TGI% of 55% after a single dose of IBI343 at 1 mg/kg. In the NUGC-4 (low CLDN18.2 expression) tumor-bearing CB17-SCID mouse model, IBI343-10 mg/kg treatment also significantly inhibited the growth of CB17-SCID tumor (TGI% 66.55%). In preclinical pharmacokinetic (PK) studies, IBI343 and total antibody exhibited similar PK profiles in rhesus monkeys, indicating acceptable stability in monkeys. Toxicology studies showed that the maximum tolerated dose (MTD) of IBI343 in rhesus monkeys was 60 mg/kg or 30 mg/kg after single or repeated administration. Given the robust

preclinical evidence supporting the potential efficacy of IBI343 in several tumor types and an acceptable preclinical safety profile, a dose regimen exploration trial in multiple tumor types is warranted in clinical studies.

1.3 Benefit/Risk Assessment

There is no clinical information available on participants treated with IBI343, therefore the benefit and safety profile of IBI343 has not been fully understood. Results from nonclinical studies demonstrated that IBI343 binds with high affinity to cells expressing human/rat/rhesus monkey CLDN18.2 and specifically to target-dependent internalization and potent target-mediated cell killing. A significant bystander killing effect of IBI343 was also detected. Consistent with in vitro studies, IBI343 demonstrated potent tumor growth inhibitory efficacy in both hCLDN18.2 high and low expressing mouse tumor-bearing models. Overall, the pharmacodynamic data suggest the potential clinical efficacy of IBI343 in participants with solid tumors.

Based on the nonclinical toxicology findings in rhesus monkeys, the general toxicity pattern was as follows: 1) gastrointestinal (GI) symptoms, such as vomiting, abnormal defecation, and corresponding histopathological GI changes; 2) Total protein and/or albumin loss, possibly related to gastrointestinal toxicity; 3) Hematological toxicity, especially decreased numbers of reticulocytes, neutrophils and platelets. Given that CLDN18.2 is also expressed in normal differentiated epithelial cells of the gastric mucosa and the mechanism of action of topoisomerase inhibitors, special attention should be paid to gastrointestinal toxicity and hematological toxicity.

During this trial, continuous risks assessment and periodical safety evaluation will be conducted. The trial will be terminated if any new findings indicate a risk that makes continuation of the trial unreasonable. The Safety Review Committee will continuously review clinical and laboratory safety data and decide whether to continue escalation and/or dose escalation.

To reduce potential risks, the trial is designed to detect dose limiting toxicity (DLT) and determine the MTD according to the planned dose escalation scheme of the trial. If a dose in a cohort is well tolerated, dose escalation may continue and subsequent cohorts may be enrolled to determine the recommended phase 2 dose (RP2D). Section 5 of this clinical study protocol outlines potential safety risks and mitigation strategies.

As with all first in human (FIH) dose-finding, PK/pharmacodynamic studies, there are risks associated with venipuncture and multiple blood sampling. In order to avoid additional discomfort and other potential toxic effects due to multiple venipunctures, the use of indwelling intravenous catheters was allowed in this study. The purpose of the protocol was to accurately and completely describe the PK of the study drug by collecting a minimum number of blood samples. This design minimizes the number of venipunctures and the total volume of blood taken.

2 Study Objectives and Endpoints

Objectives and Endpoints of the Phase Ia part 1:

Study Objectives	**Study Endpoints**
Primary Objective	Primary Endpoints
● To assess the safety and tolerability of IBI343 in participants with advanced malignant solid tumors. ● To determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of IBI343.	● Incidence, severity, and relationship to the study drug of all adverse events, treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs) and serious adverse events (SAEs), etc. Changes in laboratory tests, physical examination, vital signs, etc. after the administration of the study drug. ● Dose-limiting toxicities (DLT).
Secondary Objectives	Secondary Endpoints
● To assess the pharmacokinetic (PK) profile of IBI343, total anti-tight junction protein 18.2 (CLDN18.2) antibodies, and exatecan. ● To assess the immunogenicity of IBI343. ● To assess the preliminary efficacy of IBI343.	● Major PK parameters after single and multiple doses, including but not limited to: area under the curve (AUC), maximum concentration (C_{max}), time to maximum concentration (T_{max}), trough concentration (C_{trough}), clearance (CL), volume of distribution (V) and half-life ($t_{1/2}$). ● The incidence of anti-drug antibody (ADA). ● Preliminary efficacy: objective response rate (ORR), duration of response (DoR), disease control rate (DCR), time to response (TTR), and progression-free survival (PFS) evaluated according to RECIST v1.1. and overall survival (OS)
Exploratory Objectives	Exploratory Endpoints
● To evaluate the correlation between CLDN18.2 expression level in tumor tissue and anti-tumor activities of IBI343.	● Baseline CLDN18.2 expression level in tumor and relationship with efficacy.

Objectives and endpoints of the Phase Ia part 2:

Study Objectives	**Study Endpoints**
Primary Objective	Primary Endpoint

● To determine RP2D of IBI343. ● ORR assessed by the investigator based on RECIST version 1.1.	● ORR assessed by the investigator based on RECIST version 1.1. ● Incidence, severity, and relationship to the study drug of all adverse events, TEAEs, AESIs and SAEs, etc. Changes in laboratory tests, physical examination, vital signs, etc. after the administration of the study drug.
Secondary Objectives	Secondary Endpoints
● To assess the preliminary efficacy of IBI343. ● To assess the population pharmacokinetic (PK) profile of IBI343, total anti-CLDN18.2 antibodies, and exatecan. ● To assess the immunogenicity of IBI343.	● Efficacy endpoints: DoR, DCR, TTR, and PFS evaluated according to RECIST v1.1, and OS. ● Major PK parameters, including but not limited to: AUC, C_{max}, T_{max}, C_{trough}, CL, V, and $t_{1/2}$. ● The incidence of ADA.
Exploratory Objectives	Exploratory Endpoints
● To evaluate the correlation between CLDN18.2 expression level in tumor tissue and anti-tumor activities of IBI343.	● Baseline CLDN18.2 expression level and relationship with efficacy.

Objectives and Endpoints of Phase Ib

Study Objectives	**Study Endpoints**
Primary Objective	Primary Endpoint
● To evaluate the efficacy of IBI343 in participants with advanced gastric/gastroesophageal junction adenocarcinoma.	● ORR as assessed by the Independent Radiological Review Committee (IRRC) according to RECIST v1.1 criteria in Cohort A.
Secondary Objectives	Secondary Endpoints
● To evaluate the efficacy of IBI343 in participants with advanced gastric/gastroesophageal junction adenocarcinoma using other efficacy measures.	● ORR as assessed by the investigator per RECIST v1.1 criteria in Cohort A. ● DoR, DCR, TTR, PFS as assessed by IRRC and investigator per RECIST v1.1 in Cohort A.

● To evaluate the efficacy of IBI343 in participants with advanced pancreatic ductal adenocarcinoma, biliary tract cancer, and other tumor types. ● To assess the safety and tolerability of IBI343 in participants with advanced malignant solid tumors. ● To assess the PK profile of IBI343, CLDN18.2 antibody, and exatecan. ● To assess the immunogenicity of IBI343.	● ORR, DoR, DCR, TTR, PFS as assessed by the investigator according to RECIST v1.1 in Cohorts B/C/D. ● OS. ● Incidence of AE, TEAE, AESI, SAE, etc., and relationship with the study drug; Changes of laboratory tests, physical examination and vital signs after the administration of the study drug. ● Major PK parameters, including but not limited to: AUC, C_{max}, T_{max}, C_{trough}, CL, V, and $t_{1/2}$. ● The incidence of ADA.

3 Study Design

3.1 Overall Design

3.1.1 Study Design

This is a Phase Ia/Ib, multicenter, open-label, first-in-human study to evaluate the safety, tolerability, PK, and efficacy of IBI343 in participants with locally advanced unresectable or metastatic solid tumors. It is planned to be carried out in different countries or regions such as China, Australia and US. There are two parts in phase Ia, part 1 includes dose escalation and expansion phase, and part 2 is designed for dose optimization.

Phase Ia

Part 1 (not applicable in US)

Dose Escalation Phase

The phase Ia dose escalation phase will enroll participants with advanced malignant solid tumors who have failed or were intolerant to standard treatment or have no standard treatment, mainly focusing on participants with gastric/gastro-esophageal junction adenocarcinoma (G/GEJ AC) or pancreatic ductal adenocarcinoma (PDAC). The dose escalation will use accelerated titration combined with classical "3 +3" design. The 5 dose groups intended for dose escalation are 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg, respectively. The accelerated titration will be used for 0.3 mg/kg and 1 mg/kg dose groups, and the classical "3 +3" dose escalation design will be used for subsequent dose groups. IBI343 will be administered intravenously (IV) Q3W on Day 1 of every 3 weeks (21 days). The DLT observation period is 21 days after the first dose. After all participants receiving the current highest dose will have been observed for at least 21 days, the decision on whether to continue dose escalation will be made based on the safety data obtained during the DLT observation period.

In the accelerated titration phase, 1 participant will be enrolled and treated with IBI343 0.3 mg/kg firstly. If no ≥ Grade 2 treatment-related adverse event (TRAE) occurs during

the DLT observation period, 1 participant will be enrolled and treated with 1 mg/kg. If no ≥ Grade 2 TRAE occurs during the DLT observation period, subsequent dose levels (3 mg/kg, 6 mg/kg and 10 mg/kg) will follow the classical "3 +3" dose escalation design; If a participant in the accelerated titration phase experienced ≥ Grade 2 TRAE during the DLT observation period, the classical "3 +3" dose escalation will start at that dose level.

The classic "3 +3" dose escalation design is as follows: 3 participants will be enrolled in each dose group first, and if none of these 3 participants experience DLT during the DLT observation period, the next higher dose group will be administered. If 1 of the first 3 participants experiences DLT, another 3 participants will be included in the same dose group; If no DLT occurs in the additional 3 participants, the administration of the next higher dose group will be started; If DLT occurs in ≥ 1 of the additional 3 participants or ≥ 2 of the total 6 participants, or ≥ 2 of the first 3 participants, the dose is defined as intolerable, and no further dose escalation will be allowed; At the same time, the former lower dose group will be supplemented to 6 participants until the MTD is determined. It is allowed to explore the intermediate dose between the intolerable dose and the previous lower dose according to the "3 +3" design to determine the MTD more precisely. For example, if > 1 participant in the 6 mg/kg dose group experiences a DLT during the DLT observation period, 4.5 mg/kg will be explored according to the "3 +3" design; If > 1 participant in the 10 mg/kg dose group experiences a DLT during the DLT observation period, the 8 mg/kg dose group will be explored according to "3 +3". If ≤ 1 participant in the anticipated highest dose of 10 mg/kg experienced a DLT, a higher dose was allowed to be further explored to determine the MTD after adequate discussion of the safety, toxicity, and PK data between the sponsor and the investigator.

No intra-participant dose escalation will be allowed throughout the dose escalation phase. After completion of the DLT observation period and confirmation of safety, participants will continue treatment with the current IBI343 dose group regimen until disease progression, intolerable toxicity, withdrawal of consent, other reason for discontinuation of study treatment, or 24 months of treatment, whichever occurs first. After discontinuation of treatment, participants will be followed for safety and survival. After the DLT observation period, participants will continue to be observed for safety and tolerability.

During the study, the investigator and the sponsor will jointly review and evaluate the safety, PK and efficacy data to decide whether to explore the next dose group and whether to adjust the dose escalation scheme (e.g., dose level, number of dose groups, dosing cycle, etc.).

In the Phase Ia dose escalation phase, countries will compete for enrollment.

Dose Expansion Phase

If participants in a dose group in the dose escalation phase have completed the DLT

observation period and confirmed safety and tolerability, the sponsor may request that this dose and/or doses below this dose level (4.5 mg/kg Q3W if the dose is 6 mg/kg Q3W and above; 8 mg/kg Q3W if the dose is 10 mg/kg Q3W) be allowed to expand enrollment based on safety, efficacy and/or PK data to further characterize the safety, PK profile and preliminary efficacy of IBI343 and to determine the RP2D.

The dose expansion phase will include participants with CLDN18.2-positive advanced malignant tumors who have failed or were intolerant to the following standard therapies or for whom no standard therapies are available:

G/GEJ AC: preferentially enroll participants with moderate to high CLDN18.2 expression (Claudin18.2 immunohistochemical membrane staining intensity ≥ 2 + in ≥ 40% of tumor cells);

PDAC, preferentially enroll participants with moderate to high expression of CLDN18.2 (Claudin18.2 immunohistochemical membrane staining intensity ≥ 2 + in ≥ 40% of tumor cells);

CLDN18.2-positive Biliary Tract Cancer or other solid tumors.

For each tumor type, it is planned to select 2 ~ 4 doses for expansion, and about 6 ~ 60 participants are planned to be enrolled at each expanded dose. The tumor type, dose, timing, and region to initiate dose expansion will be determined by the sponsor, and the CLDN18.2 expression level of enrolled participants will be adjusted according to the study progress. Real-time safety monitoring will be performed for each dose group in the dose expansion phase using the Bayesian toxicity monitoring method. The parameters of the Bayesian toxicity monitoring method are set as follows: the maximum probability of significant adverse events of interest to the sponsor in each dose group is not more than 20%, the Bayesian prior distribution is (1, 1), the minimum sample size at the time of implementation of the monitoring method is 6 cases, and the Bayesian posterior probability is > 80%. Significant adverse events of interest to the sponsor are defined as adverse events related to the study drug that meet the 5 categories of DLT specified in the protocol.

During the course of the study, the investigator and the sponsor will discuss together to determine the dose and number of participants enrolled in the dose expansion phase.

Table 4. Real-time safety monitoring of each dose group in dose expansion phase-Bayesian toxicity monitoring method

Safety Evaluable Cases	6	7 ~ 10	11 ~ 14	15 ~ 19	20 ~ 23	24 ~ 27	28 ~ 31	32 ~ 36	37 ~ 40	41-45	46 ~ 49	50 ~ 54	55 ~ 58	59 ~ 60
Number of participants with significant	⩾ 2	⩾ 3	⩾ 4	⩾ 5	⩾ 6	⩾ 7	⩾ 8	⩾ 9	⩾ 10	⩾ 11	⩾ 12	⩾ 13	⩾ 14	⩾ 15

adverse events of interest to the sponsor														

Participants will continue treatment with IBI343 until disease progression, intolerable toxicity, withdrawal of consent, other reason for discontinuation of study treatment, or 24 months of treatment, whichever occurs first. In the Phase Ia dose expansion phase, participants will be allowed to receive higher than the starting dose of IBI343 from the second cycle based on the safety, tolerability and preliminary efficacy observed in the study after communication between the investigator and the sponsor, but this dose must be the safe dose assessed for DLT in the dose escalation phase. After discontinuation of treatment, participants will be followed for safety and survival.

Part 2

Dose Optimization Phase

The dose optimization phase may be initiated under comprehensive discussion between Sponsor and Investigator. Randomized, parallel cohorts may be designed to determine the optimal dose for further parts if needed. The study will be conducted in advanced G/GEJ AC and PDAC participants with CLDN18.2 expression. Approximately 50-60 participants with G/GEJ AC from China and 30-40 participants with PDAC are planned to be enrolled in China, US and Australia.

For each tumor type, participants will be randomized in a 1:1 ratio to 2 different dose groups:4.5mg/kg and 6mg/kg, which will be selected by the sponsor based on the emerging clinical data.

G/GEJ AC (not applicable in US)

Preferentially enroll participants with high CLDN18.2 expression (Claudin18.2 immunohistochemical membrane staining intensity ≥ 2 + in ≥ 75% of tumor cells). Stratification factor is history of prior gastrectomy (Yes vs No).

PDAC (If applicable)

Preferentially enroll participants with moderate to high expression of CLDN18.2 (Claudin18.2 immunohistochemical membrane staining intensity ≥ 2 + in ≥ 40% of tumor cells). The randomization stratification factors include: prior anti-cancer therapy line (1L vs. 2L+), prior irinotecan therapy (Yes vs. No), and CLDN18.2 expression level (< 75% vs. ≥75%), region (China vs. other).

Participants will continue treatment with IBI343 until disease progression, intolerable toxicity, withdrawal of consent, other reason for discontinuation of study treatment, or 24 months of treatment, whichever occurs first. After discontinuation of treatment, participants will be followed for safety and survival.

Phase Ib (not applicable in US)

After the RP2D and preliminary efficacy have been determined by the investigator and

the sponsor based on the results of the Phase Ia study, a Phase Ib study to evaluate the efficacy and safety of IBI343 monotherapy in participants with advanced malignant solid tumors will be initiated at the request of the sponsor. The timing of initiation of each study cohort in Phase Ib will be determined by joint discussion between the sponsor and the investigator.

The following cohorts are planned for Phase Ib, **sponsor will submit a protocol amendment should the sample size increase beyond the number specified in each of the cohorts below:**

Cohort A: Approximately 50 participants with advanced G/GEJ AC with high CLDN18.2 expression (Claudin18.2 immunohistochemical membrane staining intensity ≥ 2 + in ≥ 75% of tumor cells) who have received at least 2 prior lines of systemic therapy and have progressed are planned to be enrolled.

Cohort B: Approximately 50 participants with CLDN18.2-positive advanced G/GEJ AC who have failed first-line standard therapy are planned to be enrolled.

Cohort C: Participants with advanced PDAC who have received at least one systemic therapy and have progressed, and approximately 50 participants are planned to be enrolled (including the number of participants who received the RP2D in the dose expansion phase Ia).

Cohort D: Approximately 50 participants with CLDN18.2-positive advanced BTC who have failed at least one systemic therapy (including the number of participants who received the RP2D in dose expansion phase Ia) are planned to be enrolled.

Participants will continue treatment with IBI343 until disease progression, intolerable toxicity, withdrawal of consent, other reason for discontinuation of study treatment, or 24 months of treatment, whichever occurs first. After discontinuation of study treatment, participants will be followed for safety and survival.

During the course of the study, participants in Phase Ib Cohort A will undergo radiological assessment by IRRC and investigator according to RECIST v1.1; Participants in Phase Ia and Phase Ib B/C/D cohorts will undergo radiographic assessments by the investigator according to RECIST v1.1.

3.1.2 Dose limiting toxicity

Toxicity evaluation will be performed according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. DLT is defined as any of the following AEs (unless clearly attributable to underlying disease or an extraneous event) within 21 days after the first dose in the dose escalation phase of Phase Ia:

1. **Hematologic Toxicity**

- Grade 4 neutrophil count decreased lasting > 7 days

- Grade ≥ 3 febrile neutropenia [absolute neutrophil count (ANC) < 1×10^9/L and a single temperature > 38.3 ℃ or a sustained temperature ≥ 38.0 ℃ for more than 1 hour]
- Grade 4 anemia that cannot be explained by underlying disease
- Grade 4 platelet count decreased
- ≥ Grade 3 decreased platelet count lasting > 7 days
- ≥ Grade 3 platelet count decreased with bleeding
- Grade 4 lymphocyte count decreased lasting ≥ 14 days

2. Hepatotoxicity

- Grade 4 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation
- AST or ALT > 5 × upper limit of normal (ULN), if accompanied by≥ Grade 2 elevated total bilirubin (TBIL)In participants without liver metastases, AST or ALT > 5 × ULN lasting > 7 days following optimal therapy
- In participants with liver metastases, AST or ALT > 5 × ULN lasting > 7 days following optimal therapy, if baseline ≤ 3 × ULN
- In participants with liver metastases, AST or ALT > 8 × ULN lasting > 7 days following optimal therapy if baseline > 3 × ULN

3. Non-hematological, non-hepatotoxic

1）Any Grade ≥ 3 non-hematologic, non-major hepatotoxicity (other than laboratory abnormalities) with the following exceptions:

- Grade 3 arthralgia
- Grade 3 myalgia
- Grade 3 rash
- Grade 3 alopecia
- Grade 3 fatigue/asthenia
- Grade 3 hypertension or hypotension
- Grade 3 nausea, vomiting, diarrhea, or anorexia that resolves to ≤ Grade 2 within 3 days with best supportive care

2）Any Grade ≥ 3 non-hematologic, non-major hepatotoxicity laboratory abnormality that requires treatment or results in hospitalization, with the

following exceptions:

- Grade 3 Electrolyte Abnormalities
- Grade 3 gamma-glutamyl transferase (GGT) increased
- Asymptomatic laboratory abnormalities including Grade 3/4 alkaline phosphatase increased, hyperuricemia, serum amylase increased, and lipase increased

4. **Any Grade 5 AE**
5. **Other AE determined to be DLT after discussion between the investigator and the sponsor**

Notes:

- Grade 3 or 4 infusion related reaction (IRR) is not considered as DLT. However, in the event of a Grade 3 or 4 IRR, the participant will be discontinued from study treatment and replaced with a new participant. If ≥ 2 participants in a dose group experience a Grade 3 or 4 IRR, enrollment must be suspended, and the sponsor will need to review the safety data of the study to determine whether to continue enrollment.
- The above criteria will be used to make individual participant determinations regarding dose delays or discontinuation assess throughout the course of the trial. However, only those DLTs occurring during the DLT observation period after the first dose will determine dose escalation and tolerability.
- If any of the above toxicities occur during the DLT observation period, whether or not the toxicity is regarded as a DLT will be determined based on the consultation between the investigator and the sponsor. In addition, for other toxicities affecting study drug treatment, whether or not the toxicity is regarded as a DLT will be determined based on the consultation between the investigator and the sponsor.
- "Adverse events are lasting > 7 days following optimal therapy" means "despite optimal therapeutic intervention, the adverse events are lasting > 7 days".

3.1.3 DLT Evaluable Participants

DLT evaluable participants will be required to meet any of the following criteria:

1. The DLT occurred in the DLT observation window.
2. Received ≥ 75% of the scheduled dose for the first dose and completed the DLT observation window.

Participants who do not meet one of the above conditions need to be enrolled in a new participant supplement.

3.1.4 Maximum tolerated dose

MTD is defined as the maximum dose at which ≤ 1/6 participants experience DLT during the DLT observation period (21 days) in the dose escalation phase of Phase Ia, and only when there are at least 6 DLT-evaluable participants in this dose group can it be confirmed. If ≤ 1/6 participants in the highest dose group expected to undergo dose escalation experience a DLT, this dose level will be defined as the maximum ascending dose (MAD).

3.1.5 Recommended Phase 2 Dose

The RP2D will be assessed and determined overall based on the MTD and safety, tolerability, PK, and efficacy data collected during the course of the study.

3.2 Rationale for Dose Selection

Considering the pharmacologically active dose (PAD) and toxicological findings, 0.3 mg/kg was selected as the recommended FIH dose selection based on the following rationale:

✧ **Pharmacokinetics**

- CLDN 18.2 is not an immune agonist target and toxicology data from this study showed no evidence or evidence of immune activation with IBI343. The tolerance threshold established for IBI343 in single-and repeat-dose studies exceeded 30 mg/kg in different species (rats and monkeys). Therefore, the MABEL method is not considered appropriate for the calculation of the FIH starting dose.
- In the DAN-G-Claudin18.2 tumor bearing CB17-SCID mouse model, the TGI% after a single dose of 1mg/kg IBI343 was 55%, representing the PAD level of the drug in this model. Based on the plasma concentrations measured by this model, the AUC at this dose level was calculated to be 1209 mg • h/mL, and the corresponding human equivalent dose was calculated to be 0.53 mg/kg (based on allometric scaling) to 1 mg/kg (body weight conversion). The sub-efficacious dose (0.3 mg/kg) was selected as the clinical starting dose of IBI343 from a safety perspective.
- In the 3-week dose range-finding study in rhesus monkeys, the MTD after a single dose was determined to be 60 mg/kg. FIHD of 0.3 mg/kg with a safety range of at least 64-fold (body surface area) to 200-fold (body weight); In the same species, 6-week repeat-dose toxicity established an HNSTD of 30 mg/kg, which represents a safety margin of 32 times (body surface area) to 100 times (body weight) the selected FIHD.

- In a 6-week repeat-dose study in Sprague-Dawley rats, the HNSTD after 3 consecutive doses was determined to be 60 mg/kg, and the safety range was 32 times (body surface area) to 200 times (body weight) the selected FIHD.

In conclusion, the selection of 0.3 mg/kg as the first-in-human dose of IBI343 provides an adequate safety margin.

Also, 10 mg/kg was selected as the proposed MTD for this study based on the following rationale:

- According to the study results of IBI343 in CB17-SCID mice bearing DANG-CLDN18.2 tumors, tumor growth was significantly inhibited 28 days after inoculation with DAN-G-Claudin18.2 cells, compared with h-IgG-Exatecan-10 mg/kg group and IBI343-10 mg/kg group, with a tumor inhibition rate of 108.72%, and no significant adverse reactions were observed. No significant body weight changes were observed at the highest dose, indicating a good safety profile.
- In rhesus monkeys, the HNSTD was determined to be 30 mg/kg for 6-week repeat-dose toxicity and the MTD after a single dose was determined to be 60 mg/kg, both doses tested being well above the proposed MTD in this study.

For phase Ia Part 2, based on the emerging clinical data (clinical data cut-off: Oct 13, 2023 PK data cut-off: July 28, 2023), 4.5 mg/kg and 6 mg/kg were selected for dose optimization:

- In 1-6 mg/kg, the exposure-safety relationship is flat and the overall safety of 6 mg/kg is favorable. When the dose was > 6 mg/kg, the exposure-safety relationship was steep and the safety risk increased significantly.
- The evaluation of exposure-efficacy relationship showed that the probability of PR had no significant trend of exposure dependence in the dose range of 3-6 mg/kg, and the probability of PR reached the plateau. The probability of DC was significantly exposure-dependent, and it reached plateau at the dose of 6 mg/kg.
- To optimize the clinical dose, 4.5 mg/kg and 6 mg/kg were selected to further assess the clinical efficacy and safety.

✧ **Clinical Safety**

Based on the clinical data from the phase Ia Part 1, the dose of IBI343 8 mg/kg was generally safe and tolerated. An increase in the frequency of severe AEs, dose reduction, dose interruption, and study drug discontinuations were observed with the increase in dose from 3 to 8 mg/kg. The most common AEs were hematological events and gastrointestinal events, which are consistent with the mechanism of action of the study drug IBI343.

✧ **Clinical efficacy**

Anti-tumor activity was observed at the doses of 3, 6 and 8 mg/kg. As of January 15, 2024, in the dose expansion phase, for participants with CLDN18.2 high expression (defined as ≥75% tumor cells with membranous staining intensity ≥2+ by IHC) G/GEJC, participants in 3 mg/kg cohort had lower ORR and DCR. However, the ORR and DCR in 6 mg/kg dose group and 8 mg/kg dose group are not significantly different, and both are higher than 3 mg/kg cohort.

Participants in 6 mg/kg and 8 mg/kg cohorts had similar efficacy and favorable safety profile. However, subjects in 8 mg/kg cohort had higher incidence of ≥G3 TEAE and TRAE and earlier onset of hematological events. Based on the comprehensive analysis of the clinical safety, efficacy and PK of IBI343, 6 mg/kg and the lower dose 4.5 mg/kg were selected as the proposed dose regimens for the dose optimization part.

3.3 Rationale for Biomarker Analysis

IBI343 is a conjugate of an anti-CLDN18.2 antibody and a small-molecule cytotoxic drug. IBI343 exerts its antitumor effect by binding to the CLDN18.2 protein expressed on the tumor cell membrane and then endocytosing into cells. Preclinical data suggest that tumor growth inhibition by IBI343 correlates with CLDN18.2 expression levels, and it is necessary to explore the relationship between CLDN18.2 expression and efficacy of IBI343 in clinical studies.

In this study, CLDN18.2 expression in tumors will be assessed using the CLDN18 IHC method. CLDN18.2 and CLDN18.1 can be detected by this method, but according to the TCGA database analysis, CLDN18.2 is specifically highly expressed in gastric and pancreatic cancers, and CLDN18.1 is hardly expressed in these two types of tumors. In summary, the detection results of this method can specifically indicate the expression level of CLDN18.2 in gastric and pancreatic cancer[24]. In addition, in the zolbetuximab FAST (NCT01630083) study, this assay was used to measure CLDN18.2 expression levels and enrolled CLDN18.2-positive participants according to the results of this assay [22], and clinical study results demonstrated that CLDN18.2-positive participants achieved efficacy with zolbetuximab treatment [25].

3.4 Definition of End of Study

The end of the study is defined as the last participant has completed the last study-related assessment, or at the discretion of the Sponsor, whichever occurs first.

If a participant is lost to follow-up, withdraws consent to participate in the study, or dies, the participant is considered to have completed the study.

3.5 Study Termination

The Sponsor reserves the right to close the study site, suspend or prematurely terminate the study for sufficiently reasonable reasons.

Reasons that may warrant suspension or early termination of the study include, but are not limited to:

- Incomplete and/or insufficient data for assessment
- Inability to meet the requirements for protocol compliance
- Determine that there is an unexpected, significant, or unacceptable risk to the participant
- Changing or stopping the development of the study drug
- Justification on efficacy that the study should be terminated/suspended
- Intolerable at lowest dose level

The study will be continued only if issues related to safety, protocol compliance, and data quality are addressed and the requirements of the EC and/or the National Medicines Administration are met.

If the sponsor decides no longer to supply study drug, sufficient notification will be made to allow appropriate adjustments to the participant's treatment.

3.6 Safety Evaluation Team

The Safety Evaluation Team (SET) will consist of investigators and sponsor staff, including the Clinical Medical Director, Clinical Research Physician, Clinical Research Associate (CRA), Pharmacovigilance Safety Physician, Biostatistician, Data Management Specialist, Clinical Pharmacologist (if needed), Translational Medicine Specialist (if needed), etc. Safety evaluation team discussion will be triggered when a DLT review meeting or an urgent safety event occurs during the study.

4 Study Population

4.1 Inclusion Criteria

Participants must meet all of the following criteria to participate in the study:

Enrollment criteria to be met for both Phase Ia and Phase Ib:

1. Has signed written Informed Consent Form (ICF), willing and able to comply with protocol-specified visits and related procedures.
2. Phase Ia dose escalation phase: Has at least 1 evaluable lesion according to RECIST v1.1; Phase Ia dose expansion and dose optimization phase, Phase Ib: Has at least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors RECIST v1.1.
3. Age ≥ 18 years, of either sex.
4. Has an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0

or 1.

5. Has an expected survival ≥ 12 weeks.
6. Has adequate bone marrow and organ function. Defined as:
    - Hematology: ANC ≥ 1.5 × 10^9/L; Platelet count ≥ 100 × 10^9/L; Hemoglobin ≥ 9.0 g/dL, participants must not have received transfusion of blood products (including red blood cell suspension, apheresis platelets, cryoprecipitate, etc.), erythropoietin (EPO), G-colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) within 7 days prior to blood sample collection;
    - Hepatic function: TBIL ≤ 1.5 × ULN (TBIL ≤ 3 × ULN is allowed for participants with Gilbert's syndrome); ALT and AST ≤ 2.5 × ULN for participants without liver metastasis and ≤ 5 × ULN for participants with liver metastasis; Albumin ≥ 28 g/L;
    - Renal function: creatinine clearance ≥ 60 mL/min (using the Cockcroft-Gault formula).
    - Coagulation function: international normalized ratio (INR) ≤ 1. 5 and activated partial thromboplastin time (APTT) ≤ 1. 5 × ULN (participants receiving anticoagulant therapy with coagulation function within the above range are allowed).
7. Female participants of childbearing potential or male participants whose partners are female of childbearing potential are required to use effective contraceptive measures throughout the final treatment period and for 6 months after the treatment period.

Inclusion Criteria for Phase Ia Dose Escalation:

1. Participants with histopathologically confirmed unresectable locally advanced or metastatic malignant solid tumors that have failed or were intolerant to standard therapy or for whom no standard therapy is available.

Inclusion Criteria for Phase Ia Dose Expansion and Dose Optimization:

1. Participants with histopathologically confirmed unresectable locally advanced or metastatic G/GEJ AC, PDAC, BTC, or other solid tumors who have failed or were intolerant to standard therapy or for which no standard therapy is available.
2. * CLDN18. 2 positive confirmed by pathological examination (in dose expansion phase, G/GEJ AC and PDAC preferentially enrolled *** moderate to high expression of CLDN18. 2； in dose optimization phase, G/GEJ AC preferentially enrolled **high expression of CLDN18.2 and PDAC preferentially enrolled moderate to high expression of CLDN18.2).

Enrollment Criteria for Phase Ib Cohort A:

1. Histopathologically confirmed unresectable locally advanced or metastatic G/GEJ AC.
2. Have received at least 2 lines of systemic therapy [anti-PD-(L) 1 + platinum, fluoropyrimidines, paclitaxel/docetaxel, or irinotecan; participants with HER2 overexpression (defined as 3 + or 2 + by immunohistochemistry and ISH +) must have received anti-HER2 therapy, and participants who have not received prior anti-PD-(L) 1 or anti-HER2 therapy must have had a contraindication or reasonable reason for no benefit] and have had disease progression.
3. High expression of **CLDN18. 2 was confirmed by pathological examination.

Enrollment Criteria for Phase Ib Cohort B:

1. Histopathologically confirmed unresectable locally advanced or metastatic G/GEJ AC.
2. Disease progression after first-line standard therapy (HER2-overexpressing participants must have received prior anti-HER2 therapy unless contraindicated or justified non-benefit).
3. Confirmed * CLDN18. 2 positive by histopathological examination.

Enrollment Criteria for Phase Ib Cohort C:

1. Histopathologically confirmed unresectable locally advanced or metastatic PDAC.
2. Disease progression after at least one prior systemic therapy.

Enrollment Criteria for Phase Ib Cohort D:

1. Histopathologically confirmed unresectable locally advanced or metastatic BTC.
2. Disease progression after at least one prior systemic therapy.
3. Confirmed * CLDN18. 2 positive by histopathological examination.

Notes:

* CLDN18.2-positive: defined as ≥ 1% of tumor cells with membranous staining of any intensity in tumor tissue by immunohistochemistry, when tested previously, at the study site, or at the central laboratory.

** High expression of CLDN18.2: Claudin18.2 immunohistochemical membrane staining intensity ≥ 2 + in ≥ 75 % of tumor cells.

*** Moderate to high expression of CLDN18.2: Claudin18.2 immunohistochemical membrane staining intensity ≥ 2 + in ≥ 40% of tumor cells.

4.2 Exclusion Criteria

Participants will not be enrolled in the study if any of the following criteria are met:

Exclusion criteria common to Phases Ia and Ib:

1. Is participating in another interventional clinical study other than an observational (non-interventional) clinical study or is in the survival follow-up phase of an interventional study.
2. Has received the Last dose of antineoplastic therapy within 4 weeks or 5 half-lives of an antineoplastic therapy, whichever is shorter, prior to the first dose of study drug.
3. Plans to receive other anti-tumor therapy during treatment with the study drug [palliative radiotherapy for symptomatic relief (e.g., pain) that does not affect response assessment is allowed].
4. Has received a strong cytochrome P450 3A4 (CYP3A4) inhibitor within 2 weeks or 5 half-lives (whichever is longer) prior to the first dose of study drug.
5. Has received Vaccination with any live vaccine within 4 weeks prior to the first dose of study drug or planned during the study.
6. Toxicities due to prior therapy that have not recovered to NCI CTCAE v5.0 Grade 0 or 1 per NCI CTCAE v5.0 prior to the first dose of study drug (excluding alopecia, asthenia, hyperpigmentation, and other conditions with no safety risk, per the judgment of the investigator).
7. Has undergo Any major surgical procedure (craniotomy, thoracotomy, laparotomy or others per the investigator, excluding needle biopsy) or has unhealed wounds, ulcers, or bone fracture within 4 weeks prior to the first dose of study drug; Or plans to undergo major surgery during the study period; Note: Local surgical treatment of isolated lesions for palliative purposes is acceptable.
8. Has received whole pelvic radiotherapy.
9. Has gastric pyloric obstruction and/or persistent recurrent vomiting ($\geqslant$ 3 episodes in 24 hours).
10. Has a history of gastrointestinal perforation and/or fistula within 6 months that has not resolved surgically prior to the first dose of study drug.
11. Has symptomatic central nervous system metastases. Participants with asymptomatic brain metastases (i.e., no neurological symptoms, no need for glucocorticoid treatment, all brain metastasis $\leqslant$ 1. 5 cm) or stable symptoms after treatment of brain metastasis must meet all of the following criteria to participate in the study: no metastasis in the midbrain, pons, cerebellum, meninges, medulla oblongata or spinal cord; Stable clinical status for at least 4 weeks with definitive clinical evidence of no

new or enlarging brain metastases and discontinuation of corticosteroids and anticonvulsants for at least 2 weeks prior to the first dose of study drug. Note: lesions of the central nervous system will not be considered as a target lesion.

12. Has a history of pneumonitis requiring corticosteroids therapy, or a history of interstitial lung disease, non-infectious pneumonitis, severely impaired lung function or uncontrolled lung disease, such as pulmonary fibrosis, severe radiation pneumonitis, acute lung injury, or suspected of having the above diseases during the screening period.
13. Has uncontrolled medical conditions such as:
    - Active or clinically uncontrolled serious infection requiring treatment with systemic anti-infectives (antibiotics, antivirals, or antifungals) within 1 week prior to the first dose of study drug, including but not limited to the infection of respiratory tract, urinary system, biliary tract infection, etc.
    - Participants infected with human immunodeficiency virus (HIV) (HIV 1/2 antibody positive).
    - Acute or chronic active hepatitis B (defined as hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibody positive (HBcAb) with hepatitis B virus DNA copies $\geq 10^4$ copies/mL or $\geq$ 2000 IU/mL or above the lower limit of detection) or acute or chronic active hepatitis C [hepatitis C virus antibody (HCVAb) positive with HCV RNA > 10^3 copies/mL]. Participants whose test results are below the above criteria after receiving antiviral therapy with nucleotides, or participants with positive serology but negative HCV RNA test result negative eligible.
    - Has active COVID-19 infection.
    - Has active pulmonary tuberculosis, is being treated with anti-tuberculosis therapy or having received anti-tuberculosis therapy within 1 year prior to the first dose of study drug.
    - Has active syphilis or latent syphilis requiring treatment.
    - Has symptomatic congestive heart failure (New York Heart Association classification NYHA class II-IV), symptomatic or uncontrolled arrhythmia, QTc interval > 480 ms, or personal or family history of congenital long/short QT syndrome.
    - Uncontrolled hypertension (systolic blood pressure $\geq$ 160 mmHg or diastolic blood pressure $\geq$ 100 mmHg) by standard treatment.
14. Has one or more arterial thromboembolic event, including myocardial infarction, unstable angina, cerebrovascular accident, transient ischemic attack, etc., within 6

months prior to the first dose of study drug.

15. Has tumor invasion of surrounding vital structures or organs (e.g., great vessels, trachea, etc.) or risk of gastrointestinal/respiratory fistula.
16. Has received stent implantation in tracheal or digestive tract.
17. Has symptomatic pleural, ascites, or pericardial effusion requiring intervention (e.g., drainage, peritoneal shunt, or cell-free and concentrated ascites reinfusion therapy [CART]). Asymptomatic participants with a small amount of pleural effusion, ascites or pericardial effusion on imaging are allowed. (Drainage and CART are not allowed within 2 weeks prior to screening assessment).
18. Has esophageal or gastric varices that require immediate intervention (eg, ligature or sclerotherapy) or are considered to be at high risk for bleeding in the opinion of the investigator or in consulting gastroenterologist or hepatologist. Participants with evidence of portal hypertension (including splenomegaly on imaging) or a history of prior variceal bleeding must undergo endoscopic evaluation within 3 months prior to the first dose of study drug.
19. Has one or more life-threatening bleeding event or Grade 3 or 4 gastrointestinal/variceal bleeding requiring blood transfusion, endoscopic or surgical treatment within 3 months prior to the first dose of study drug.
20. Has a history of deep vein thrombosis, pulmonary embolism, or any other serious venous thromboembolism within 3 months prior to the first dose of study drug (implantable venous access port or catheter-derived thrombosis, or superficial vein thrombosis is not considered "serious" venous thromboembolism).
21. Has hepatic encephalopathy, hepatorenal syndrome, or Child-Pugh B or more severe cirrhosis.
22. Has complete or incomplete intestinal or bowel obstruction at the time of screening or a history of complete or incomplete intestinal or bowel obstruction within 3 months prior to first dose, or is at risk of intestinal perforation (including but not limited to acute diverticulitis, history of intra-abdominal abscess), or a history of any of the following disease: inflammatory bowel disease or extensive bowel resection (partial colectomy or extensive small bowel resection with concurrent chronic diarrhea), Crohn's disease, ulcerative colitis, and chronic diarrhea.
23. Has significant malnutrition (loss of more than 5% of body weight within 1 month or more than 15% of body weight within 3 months, or loss of more than 50% or more food intake within 1 week, if intravenous nutrition is required). Participants with malnutrition corrected over 4 weeks before the first dose of study drug are allowed.
24. Has other acute or chronic disease or laboratory abnormality that may result in an increased risk associated with study participation or study drug administration, or

interfere with the interpretation of study results, and is considered unfit for this study per the Investigator’ s judgement.

25. Is under neurological, psychiatric illness or social situation that affects compliance with study requirements, significantly increases the risk of AE, or affects the participant's ability to provide written ICF.
26. Has a history of other primary malignancies, with the following exceptions:

- Curatively treated malignancy with no known active disease for ≥ 2 years prior to study enrollment and is at minimal risk of recurrence;
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease recurrence;
- Adequately treated carcinoma in situ with no evidence of disease recurrence.

27. Has a known history of immunodeficiency.
28. Has a history of allogeneic organ transplantation and history of allogeneic hematopoietic stem cell transplantation.
29. Has a history of severe allergic reaction to other monoclonal antibodies and/or hypersensitivity to any of the formulation components of IBI343.
30. Female participants who are pregnant or lactating.
31. Has other conditions considered not eligible to participate in this study per the Investigator’ s judgement.

4.3 Lifestyle Considerations

No specific lifestyle restrictions.

4.4 Participant Screening

For participants without documented tumor tissue CLDN18.2 expression prior to enrollment, prescreening is allowed in this study. CLDN18.2 expression in tumor tissue may be tested outside the 28-day screening period, and pre-screening informed consent is required before testing.

The screening period is the time interval from the signing of the main ICF to the date on which the participant is enrolled in the study (Cycle 1 Day 1). The screening period must not exceed 28 days. The Investigator or qualified designee will review all inclusion and exclusion criteria during the screening period to ensure that the participant is eligible for the trial.

Participants who do not meet the relevant criteria for this study (screen failures) may be rescreened. If rescreening of a participant is considered, the Investigator must contact the the Sponsor’s medical monitor. Each participant is allowed to re-screened once. At the

time of rescreening, the participant must re-sign the ICF and will be re-assigned an identification number. Assessments performed during the initial screening period were acceptable without repeat testing if they were within the study-specified timeframes and met the eligibility criteria. The Investigator or qualified designee will review all inclusion and exclusion criteria to ensure that the participant is eligible for the trial.

4.4.1 Enrollment Error Handling

The eligibility criteria must be strictly adhered to. If participants who meet any exclusion criteria or do not meet all inclusion criteria are enrolled, the Sponsor's medical monitor and the Investigator will discuss whether to continue the participant's participation in the study, and whether to use the study drug. If the Investigator determines that it is appropriate for the participant to continue the study from a medical perspective and the Sponsor's medical manager agrees with the Investigator's decision, the participant may continue the study and receive the study drug. But if the Sponsor's medical manager disagrees with the Investigator's decision, the participant must not continue the study (with or without study drug treatment). In the situation of randomization error, the participant will not be substituted. The Investigator will allow an erroneously enrolled participant to continue participation in the study only after receiving written approval from the Sponsor.

4.5 Participant Discontinuation from Treatment and Study

4.5.1 Participant discontinued treatment

Discontinuation of study treatment does not represent withdrawal from the study. Because some data on clinical events after discontinuation of study treatment may be important for the study, this information must be collected until the participant' s last scheduled visit, even if the participant has discontinued study treatment.

Participants may discontinue study treatment at any time for any reason or at the discretion of the investigator in the event of any AE. In addition, the investigator may discontinue a participant's treatment if the participant is unsuitable for treatment, violates the protocol, or for administrative and/or other safety reasons.

Participants must be discontinued from study treatment for any of the following, but may continue to be monitored in the study:

- Discontinuation of study treatment at the request of the participant or his/her legally acceptable representative.
- Occurrence of a protocol-specified AE requiring discontinuation of study treatment.
- Progressive disease (PD) confirmed by radiological assessment or assessed by the investigator, and deemed inappropriate for continued treatment by the

investigator, unless agreed by the sponsor.

- Occurrence of other malignancies requiring active treatment during the study.
- The investigator or sponsor assessed the participant as unsuitable for continuation of study treatment or at greater risk.
- Participant has a positive serum pregnancy test.
- Participant compliance was poor.
- In the opinion of the investigator, depending on the participant's clinical status or personal circumstances, continued administration of the study drug would place the participant at undue risk.
- The participant was lost to follow-up.
- The maximum duration of study drug treatment was reached.

The reason for discontinuation of study treatment and the stop date will be collected for all participants. For participants who discontinue study treatment but continue to be monitored in the study, all visits and procedures listed in the Study Visit Flow Chart should be completed, including Safety Follow-up and Survival Follow-up.

4.5.2 Participant Withdrawal from the Study

A participant has the right to withdraw from the study at any time for any reason, and if the participant or the participant's legally acceptable representative withdraws the ICF, the participant must be withdrawn from the study.

The Investigator may withdraw a participant from the study for the following reasons:

- Participants who do not meet the inclusion/exclusion criteria and are determined to be ineligible for continued participation in the study by discussion between the Sponsor and the Investigator.
- Withdrawal of consent by the participant or his/her legally acceptable representative.
- The participant died.
- The participant was lost to follow-up.
- The Sponsor terminates the study for medical, safety, regulatory or applicable laws, regulations and Good clinical practice (GCP) reasons.

If a participant withdraws from the study, he/she will no longer receive treatment and follow-up as specified in the protocol, but every effort will be made to persuade the participant to complete the safety follow-up visit and necessary follow-up imaging assessments.

The reason for withdrawal of the participant from the study should be recorded in the electronic case report form (eCRF).

4.5.3 Participant Replacement

If a participant discontinues study drug for reasons other than DLT (including Grade 3 or 4 IRR) or prematurely withdraws from the DLT observation period prior to completing Cycle 1 observation, or does not meet the protocol-specified DLT-evaluable participants (refer to 3.1.3), additional participants will be enrolled using the original eligibility criteria at the discretion of the sponsor to ensure sufficient DLT-evaluable participants in the dose escalation phase. Participants who discontinue the study due to a DLT will not be replaced.

4.6 Lost to follow-up

A participant will be considered lost to follow-up if he or she fails to return to the study site for 2 consecutive scheduled visits and is unable to be contacted by the study site.

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

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (3 telephone calls, made at least 2 weeks apart, and, if necessary, a letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

5 Study Treatment

5.1 Study Treatment Regimen

The study drug is defined as IBI343 in the study. Study drug doses and treatment regimens are presented in Table 5. The dose per administration is allowed to vary by ±5% deviation in the calculated dose will be allowed per administration.

Table 5. Dosage and Treatment Regimen

Study drug:	IBI343
Dose Administered	● The investigator (or designee) will be responsible for calculating the dose of study drug to be administered based on the participant's dose group or cohort. ● Five dose groups of IBI343 were projected: 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg, 10 mg/kg. ● If 6 mg/kg or 10 mg/kg were not tolerated, 4.5 mg/kg and 8 mg/kg, respectively, were to be explored. ● The actual dose administered (mg) will be calculated based on the participant's body weight (kg). The first dose was calculated based on the participant's baseline body weight. If the participant's weight changes less than ± 10% from baseline (at the time of the first dose of study treatment), the dose will be calculated using the baseline weight, otherwise the actual dose will be calculated based on the weight on the scheduled day of dosing or the day before dosing.
Route of Administration	Intravenous infusion (peripheral vein, central venous catheter or port). An infusion pump may be used if indicated.
Frequency of administration	IBI343 will be administered once on Day 1 of each cycle in a 3-week/21-day cycle (Q3W).
Dosing Instructions	● Study drug infusions should be performed under the supervision of study site personnel and in an environment with complete resuscitation facilities. ● IBI343 infusions will be prepared as described in the Medication Manual. ● Refer to Section 5.4.4 for details on pretreatment medications. ● Additional dose levels and cycles may be further explored by the sponsor and the investigator after adequate discussion based on safety, toxicity, and PK data.

5.2 Study drug

5.2.1 Description

The active ingredient of IBI343 is a recombinant anti-claudin 18.2 monoclonal antibody-exatecan conjugate. The dosage form is lyophilized product for injection at a strength of 100 mg/vial. The IBI343 drug product (DP) contains IBI343 drug substance at 20 mg/mL, histidine, histidine hydrochloride, sucrose, and polysorbate 80.

5.2.2 Preparation and use

IBI343 should be prepared by health professionals using aseptic technique. IBI343 DP should be diluted with 5% glucose solution for injection. The final concentration of IBI343 should be between 1~6 mg/mL. The administration of IBI343 should be performed through an intravenous infusion tube equipped with an 0.2~5 μm in-line filter. During IBI343 DP preparation and handling, avoid vigorous shaking and mixing. Since the product does not contain antimicrobial preservatives or bacteriostatic agents, the sterility of the prepared solution must be ensured. Please find detailed drug preparation and administration instructions in the Pharmacy Manual.

5.2.3 Packaging and Labeling

IBI343 DP is packaged in the form of vial, stopper and aluminum-plastic cap.

On the packaging box are printed the drug name, running number, strength, quantity, R & D code, lot number, expiry date, storage conditions, dosage and administration instructions, precautions, main ingredients, and Sponsor information.

The same information is printed on the vial and box labels, but the vial label does not specify quantity, dosage and administration instructions, precautions, or main ingredients. All boxes and vials are labeled “for clinical trial use only”.

5.2.4 Storage and Stability

The shelf life of IBI343 DP is temporarily determined to be 24 months when stored at 5 °C ± 3 °C away from light. This will be revised subsequently based on the long-term stability study results.

For China and Australia site, storage time after dissolution of lyophilized powder, should not exceed 24 hours at 2-8 °C and 6 hours at room temperature away from light. After compounding with glucose injection, the storage time should not exceed 8 hours at 2-8 °C and 4 hours at room temperature away from light.

For US site, the combined storage time of reconstituted IBI343 DP solution in the vial and the diluted solution in the infusion bag containing glucose injection is a total of 4 hours at room temperature or up to 4 hours under refrigerated conditions 2-8°C away from light.

5.3 Treatment adjustment

5.3.1 General Principles

After the first dose, participants may continue to receive study drug in the absence of unacceptable toxicity or unequivocal disease progression.

Beginning from Cycle 2, prior to study drug administration, participants must meet the following criteria:

1. Adequate bone marrow and organ function (platelet count $\geqslant 75 \times 10^9$/L, refer to inclusion criteria 6)
2. All toxicities resolved to $\leqslant$ CTCAE v5.0 Grade 0-1 or baseline, except for Grade 2 alopecia, Grade 2 clinical events that has adequately managed with best supportive care(eg, fatigue, asthenia), and non-clinically significant, asymptomatic laboratory abnormalities or toxicities not requiring clinical management.

If the above criteria are not met, dosing must be delayed until further assessments are completed and it is determined that the participant meets the criteria for continued

treatment.

In situations not included in the criteria described above and in which the Investigator considers the participant suitable for continued study treatment, the study drug treatment may be conducted after discussion with the Sponsor, and the participant should be closely followed up.

5.3.2 Dose interruption and dose delay

All study drug interruptions must be reported promptly to the sponsor (or designee). Dosing delay is allowed if the TEAEs (unless clearly attributable to underlying disease or an extraneous event) does not meet the criteria for permanent discontinuation (see Section 5.3.4) or study drug discontinuation (see Section 4.5.1).

Dose delays of IBI343 due to TEAEs (unless clearly attributable to underlying disease or an extraneous event) are allowed for a maximum of 12 weeks from the scheduled day of dosing. If a participant does not meet the criteria for continuing treatment for more than 12 weeks, treatment will be discontinued for him/her. If a dose delay has extended beyond 12 weeks and the Investigator considers the participant suitable for continued treatment, the Investigator should discuss with the Sponsor to decide whether to continue the treatment.

5.3.3 Dose adjustment

If the participant has poor tolerance to the study drug, but the Investigator assesses that the participant may still benefit from continued treatment with the study drug, in compliance with the dose modification principles, based on the safety, tolerability, and preliminary efficacy data from the study, the participant may continue subsequent treatment with IBI343 at modified doses after a discussion between Investigator and Sponsor.

Participants should be carefully monitored and evaluated for toxicities prior to each administration. The dose of IBI343 should be adjusted according to each participant's tolerance. All dose modifications should be based on the most severe previous toxicity. Based on current safety and efficacy results, the disease control rate increases with the increased IBI343 exposure within 3~8mg/kg IBI343, and the probability of occurrence for TRAEs is positively correlated with IBI343 exposure. The dose level should be lowered if the participants is intolerable. In order to ensure the greatest benefit to the participants after study drug administration, the dose should be gradually reduced, with 4.5 mg/kg as the intermediate level, and 3mg/kg which has been verified the lowest dose reduction to benefit the participants. Reduction by 1~2 dose levels is allowed per dose modification principles. Dose modifications may be conducted after agreement has been reached between the Investigator and Sponsor. Once a dose reduction is made, there is no dose re-escalation allowed.

Dose modifications of IBI343 in this study should follow the following sequence:

Dose level 1	Dose level 2	Dose level 3	Dose level 4
8mg/kg	6mg/kg	4.5mg/kg	3mg/kg

5.3.4 Permanent Discontinuation

Indication for permanent discontinuation of IBI343:

- Grade 4 TEAEs (unless clearly attributable to underlying disease or an extraneous event) or laboratory abnormalities that cannot be corrected by active treatment, unless the participant is considered to be eligible to continue treatment by the investigator and the sponsor based on a comprehensive assessment of the type, severity and clinical benefit of the AE.
- Persistent TEAEs (unless clearly attributable to underlying disease or an extraneous event) that does not resolve to ≤ Grade 1 or baseline level within 12 weeks, except that the participant can continue treatment according to the comprehensive assessment by the investigator and sponsor based on the type and severity of AE and clinical benefit.
- Any AE, laboratory abnormality, or complication that, in the opinion of the investigator, placed the participant at risk required discontinuation of treatment.
- Grade ≥ 3 infusion-related AE required treatment discontinuation.

5.3.5 Subsequent Medication for Participants with DLT in Dose Escalation Phase

In the dose escalation phase of Phase Ia, if a participant experiences a protocol-specified DLT event during the DLT assessment period, the investigator and the sponsor communicate with each other, and based on the safety, tolerability and preliminary efficacy observed in the study, participants in subsequent cycles will be allowed to receive a reduced dose (the dose preceding the current dose) of IBI343, provided that the protocol drug modification principles are met, and the participant will not be considered as DLT-evaluable participant in the reduced dose group.

5.3.6 Infusion related reaction

There may be a risk of infusion-related reactions (IRRs) during the infusion of IBI343. Signs and symptoms of IRRs may include, but are not limited to: fever/chills/chills, urticaria/pruritus, flushing/headache, hypotension, hypertension, shortness of breath, cough/wheezing, hypoxemia, bronchospasm, vertigo/syncope, sweating, arthralgia/myalgia, dry mouth, chest/back/abdominal pain/discomfort, etc. IRRs usually occur the day after drug infusion or the next day and recover within a short period of time (typically ≤ 48 hours). Guidelines for severity grading and management of IRRs in this study are recommended in Table 6.

Table 6. Guidelines for Grading and Management of Infusion Reactions

NCI CTCAE Grade	Treatment	Pretreatment medication for subsequent doses
Grade 1 Mild reaction; There is no need to interrupt the infusion; No Intervention	Closely monitor vital signs as indicated until the investigator considered the participant to be stable.	None
Grade 2 Requires treatment or infusion interruption, but responds promptly to symptomatic treatment [e.g., antihistamines, anesthetics, IV fluids] as soon as possible; Prophylactic medication required for ≤ 24 hours	**Stop the infusion and monitor for symptoms.** Other appropriate medical therapy may include, but is not limited to: intravenous fluids, antihistamines, acetaminophen, narcotics. Closely monitor vital signs as indicated until the investigator considered the participant to be stable. If symptoms resolve within one hour after stopping the drug infusion, the infusion may be resumed at 50% of the prior infusion rate (e.g., decrease from 100 ml/hr to 50 ml/hr). Otherwise, the dose should be withheld until symptoms resolve and the participant should receive pretreatment medication prior to the next scheduled dose.	Participants should receive the following pretreatment medications prior to administration of the corresponding drug: 1. Oral administration of 50 mg diphenhydramine (or equivalent dose of antihistamine). 2. 500-1000 mg acetaminophen orally (or equivalent dose of antipyretic).
Grade 3 or 4 Grade 3: Prolonged (ie, failure to respond rapidly after symptomatic medication and/or brief interruption of infusion); Recurrence of symptoms after initial improvement; Hospitalization for other clinical sequelae (e.g. Renal impairment,	**The infusion was stopped.** Other appropriate medical therapy may include, but is not limited to: epinephrine *, intravenous fluids, antihistamines, acetaminophen, anesthetics, oxygen, vasopressors, corticosteroids. Closely monitor vital signs as indicated until the investigator considered the participant to be stable. Hospitalization may be required. * In case of an allergic reaction,	No subsequent doses

NCI CTCAE Grade	Treatment	Pretreatment medication for subsequent doses
pulmonary infiltrates) Grade 4: Life-threatening; Need for vasopressors or ventilatory support	epinephrine should be used immediately. **Participants should permanently discontinue further study drug treatment.**	
Appropriate emergency equipment should be available in the ward and the physician should be readily available during administration. Refer to CTCAE v5.0 for further information.		

5.4 Prior and Concomitant Therapies

5.4.1 Prior Therapy

5.4.1.1 Medical history

Medical history will be obtained by the investigator or qualified designee, where prior and current details of the tumor will be recorded on a separate eCRF page.

5.4.1.2 Prior Therapy

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirements. Prior antineoplastic therapy will be recorded separately and not listed as prior medication. Other concomitant medications were to be recorded within 30 days prior to the first dose of study drug.

The investigator or qualified designee will review and document all prior antineoplastic therapies, including systemic therapy, radiation therapy, and surgery.

5.4.2 Concomitant Therapy

Any drugs or vaccines (including over-the-counter or prescription drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or during the study should be recorded, such as reason for use, date of administration (including start and end dates), dose information (including dose and frequency), etc. The CRA should be contacted if there are any questions regarding concomitant or prior therapy.

5.4.2.1 Acceptable Concomitant Therapies

Accepted concomitant therapies during the treatment period in this study included:

1. Medications that meet the protocol requirements as judged by the investigator (e.g., medications used to treat disease-related symptoms and to treat AE);
2. Drugs requiring long-term use due to underlying diseases such as hypertension and diabetes;

3. Supportive treatment to relieve tumor-related symptoms, such as bisphosphonate therapy for bone metastases;
4. Participants with viral hepatitis should receive antiviral treatment according to relevant treatment guidelines;
5. Antiemetics and gastric mucosal protective agents as specified in the protocol.

5.4.2.2 Prohibited Concomitant Therapy

The following treatments are prohibited during the treatment period of this study:

1. Systemic anti-tumor therapy other than IBI343, including cytotoxic therapy, targeted agents, immunotherapy, biologic therapy, endocrine therapy, hormonal therapy, Chinese patent medicine or herbal medicine with anti-tumor indications, and other investigational anti-tumor agents, etc. Hormone replacement therapy for non-antineoplastic purposes is allowed.
2. Other investigational drugs.
3. Radiotherapy for tumor control (local palliative radiotherapy for non-target lesions that is intended to relieve symptoms, does not affect response assessment, and does not cause dose interruption beyond the longest interval specified in the protocol is allowed).
4. Vaccination with live vaccines.
5. Strong CYP3A4 inhibitors (see Table 7). If the use of such concomitant medications cannot be avoided, consideration may be given to delaying the administration of IBI343 until such drugs are metabolically cleared from the circulation (e.g., 3 half-lives). If the use of such concomitant medications cannot be avoided and the administration of IBI343 cannot be delayed, the patient should be closely monitored and possible adverse reactions should be managed promptly.
6. Strong CYP3A4 inducers (see Table 7).

Table 7. CYP3A4 Inducers and Inhibitors

Strong inhibitor	Boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, parirevir and ritonavir and (obitasvir and/or dasabuvir), posaconazole, saquinavir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole
Strong inducer	Apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

5.4.3 Subsequent Antineoplastic Therapy

Subsequent antineoplastic therapy administered after the last dose of study drug should be recorded in the eCRF. If applicable, start and end dates and best response were recorded in the eCRF.

5.4.4 Premedication

5.4.4.1 Antiemetic and gastric mucosal protective agent

A 4-drug regimen containing: a neurokinin-1 (NK-1) receptor antagonist, a serotonin type 3 (5-HT3) receptor antagonist, dexamethasone, and a proton pump inhibitor is recommended for prophylaxis before and during the first dose for all participants. Alternative antiemetics or gastric mucosal protective agents (eg, sucralfate) may be considered by the investigator, if clinically indicated, or as per guidelines. Prophylactic medication before the second and subsequent doses may be determined by the investigator based on the first dose and clinical experience of the participant.

5.5 Dosing during pregnancy, lactation, or childbearing potential

5.5.1 Pregnancy

This study drug must not be used during pregnancy. Females who are pregnant or plan to become pregnant during the study cannot be enrolled in this study.

5.5.2 Lactation

It is not known whether IBI343 is excreted in human milk. Because many drugs are excreted in human milk, IBI343 may be potentially toxic in infants. For safety reasons, lactating women cannot be enrolled in this study.

5.5.3 Childbearing age

Female participants of childbearing potential who are sexually active with a non-sterilized male partner, and non-sterile male participants who are sexually active with a female partner of childbearing potential must use at least 1 of the acceptable effective methods of contraception listed in Table 8 from screening until 6 months after the last dose and should discuss their discontinuation with a responsible physician after that time point. Periodic abstinence, rhythm methods, and extracorporeal sperm withdrawal methods are not acceptable methods of contraception. Females of childbearing potential are defined as those who have had menarche, have not undergone sterilization (i.e., bilateral tubal ligation, bilateral salpingectomy, or total hysterectomy), and have not yet reached menopause.

Table 8. Effective contraception (at least 1 method must be used)

Barrier method	IUD method	Hormonal method
Male condom with spermicide	With copper T-ring	Implants
Diaphragm plus spermicide	Progesterone-containing T-ring a	Hormonal contraceptive injection or injection
Diaphragm plus spermicide	Levonorgestrel-releasing IUD system (e.g., Mirena ®) a	Combined contraceptive pill Low-dose oral contraceptive pill Contraceptive patch

a This is also considered a hormonal approach

Women were considered postmenopausal after 12 months of menopause without an alternative medical cause. The requirements according to age are as follows:

- Women > 50 years of age are considered postmenopausal if they have been amenorrhoeic for 12 months or more after cessation of exogenous hormone therapy and their luteinizing hormone and follicle-stimulating hormone levels are within the accepted postmenopausal range.
- Women ≤ 50 years of age were considered postmenopausal if they had been amenorrhoeic for 12 months or more after cessation of all exogenous hormonal therapy, had had radiation-induced oophorectomy with the last menses occurring > 1 year earlier, had had chemotherapy-induced amenorrhoeic with the last menses > 1 year apart, or had undergone surgical sterilization (bilateral oophorectomy or hysterectomy).

5.6 Treatment compliance

Study treatment was administered at the study site, and treatment compliance was monitored using drug receipt and dispatch records, participant medical records, and eCRFs.

IBI343 will be administered intravenously in a controlled environment at the clinical site under the direct observation of qualified site personnel. Details of each dose will be recorded in the CRF (including the date, start and stop time of the IV infusion, and infusion volume). The Sponsor will review precautions related to the use of study drug and prohibited concomitant medications.

5.7 Drug management

5.7.1 Study Drug Receipt and Accountability

The sponsor will provide IBI343 according to the anticipated enrollment plan at the study site. IBI343 will be shipped to the study site via a third party shipping qualified logistics company. Authorized personnel at the site will sign the dispatch form to acknowledge

receipt of the drug.

IBI343 will only be used in this study and will only be administered by personnel authorized by the investigator. In order to fully control the distribution and use of IBI343, the quantity will be registered at each visit. All dosing aspects of the study will be performed at the study site, therefore there is no dispensing and recovery of the drug to the participants.

5.7.2 Storage and Management of Study Drug

IBI343 should be refrigerated at 5 ℃ ± 3 ℃, protected from light and stored dry, not frozen, and should be transported to each study site in a cold chain for storage and distribution by a specially-assigned person.

The study drug should be stored in a refrigerator that can only be opened by authorized personnel. After receiving the drug, the study personnel should confirm that the transportation temperature of the drug is within the specified range, check and sign the receipt, and store the drug at the specified temperature. In case of abnormal temperature during transportation or storage at the study site, the drug should be transferred to the specified temperature as soon as possible, made temporarily inaccessible to participants, reported timely to the Sponsor, and disposed of according to the Sponsor's opinions.

All study drugs provided by the Sponsor will be used only for this study and not for purposes other than those specified in this protocol. The Investigator must commit to not supplying the study drug to any person unrelated to the study.

5.7.3 Return and Destruction of Study Drug

In this study, empty bottles/packages of used IBI343 will be returned and the containers may be destroyed locally according to applicable guidelines and procedures at the study site and local institutions. In the event that a site has difficulty in recovering empty bottles/packages, local destruction may be allowed upon the agreement of the Sponsor in compliance with applicable guidelines and procedures at the site.

All unused study drugs should be returned to the Sponsor for destruction after completion/termination of the study or after the expiry date. Recovery of the study drug will be arranged by the CRA designated by the Sponsor.

5.7.4 Study Drug Records

The personnel designated by the study site should timely record the receipt, distribution, use, inventory, destruction, recovery, and damage of the study drug according to the requirements of relevant regulations and guidelines.

5.8 Complaint Handling

In order to ensure the safety and monitoring quality of study participants and to assist in procedural and drug improvement, the Sponsor will collect product complaints related to

the study drug used in the clinical trial.

Complaints related to concomitantly used drugs will be reported directly to the manufacturer according to the product description.

The Investigator or his/her designee is responsible for completing the following product complaint process as specified in this study:

Document the reported product complaints and a complete description thereof in a study-specific complaint form.

Fax or email the completed product complaint form to the Sponsor or its designee within 24 hours.

Return a copy of the product complaint form with the product if the Investigator is required to return the product for investigation.

6 Study Procedures and Assessments

Assessments and procedures to be completed during the study are described in the Schedules of Activities (SoAs) and are described in detail below. Unscheduled visits may be performed if clinically indicated, and the Investigator may perform relevant examinations according to the participant's condition. All scheduled and unscheduled visit test results should be recorded in the eCRF.

6.1 Safety Assessments

6.1.1 Vital Signs

Vital signs will be performed according to the SoAs. Date and time of collection and measurement will be recorded in the appropriate section of the eCRF.

Additional monitoring of vital signs assessments may be performed according to standard clinical practice or at the discretion of the investigator as clinically indicated.

In the event of an AE/SAE, additional vital sign records may be collected on the eCRF (if applicable). Date and time of collection and measurement will be recorded in the appropriate section of the eCRF.

Blood pressure and pulse were measured after the participant had rested for at least 5 minutes. Date and time of collection and measurement will be recorded in the appropriate section of the eCRF.

Vital signs (temperature, blood pressure, pulse, and respiratory rate) should be recorded within 15 minutes prior to dosing, immediately after the end of infusion (+15 minutes), and 2 hours (± 1 hour) after the end of infusion. During the first infusion of IBI343, blood pressure and pulse will be monitored within 15 minutes prior to the start of drug infusion and every 15 minutes (± 3 minutes) after the start of drug infusion until the end of infusion (blood pressure and pulse will be measured at the end of infusion). Beginning with the

second infusion, vital signs will be monitored and assessed during the infusion as clinically indicated.

6.1.2 Height and weight

Height and weight will be measured and recorded according to the SoAs.

6.1.3 Physical examination

6.1.3.1 Complete physical examination

The investigator or clinical designee will perform a complete physical examination during the screening period. A complete physical examination will include: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and pharynx), lymph nodes, thyroid, musculoskeletal (including spine and extremities), genital/anal, and neurological assessments, if indicated. Clinically significant abnormal findings at screening will be recorded as medical history or AE based on the investigator's analysis and judgment. In addition, a complete physical examination will be performed as specified in the SoAs. After the first dose of study drug, abnormal findings that are newly identified and clinically significant or that worsen from baseline will be recorded as AE.

6.1.3.2 Targeted physical examination

For Cycle 2 and subsequent visits not required in the SoAs, the investigator or qualified designee will perform a targeted physical examination as clinically indicated, scheduled prior to dosing on Day 1 of each treatment cycle. New clinically significant abnormal findings or worsening from baseline should be recorded as AE.

6.1.4 Eastern Cooperative Oncology Group Performance Status (ECOG) Assessment

The investigator or qualified designee will assess ECOG performance status at screening, pre-dose on Day 1 of Cycle 2 and every subsequent cycle, and at the End of Treatment Visit and Safety Follow-up Visit as specified in the SoAs.

The ECOG PS score criteria are shown in the table below:

Table 9. Eastern Cooperative Oncology Group Performance Status Criteria

Scoring	Activity Level
0	Fully normal and able to carry out all normal activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light or office work
2	Ambulatory, able to carry out any work but unable to carry out any work, and confined to bed no more than 50% of daytime hours
3	Capable of barely caring for oneself, confined to bed or chair more than 50% of the

	day
4	Completely incapacitated, severely incapable of self-care, confined to bed or wheelchair
5	Death

6.1.5 12-lead ECG

Resting 12-lead ECGs will be analyzed at the local laboratory according to the SoAs.

A 12-lead ECG will be performed after the participant has rested in a recumbent position for at least 5 minutes. Further ECGs will be performed when clinically indicated, e.g. In the event of a cardiac-related AE. After the examination, the investigator completed the ECG assessment and recorded the assessment on the ECG. The same method of assessment should be used throughout the study.

The investigator should assess all ECGs according to the clinically significant abnormal/not clinically significant abnormal category. In case of clinically significant abnormal findings, the investigator should record the findings as AE in the eCRF.

6.1.6 Clinical Laboratory Assessments

6.1.6.1 Pregnancy test

If the result is positive and pregnancy status is confirmed, the participant is ineligible/must be discontinued from the study. If pregnancy is suspected during the study, it should be repeated.

6.1.6.2 Laboratory Safety Evaluation

Laboratory tests including hematology, urinalysis, blood biochemistry, coagulation, blood myocardial enzymes and troponin analysis are shown in Table 10.

Table 10. Routine Laboratory Safety Evaluations

Blood routine	RBC, HGB, HCT, WBC, PLT, LYM, ANC
Blood biochemistry	TBIL, DBIL, ALT, AST, γ-GGT, ALP, ALB, TP, LDH, Urea or BUN, Cr, Na, K, Cl, Mg, Ca, P, Amylase, Lipase and FBG
Urinalysis	PH, Specific Gravity, UWBC, UPRO, URBC, UGLU, UBLD
Coagulation function	APTT, PT, INR, Fbg, D-dimer
Viral serology test	HBsAg, HBsAb, HBcAb, HBeAg, HBeAb, HBV DNA, HCV antibody, HCV RNA, HIV antibody, Treponema pallidum-specific antibody
Myocardial injury markers	CK, CK-MB, Troponin I or T, BNP or NT-proBNP
Faecal analysis	occult blood (OB)

ALB=albumin; ALP = alkaline phosphatase; ALT=alanine aminotransferase; ANC = absolute

neutrophil count; APTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CK = creatine kinase; CK-MB = creatine phosphokinase isoenzyme; Cr=serum creatinine; DBIL = direct bilirubin; D-dimer = D-dimer; FBG = fasting blood glucose; Fbg = fibrinogen; γ-GGT = γ-glutamyl transferase; HBcAb = hepatitis B core antibody; HBeAb=hepatitis B E antibody; HBeAg = hepatitis B E antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV=hepatitis B virus; HCT = hematocrit; HCV=hepatitis C virus; HGB = hemoglobin content; HIV=human immunodeficiency virus; INR = International Normalized Ratio; LDH=lactate dehydrogenase; LYM = lymphocytes; OB = fecal occult blood/occult blood; PH=PH value; PLT=platelet; PT = thromboplastin time; RBC = red blood cell; TBIL=total bilirubin; TP = total protein; UBLD = urinary occult blood or occult blood; UGLU=urine glucose; UPRO=urine protein; URBC=urine red blood cells; UREA = urea; UWBC=urine white blood cells; WBC=white blood cell count.

6.2 Efficacy evaluation

Efficacy assessments will be performed as described in the SoAs.

Tumor imaging is usually performed with contrast-enhanced CT or contrast-enhanced MRI, and the sites of examination must include the chest, abdomen, and pelvis. In case of allergy to contrast agent for enhanced CT, plain CT scan or MRI scan may be performed. The same imaging technique should be used during the study for the same participant. Participants suspected to have symptoms and signs of central nervous system metastasis or known to have brain metastasis should undergo cranial enhanced MRI or CT examination at baseline; For participants who do not have brain metastases at baseline, routine cranial imaging is not required thereafter. Assessments such as bone scans and/or CT or MRI scans of other sites should be performed if clinically indicated.

Screening imaging should be performed within 28 days prior to the first dose of study drug. The investigator confirms that the participant has at least one measurable lesion per RECIST v1.1 as assessed by baseline imaging. Imaging performed as a routine clinical procedure can be used as screening imaging if it meets the quality and standards of the study and is performed within 28 days prior to the first dose of study drug. The method used for the assessment of tumor burden at baseline must be the same as that used for each subsequent follow-up assessment. Additional sites of involvement were examined as indicated by each participant's signs and symptoms.

Tumor imaging assessment will be performed every 6 weeks (± 7 days) within 48 weeks after the first dose; After Week 48, tumor imaging assessments will be performed every 12 weeks (± 7 days) until initiation of new antineoplastic therapy, disease progression, withdrawal of consent, study termination, lost to follow-up, or death, whichever occurs first. The scheduled tumor imaging should be performed at the scheduled time points and should not be delayed for reasons such as delay or interruption. Exceptions should be discussed and agreed with the sponsor. The investigator may perform unscheduled imaging assessments if clinically indicated.

Tumor response will be assessed by the investigator or qualified designee according to RECIST v1.1 and recorded as CR, PR, SD, PD, or not evaluable (NE) at each assessment timepoint. The assessment method is presented in Appendix 2. For participants who discontinue treatment, tumor imaging should be performed once at the time of confirmation of discontinuation. Imaging for confirmation of treatment discontinuation is not mandatory if the previous imaging is no more than 4 weeks away from treatment discontinuation. For participants who discontinue study drug for reasons other than radiographic PD, radiographic assessments should continue to be performed at the protocol-specified imaging schedule after discontinuation.

6.3 PK, Immunogenicity, and Biomarker Evaluations

6.3.1 PK evaluation

6.3.1.1 PK Sample Collection

Blood samples will be collected from participants to determine the concentration of IBI343, total anti-CLDN18.2 antibody, and exatecan using three separate validated assays for PK analyses. Approximately 8.0 mL blood will be collected at the time points indicated in the PK sampling table for bioanalysis of IBI343, total anti-CLDN18.2 antibody and exatecan concentration. If necessary, bioanalysis of the metabolites concentration of exatecan could be performed based on preserved blood samples. Sampling methods, sample preservation, transportation, and analysis are detailed in the "Laboratory Manual" provided by the Sponsor's designated central laboratory.

An additional blood sample should be collected from participants experiencing unexpected and/or serious AE if possible.

If necessary, IBI343 immunogenicity analysis will be performed based on PK samples.

6.3.2 Immunogenicity Evaluation

6.3.2.1 Immunogenicity Sample Collection

Participants will be tested for anti-drug antibodies (ADA), and ADA-positive serum samples may be tested for neutralizing antibodies (NAb) if necessary. Approximately 3.5 mL of whole blood will be collected by using a vacuum blood collection tube containing clot activator, serum will be separated, and frozen for storage for immunogenicity analysis.

The incidence of ADA of IBI343 will be summarized for all participants who receive at least one administration of study drug.

If necessary, PK concentration detection will be performed based on immunogenicity samples. Sampling methods, sample preservation, transportation, and analysis are detailed in the "Laboratory Manual" provided by the Sponsor's designated central laboratory.

6.3.3 Tumor Samples for Biomarker Analysis

Participant's tumor tissue (including archival or fresh) will be collected for biomarker analysis according to the SoAs (Table 1 and Table 2) as permitted by the Ethics Committee.

Phase Ia dose escalation (optional): Participants will provide archival or fresh baseline tumor tissue samples (5-10 unstained slides/participant) for central laboratory test of CLDN18.2 expression.

Phase Ia dose expansion, dose optimization and Phase Ib (mandatory): Participants are required to provide archival or fresh baseline tumor tissue samples (5-10 unstained slides/participant) during prescreening/screening period for central laboratory test of CLDN18.2 expression. Participants enrolled with historical or site results may provide baseline tumor tissue samples (5-10 unstained slides/participant) at pre-screening/screening/post-enrollment for central laboratory test of CLDN18.2 expression.

In the event of a test failure, additional slides may be requested if remaining slides are available at the clinical site.

Refer to the Laboratory Manual for details on slide sampling methods, sample storage, transportation, and analysis.

6.3.4 Storage and Destruction of Biological Samples

For participants at study sites in China, CLDN18.2 immunohistochemical (IHC) test uses tissue slide samples, which will be sent to a third-party laboratory, Teddy Clinical Research Laboratory (Shanghai) Ltd., for testing. Part of remaining samples will be transferred to Teddy Clinical Research Laboratory (Wuxi) Limited for storage and eventually destroyed with the assistance of Wuxi Industrial Waste Safety Disposal Co., Ltd. or returned to study sites. Part of remaining samples will be transferred to Q Squared Solutions (Beijing) Co., Ltd. for CLDN18.2 re-test and eventually destroyed with the assistance of Beijing Ruentex Environment Technology Corp/ Beijing Solid Waste Logistics Co., Ltd or returned to study sites.

For participants at ex-China study sites, samples will be disposed of or destroyed as per standard practice by the corresponding laboratory.

Individual or pooled samples may be used for further evaluation and validation of the analytical method, e.g., use of samples for selectivity, parallelism, or intra-immunogenicity threshold determination, if needed. The results of these analyses may be included in the clinical study report (CSR) or reported separately from the CSR.

Incurred sample reproducibility analysis can be performed concurrently with biological sample analysis. The results of the reproducibility analysis will not be documented in the CSR, but will be presented in the bioanalytical report.

After all necessary analyses have been completed, individual information will be desensitized (including anonymization and sample pooling) and then processed and destroyed.

7 Safety Reporting and Adverse Event Management

7.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence, whether or not there is a causal relationship with the study drug, in a clinical study participant from the time informed consent form is signed, and includes, but is not limited to, the following:

- Exacerbation of pre-existing (prior to clinical study) medical conditions/diseases (including worsening of symptoms, signs, laboratory abnormalities);
- Any newly developed adverse medical conditions (including symptoms, signs and newly diagnosed diseases);
- Clinically significant abnormal laboratory values or results.

7.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is an AE that meets at least one of the following criteria:

- Resulted in death, excluding death due to disease progression of study indication.
- Is life threatening ("life threatening" is defined as an AE that places the participant at risk of death from the event as it occurred, and does not include an AE that, had it occurred in a more severe form, might have caused death).
- Requires inpatient hospitalization or prolongation of hospitalization, excluding the following:
  a) Rehabilitation institutions;
  b) Nursing homes;
  c) Regular emergency room admission;
  d) Same-day surgery (e.g., outpatient/same-day/ambulatory surgery);
  e) Hospitalization or prolonged hospital stay is unrelated to SAE itself. For example, hospitalization due to original diseases and there are no new AEs and aggravation of the original diseases (e.g., to check for laboratory abnormalities that persisted even before the study trial); hospitalization for management reasons (e.g., annual routine physical examination); hospitalization during the clinical trial as specified in the study protocol (e.g., procedures required according to the study protocol); and hospitalization that is unrelated to AEs (e.g., elective surgery); admission for treatment or

surgery specified in the entire study protocol or scheduled at baseline of individual participants; admission only to use blood products.

- Results in persistent or significant disability/incapacity.
- Results in congenital anomaly/birth defect.
- Other important medical events: defined as events that jeopardize the participant or require medical intervention to prevent one of the outcomes listed above.

7.3 Adverse Events of Special Interest

Adverse events of special interest mainly include:

- Grade ≥ 3 gastrointestinal bleeding
- Grade ≥ 3 gastritis
- Grade ≥ 3 nausea or vomiting that does not resolve to grade ≤ 2 within 3 days despite best supportive care

These events will be reported to the Sponsor within 24 hours of awareness of the event irrespective of seriousness (i.e. serious and nonserious adverse events) following the procedure described for SAEs and will require enhanced data collection.

7.4 Assessment of Severity of Adverse Events

The Investigator will assess the severity of AEs per the five-Grade criteria as defined in the NCI CTCAE v5.0.

Adverse event terms that are not included in NCI CTCAE v5.0 will be graded according to the following CTCAE grading principles:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate activities of daily activities.
- Grade 3: Severe or medically significant event requiring medication but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AEs

7.5 Causal relationship judgment between adverse event and study drug

The Investigator is responsible for assessing the relationship between study treatment and each occurrence of each AE/SAE. Appendix 3 provides guidance on assessing the causal relationship between the study treatment and the AE.

7.6 Recording of Adverse Events

The investigator should record AE or SAE using medical terminology/concepts. The use of spoken language and abbreviations should be avoided. All AE (including SAE) should be recorded on the AE form of the CRF.

7.6.1 Collection and Timing of adverse events

The Investigator should ask participants non-inductive questions to be informed of the adverse events.

All AEs will be collected from signing the informed consent to 30 days after the last administration of the study drug. The Investigator is required to report all SAEs and only AEs that are considered related to the study drug or study procedures from 30 to 90 days after the last administration. From 90 days after the last administration, the Investigator is required to report only SAEs that are considered related to the study drug or study procedures. From 30 to 90 days after the last administration, if a participant starts a new antineoplastic therapy, only SAEs considered related to study drug will be recorded and reported.

7.6.2 Follow-up of adverse events

Participants should be followed up until they recover to baseline or to Grade 0-1 or the Investigator considers that follow-up is not necessary for reasonable reasons (such as inability to recover or improve). If the AE cannot be recovered, a reasonable explanation should be recorded. The participant's recovery from AEs or SAEs, whether related to study drug or not, and their dates should be recorded in the eCRF and medical records.

7.6.3 Contents of Adverse Event Records

The Investigator is to fully document any AE, including diagnosis (if not, symptoms and signs including laboratory abnormalities), start and stop date and time (if applicable), CTCAE severity grade and change (grade 3 or higher), whether it is an SAE, action taken with the study drug, the treatment administered for the AE and the outcome of the event, and the relationship of the AE to the study drug.

For serious adverse events, the Investigator should also provide the date when the AE meets the criteria for an SAE, the date the Investigator became aware of the SAE, the basis for the SAE, the date of hospitalization, the date of discharge, the probable cause of death, the date of death, whether an autopsy was performed, assessment of causality with the study procedures, assessment of causality with other drugs, and other possible causes of the SAE. The Investigator should also provide the judgment basis of relevance as well as the description of SAE. In the description of SAE, it is also required to include the participant's identification number, age, sex, height and weight; the indication and disease stage for which the participant was treated with the study drug as well as relevant general conditions; the clinical course, including occurrence, development, outcome and results,

of the SAE; laboratory test results related to the SAE (examination time, unit and normal range must be provided); SAE-related medical history, concomitant diseases and their occurrence and duration; SAE-related medication history, the initiation, duration and dosage of the concomitant treatment; initiation, duration, dosage and administration of the study drug treatment and other detailed information. From 30 to 90 days after the last administration, if a participant starts a new antineoplastic therapy, only SAEs considered related to study drug or procedures will be collected.

The matters concerning the recording of AEs are described below:

Diagnosis, Symptoms and Signs

If a diagnosis has been made, the diagnosis, instead of the individual symptoms, should be recorded in the eCRF, signs and laboratory tests (e.g., recording of hepatic failure instead of jaundice, transaminase elevation and asterixis). If symptoms and signs cannot be determined to be caused by this diagnosis at the time of reporting, they will be recorded as separate AEs/SAEs. If it is determined that the symptoms and signs are due to the diagnosis, the diagnosis is reported separately only and the symptoms and signs are included in the diagnosis. For AEs, the recording of signs and symptoms should be deleted, and for SAEs, a follow-up update report should be sent.

Adverse Events Secondary to Other Events

In general, adverse events secondary to other events (e.g., caused by other events or clinical sequelae) should have their primary event recorded unless the secondary event is severe or is a serious adverse event. Secondary events of significant clinical significance, if different from the primary event, should be recorded as independent adverse events in the eCRF. If the relationship between events is unclear, it should be recorded separately in the eCRF.

Persistent or recurrent adverse events

Persistent adverse events are those that persist without resolution between two evaluation time points.

Recurrent adverse events are those that resolved between the two evaluation time points but recurs later on. The occurrence of the events should be recorded separately in the CRF.

Laboratory Abnormalities

Clinically significant laboratory abnormalities that are not attributable to medical history and/or the disease condition under study should be reported as AEs. It is the responsibility of the Investigator to review all laboratory abnormalities and make medical judgment as to whether each laboratory abnormality should be reported as an AE.

Pre-existing medical conditions

Existing symptoms/signs of participants during the screening period of the will be

recorded and reported as adverse events only when there is aggravation of severity, frequency and nature (except for the deterioration of the disease condition under study) after entering the study. Changes from previous states, such as “increased frequency of headache”, should be reflected in the recording.

Death

All deaths occurring throughout the trial, including during the 90-day follow-up period after the last dose, regardless of relationship to the study drug, should be recorded in the death report form of the eCRF and reported to the sponsor in a timely manner by completing the SAE report form. Deaths occurring 90 days after the last dose are not required to be reported as SAE unless considered related to the study drug or study procedures.

When recording death events, if the cause of death is clear, record the cause of death as AE, the outcome of the AE is death, and report the event as SAE; If the cause of death is unknown at the time of reporting, it should be recorded as "unexplained death" on the AE form of the eCRF, and the "unexplained death" should be reported as an SAE first, and the exact cause of death should be further investigated.

Disease progression

Disease progression is defined as a worsening of the participant’s condition caused by the primary tumor targeted by the study drug, appearance of new lesions relative to the primary tumor, or progression of the original lesion. Disease progression is not reported as an AE; death, life-threatening conditions, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or other important medical events due to expected symptoms and signs of disease progression are not to be reported in an expedited manner as SAEs.

Hospitalization, prolonged hospitalization, or surgery

Any AE that results in hospitalization or prolongation of hospitalization should be recorded and reported as an SAE, with the following exceptions:

- Hospitalization or prolongation of hospitalization that is planned as required by the protocol (e.g., for dosing, efficacy assessment, etc.).
- Hospitalization due to an unchanged medical condition that was present prior to study entry, e.g., elective surgery/treatment scheduled prior to study entry.

However, if pre-existing disease deteriorates (e.g., surgery/treatment is performed earlier than originally planned) during the course of the study, the required elective surgery/treatment due to disease worsening will be considered an AE.

Overdose

Accidental or intentional administration of a dose exceeding 20% of that specified in the

protocol was considered an overdose (Excluding cases of dose adjustments specified in the protocol). Overdoses or any AEs due to overdose will be recorded in the eCRF. If a participant experiences an SAE due to overdose, the event should also be reported according to SAE procedures.

7.7 Expedited Reporting of SAE, Pregnancy, and AESIs

7.7.1 SAE Reporting

The reporting period of SAE is from the signing of the informed consent to 90 days (inclusive) after the last dose. If the participant has an SAE, the investigator should immediately report the SAE to the sponsor Pharmacovigilance Department within 24 hours after awareness according to the specified procedures and requirements. If you have any questions, please contact Pharmacovigilance Department public email: drugsafety@innoventbio.com. For death and life-threatening SAE, the investigator should urgently follow up the missing information and provide a complete SAE report.

If a participant starts a new anti-tumor treatment within 30 ~ 90 days of the last dose, only SAE related to the study drug or study procedures should be reported subsequently.

If an SAE occurring outside the above period is considered related to the study drug or study procedures, it will also be reported to the sponsor.

7.7.2 Pregnancy

Drugs of the same class may have safety risks of embryotoxicity. All participants of childbearing potential participating in this clinical study must take effective contraceptive measures.

If a pregnancy occurs in a female participant exposed to the study drug during the clinical study, the investigator should report the pregnancy to the sponsor in the manner and requirements specified by the sponsor within 24 hours of becoming aware of the pregnancy.

If a male participant exposed to the study drug becomes pregnant during the clinical study, the participant may continue in the clinical study. The investigator should report the pregnancy to the sponsor in the manner and requirements specified by the sponsor within 24 hours of becoming aware of it.

The investigator should continuously monitor and follow up the pregnancy outcome until 8 weeks after delivery of the mother, and report the outcome to the sponsor.

If the outcome of the pregnancy is stillbirth, spontaneous abortion, fetal anomaly (any congenital anomaly/birth defect), and induced abortion for medical reasons, it is considered as an SAE and needs to be reported according to the procedures and timelines for SAE.

If a participant experiences SAE during pregnancy, it will also be reported in accordance

with the SAE reporting procedure

7.7.3 AESI Reporting

For AESI specified in the clinical trial protocol, the investigator should report the AESI to the sponsor in the manner and requirements specified by the sponsor within 24 hours of becoming aware of it. If the criteria for SAE are met, please also report according to the requirements and timelines for SAE.

7.8 Hepatic function abnormal events

Abnormalities in AST and/or ALT levels accompanied by abnormally elevated total bilirubin levels that meet the following criteria and do not have other causes of liver injury will be considered as drug-induced liver injury. Such situations should always be considered important medical events.

Table 11. Hepatic impairment requiring reporting as an SAE

Baseline Period	Normal (AST/ALT and total bilirubin)	Abnormal (AST/ALT and total bilirubin)
Treatment Period	ALT or AST ≥ 3 × ULN With total bilirubin ≥ 2 × ULN And alkaline phosphatase ≤ 2 × ULN And no hemolysis	AST or ALT ≥ 8 × ULN With an increase in total bilirubin ≥ 1 × ULN or a value ≥ 3 × ULN

Participants should return to the study site for evaluation as soon as possible (preferably within 48 hours) after learning of an abnormal result. The evaluation should include laboratory tests, detailed medical history and physical assessment, and the possibility of liver neoplasia (primary or secondary) should be considered.

In addition to repeated AST and ALT tests, laboratory tests to be performed should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time/international normalized ratio, and alkaline phosphatase. Detailed medical history collection should include: history of alcohol consumption, acetaminophen, soft drugs, various supplements, traditional Chinese medicine, history of exposure to chemical drugs, family history, occupational exposure, sexual behavior history, travel history, history of contact with participants with jaundice, surgery, blood transfusion, history of liver disease or allergic disease, history of heart disease, history of immune disease, etc. Further investigations may include tests for acute hepatitis A, B, C, and E, imaging of the liver (e.g., biliary tract), autoantibodies, and cardiac ultrasound. If repeat testing still confirms that the laboratory criteria in Table 11 are met, the possibility of potential drug-induced liver injury should be considered in the absence of other causes of liver function test abnormalities, without waiting for all liver function etiologies to be tested. Such cases of potential drug-induced liver injury should be reported as SAE.

8 Statistical Considerations

This section provides statistical considerations of this study. The detailed statistical analysis plan (SAP) will be finalized before database lock. The SAP will provide the detail of the analyses to be performed in this study and presentation of the results.

8.1 Statistical Hypothesis

No formal statistical hypothesis testing is planned for this study.

8.2 Sample Size Estimation

Part 1 of Phase Ia (not applicable in US)

- Dose escalation phase: 14 to 30 DLT-evaluable participants are planned to enroll to accurately estimate MTD.
- Dose expansion phase: for each tumor type, 2 ~ 4 doses are planned to be selected for expansion. Approximately 6 ~ 60 participants are planned to be enrolled in each dose expansion group. Approximately 40 ~ 140 participants for each tumor type are planned.

Part 2 of Phase Ia

- Dose optimization: Approximately 50-60 participants with G/GEJ AC are planned to be enrolled. Approximately 30-40 participants with PDAC are planned to be enrolled.

Phase Ib (not applicable in US)

Approximately 200 participants are planned to be enrolled in Phase Ib.

- Cohort A: Approximately 50 participants are planned to be enrolled to evaluate the efficacy of IBI343 monotherapy.
- Cohort B: Approximately 50 participants are planned to be enrolled to evaluate the efficacy of IBI343 monotherapy.
- Cohorts C and D: Approximately 50 participants per cohort (including participants at the RP2D in the Phase Ia dose expansion phase) are planned to be enrolled to evaluate the efficacy of IBI343 monotherapy.

8.3 Statistical Analysis Populations

Statistical analysis sets include safety population (SP), DLT evaluable population (DEP), efficacy evaluable population (EEP), per-protocol population (PPP) and PK population:

- SP: Includes all enrolled participants who received at least one dose of study drug.
- DEP: Refers to DLT evaluable participants who meet the definition in Section 3.1.3. DEP is only used for DLT analysis in dose escalation period of Phase Ia.

- EEP: for Phase Ia, including participants who completed 2 cycles of treatment and had at least one tumor assessment after the first dose of study drug, or who prematurely discontinued study drug due to disease progression or death or AE; For Phase Ib, including all enrolled participants who meet the specific enrollment criteria for each cohort, have at least one measurable disease at baseline, and receive at least one dose of study drug.
- PPP: A subset of the EEP, i.e., participants in the EEP who have completed a pre-specified minimum exposure to study drug and have no major protocol deviations that impact efficacy assessments. The minimum study exposure and major protocol deviations impacting efficacy assessments will be defined in detail in the SAP. The PPP will be used only for Phase Ib Cohort A to support the analysis of efficacy variables.
- PK Population: Includes all participants who received at least one dose of study drug and had at least one available drug concentration data post-dose.

DLT analysis will be performed in DEP. Safety, immunogenicity and biomarker analysis will be performed in SP. Analysis of PK parameters will be performed on the PK population. Evaluation of antitumor activity will be performed in the EEP. Phase Ib Cohort A will also be analyzed in the PPP.

8.4 General Methods of Statistical Analysis

Data will be analyzed separately by dose level in Phase Ia and by cohort in Phase Ib. If applicable, Phase Ia and Phase Ib participants will also be combined together to perform statistical analysis by tumor type, CLDN18.2 expression, IBI343 dose level, and lines of prior therapy.

Descriptive statistical analysis will be provided including number, mean, standard deviation, median, maximum and minimum for continuous data; Frequency and percentage will be provided by category data.

All statistical analyses will be performed using SAS 9.4 (or higher).

8.5 Participant Disposition

The number and percentage of participants who received treatment, discontinued study treatment, and/or withdrawal from the study will be summarized. The primary reason for discontinuation of study drug and/or withdrawal from the study will also be summarized by the categories in the eCRF.

8.6 Baseline characteristics of participants

Descriptive analysis will be performed on demographic and baseline characteristics (including age, gender, race, ethnicity, height, weight, etc.), disease diagnosis (including tumor duration, pathological diagnosis, clinical stage, etc.), prior anti-tumor therapy

(including drugs, radiotherapy, surgery, etc.), baseline tumor evaluation, vital signs, ECOG PS score, laboratory tests, prior and concomitant medications, etc. Baseline characteristics will be analyzed in the SP and in the EEP if necessary.

8.7 Safety Analysis

SP will be used for safety analyses including incidence, severity, and relationship to study drug of various AE, changes in vital signs, ECG, physical examination findings, and laboratory test results before and after the drug administration.

8.7.1 Drug Exposure and Treatment Compliance

Drug exposure will be summarized by phase and dose level/cohort in the SP. The number of cycles, cumulative dose, dose intensity, and relative dose intensity, etc. will be summarized descriptively.

8.7.2 DLT Analysis

DLT analysis will be performed in the DEP only for Phase Ia dose escalation phase. DLT occur during the DLT observation window will be summarized by dose level, system organ class, and preferred term.

8.7.3 Adverse Events

All AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The incidence and severity (according to NCI CTCAE) of TEAE, TRAE, SAE, TEAE leading to discontinuation, etc. will be summarized by dose level/cohort, system organ class and preferred term.

The analysis of adverse event will focus on TEAE. The definition of TEAE will be detailed in the SAP.

Data listing will be provided for TEAE leading to treatment discontinuation, TEAE leading to death, SAE. The content of the listing includes but not limited to the start date and the end date of AE, relationship to study drug, severity, action taken, ect.

8.7.4 Laboratory Tests

Observed values and changes from baseline will be summarized with descriptive statistics for quantitative laboratory parameters. The changes post baseline will be summarized. The observed abnormal laboratory values will also be graded according to CTCAE v5.0, and the number and percentage of participants with CTCAE grade increased will be summarized.

8.7.5 Electrocardiogram examination

Observed values and changes from baseline will be summarized with descriptive statistics for ECG quantitative parameters. Shifts from baseline and post-baseline in the overall evaluation of ECGs will be summarized.

8.7.6 Vital Signs, Physical Examinations, and Other Safety-Related Tests

Observed values and changes from baseline will be summarized with descriptive statistics.

Participants with abnormal physical examinations and other safety-related tests will be listed.

8.8 Efficacy Analysis

Efficacy analyses will be summarized descriptively in the EEP. The anti-tumor activity of IBI343 will be assessed by:

- Best overall response (CR, PR, SD, or PD)
- ORR (CR + PR)
- DCR (CR + PR + SD)
- DoR and TTR
- PFS and OS

PFS and DoR will be censored at the last tumor assessment for participants who have not progressed at the time of data cutoff. For participants who have not died at the time of data cutoff, OS will be censored at the last known alive date.

ORR and DCR with 95% CI will be provided. For time-to-event variables (DoR, TTR, PFS, and OS), the Kaplan-Meier method will be used to estimate the median time and its 95% CI, and the survival rate and 95% CI at a specific time point (eg, Months 6, 12, and every 6 months thereafter if applicable). Kaplan-Meier curves will also be plotted (if applicable).

8.9 PK Analysis

PK data from Phase Ia will be analyzed primarily using non-compartmental (NCA) methods and will be used to determine the participant's primary PK parameters, including but not limited to C_{max}, AUC, T_{max}, C_{trough}, CL, V, and $t_{1/2}$. At the same time, descriptive statistics will be performed for the parameters in the PK population.

If required, PK data from Phase Ia and Phase Ib will be combined for Pop PK analysis and exposure-response analysis; they will be reported separately.

8.10 Immunogenicity Analysis

The number and percentage of ADA positive and NAb positive (if necessary) will be summarized descriptively by dose level/cohort in the SP.

8.11 Interim Analysis

No interim analysis is planned for this study.

8.12 Dose Optimization Analysis

The dose optimal analysis will be conducted to determine one optimal dose level during Part 2 of phase Ia. The optimal dose level will be decided based on overall assessment of efficacy and safety data. The following criteria will be included as part of the information used for dose selection. Additional factors such as depth of response, duration of response, and chronic toxicity will also be included.

- Assuming binomial distribution for the ORR and a beta conjugate prior, the high dose level will be considered efficacious relative to the low dose level if the posterior probability of the difference in ORR given the observed ORR data suggest that: Pr ($ORR_{high} > ORR_{low} \mid data$) > 70%.
- Assuming normal-normal conjugate prior, the high dose level will be considered toxic relative to the low dose level if the posterior probability of the differences in the percent change from baseline in neutrophil count (PCNC) given the observed data suggest that: Pr ($PCNC_{high} < PCNC_{low} \mid data$) > 70%.

8.13 Exploratory Analysis

The number and percentage of participants with different CLDN18.2 expression levels will be summarized with descriptive statistics in the SP or/and EEP. The correlation between baseline CLDN18.2 expression level and efficacy will be analyzed exploratively.

8.14 Measures to control bias

No comparison between groups will be performed in this study. The primary efficacy variable ORR in Phase Ib Cohort A will be based on IRRC tumor response assessment according to RECIST v1.1.

8.15 Randomization and Blinding

Participants in dose optimization cohort of G/GEJ AC will be randomized by the stratified blocked randomization with 1:1 ratio, the randomization stratification factor is history of prior gastrectomy (Yes vs. No).

Participants in dose optimization cohort of PDAC will be randomized by the stratified blocked randomization with 1:1 ratio, the randomization stratification factors are prior anti-cancer therapy line (1L vs. 2L+), prior irinotecan therapy (Yes vs. No), CLDN18.2 expression level (<75% vs. ≥75%), and region (China vs. Other).

The Investigator or qualified designee will log in to the system with their respective passwords, and the system will then assign unique random number to each participant. The randomization statistician should use the stratified blocked randomization to generate the randomization list (participant randomization number), and the randomization list will be submitted to the randomization system in the form of electronic documents. The details of randomization will be documented in the randomization specification. During the

conduct of the study, the randomization list of some stratum may not be used in case of the sponsor determine that dose optimization part conducts in one region instead of multiple regions.

This study is open label study. Both the investigator and the participant are open to the study drug.

8.16 Maintenance of Blinded Assessments

Not applicable.

9 Quality Assurance and Quality Control

According to the GCP guidelines, the Sponsor is responsible for implementing and maintaining the quality assurance and quality control system per corresponding standard operating procedures to ensure that the conduct of the clinical trial and the collection, recording and reporting of data comply with the protocol, GCP and corresponding regulatory requirements.

9.1 Clinical Monitoring

The Sponsor or contract research organization (CRO) authorized by the Sponsor will conduct clinical monitoring of the study. CRAs should conduct monitoring according to the standard operating procedures of the Sponsor or CRO, and have the same rights and responsibilities as the Sponsor's CRAs. CRAs should maintain regular communication with the Investigator and the Sponsor.

Prior to the start of the study, the CRAs will assess the competence of each study site and report to the Sponsor problems with facilities, technical equipment, or medical personnel. During the study, CRAs will be responsible for monitoring whether the Investigator has obtained written informed consent from all participants and whether the data records are correct and complete. CRAs will also compare the data entered into the eCRF with the raw data and inform the Investigator of any errors or omissions. CRAs will also control protocol compliance at study sites, arrange for supply of study drug, and ensure that the drugs are stored under appropriate conditions.

Monitoring visits will be conducted in accordance with applicable laws and regulations. Each site will receive periodic monitoring visits from the time of participant Enrollment. CRAs should submit a written report to the Sponsor after each visit to the Investigator.

9.2 Data Management

An electronic data capture (EDC) system will be used for this study and study data will be entered into the eCRF by the Investigator or authorized personnel. Prior to the initiation of the study or data entry, the Investigator and authorized personnel should be properly trained and appropriate safety measures should be taken for the computer and other equipment to be used.

Data entry into the eCRFs should be completed during or after visits as soon as possible. eCRFs should be updated at any time to ensure that they reflect the latest conditions of the participants. To avoid variations in outcome evaluations by different evaluators, it is recommended that the baseline and all subsequent efficacy and safety evaluations of a participant be performed by the same individual. The Investigator are required to review the data to ensure the accuracy and correctness of all the data entered into the eCRFs. If some evaluations are not conducted during the study, or some information is not evaluable, not applicable, or unknown, the Investigator should record these situations in the eCRFs. The Investigator should sign the verified data electronically.

CRAs will review the eCRFs and evaluate the completeness and consistency by comparing them with the original documents to ensuring consistency of all data. Data entry, corrections, and modifications should be performed by the Investigator or designee. The data in the eCRFs will submitted to data server(s) and any data modification should be recorded in the audit trail, including reasons, operator names, and time and dates of modifications. The roles and permission levels of the personnel responsible for data entry at the study site will be determined in advance. CRAs or data management personnel may raise a query in the EDC for suspicious data. The study site personnel are responsible for dealing with such queries. The EDC system will record the audit trail of the query, including the Investigator name, time, and date.

Unless otherwise specified, the eCRFs should only be used as forms to collect data and not as data source. Source documents are records used by the Investigators or hospital, including all those related to the participants, which capable of proving the presence, inclusion/exclusion criteria, and participation of participants including laboratory records, ECG results, pharmacy dispensing records, participant folders, and so on.

The Investigator is responsible for the maintenance of all source documents and should offer the documents to the CRA for review during each visit. In addition, the Investigator must submit a complete eCRF for each enrolled participant, regardless of the duration of participation. The protocol numbers and participant numbers of all supporting documents (such as laboratory records or hospital records) submitted along with the eCRFs should be carefully verified. All the personal identities (including the participant names) should be deleted or made illegible for participant privacy protection. The Investigator should verify that the record has been reviewed and ensure the accuracy of the recorded data by using an electronic signature. The electronic signature should be completed using the Investigator’s user ID and password. The system will automatically attach the date and time for signing to the signature. The Investigator must not share his/her user ID and password with others. If the data in the eCRFs is to be changed, the change should be performed following the procedures outlined by the EDC system. All changes and corresponding reasons should be recorded in the audit trail.

AEs, concomitant diseases/history, and so on should be coded. The dictionary used for

coding will be described in the CSR.

9.3 Quality Assurance Audit

During the course of the study, the Sponsor or designee may conduct quality assurance audits of the study sites, database, and related research documents. At the same time, the corresponding regulatory authorities may also inspect the study sites, database, and related research documents at their own discretion. The Investigator should notify the Sponsor immediately after being informed of an inspection from regulatory authorities.

The Sponsor's quality assurance department will audit the clinical study sites. The audits include the supply of drugs, required trial documents, records of the informed consent process, as well as the consistency between CRFs with the source documents. The content and scope of the audit can also be increased as the circumstances require. After reasonable notice, the Investigator should allow auditors commissioned by the Sponsor and the regulatory authorities access to the site so that they can conduct audits and inspections, respectively. The primary purpose of audits or inspections is to verify that the rights or health of trial participants have been protected, the informed consent forms properly signed, the trial process correctly implemented, and all data related to evaluation of the investigational drug processed and reported in accordance with the pre-planned arrangement, protocol, facilities, ethical standard operating procedures, GCP and applicable regulatory requirements. The Investigator should allow auditors and/or insepctors direct accesses to all trial files, original records, and raw data.

10 Ethics

10.1 Ethics Committee

The Sponsor or its authorized representative will prepare relevant documents to be submitted to the ethics committee (EC) of the study site, including the trial protocol, ICF, Investigator's brochure, participant recruitment materials or advertisements and other documents required by laws and regulations, which will be submitted to the corresponding EC for review and approval. Written approval from the EC must be obtained and provided to the Sponsor prior to initiation of the study. The EC approval letter must specify exactly the name, number, and version number of the study protocol as well as the version number of other documents (e.g., ICF) and the approval date. The Investigator should notify the Sponsor of the EC's written comments on the delay, suspension or re-approval.

The Sponsor or designee will prepare the relevant documents including the study protocol, ICF, Investigator's Brochure, participant recruitment materials or advertisements, and other documents required by regulations, which are to be submitted to the corresponding ethics committee (EC) in of the study site for approval. Prior to the start of the trial, written approval from the EC must be obtained and submitted to the Sponsor. The written approval from the EC should specify the name, number, version number of the protocol

and other documents (such as ICF), and the date of approval. The Investigator is required to notify the Sponsor of the EC's written comments regarding delay, interruption, and re-approval of the study.

The study site must follow the requirements of the correspond EC. Potential documents such as amendments or revisions to the study protocol, ICF, or recruitment materials should be submitted to the EC for approval. Safety reports prepared per local regulations should be regularly drafted, updated and its final version submitted as specified by the EC. All the above documents with EC approvals must be provided to the Sponsor or designee.

10.2 Ethical conduct in the study

The study process and ICF acquisition should comply with the Declaration of Helsinki, relevant GCP requirements and relevant local laws and regulations on drug and data protection.

GCP provides ethical, scientific, global quality standards for the design, implementation, documentation, and report of clinical studies involving human participants. This study will be conducted in accordance with the GCP and relevant national/regional laws regulations and in accordance with the relevant ethical principles of the Declaration of Helsinki to protect the rights, safety, and health of the participants.

The Investigator is required to comply with the procedures specified in this trial protocol and must not change them without the permission of the Sponsor. Any protocol deviations will be reported to the EC, Sponsor, or regulatory authorities.

10.3 Participant Information and Informed Consent

Before the start of any research process, the ICF will be used to explain to potential participants the risks and benefits of this study. The language of the informed consent should be simple and easy to understand. The ICF statement should clarify that signing the ICF is voluntary, and the risks and benefits of participating in this study should be clearly outlined. The participant can withdraw from the study at any time. Participants can only be enrolled if he/she fully understands the study in detail, has received satisfactory answers to his/her inquiries, and has sufficient time for consideration. Written consent must be obtained from the participants or his/her legally acceptable representative. All signed ICFs must be stored in the Investigator's files or in the participant's folder.

It is the responsibility of the Investigator to explain the content of the informed consent to the participant and to obtain a signed and dated informed consent form from the participant or the participant's legally acceptable representative prior to the start of the study. After signing, the Investigator should send the participant a copy of the signed informed consent form. The Investigator should record the informed consent process in the study source documents.

The original informed consent form, any subsequent amendment to the written informed consent form, and any written information provided to the participants must be approved by the Institutional Review Board/EC before use. If there is any new available information that may be relevant to the participant's willingness to continue participating in the trial, the participant or his/her legally acceptable representative should be informed promptly. Communication of this information will be provided and documented either through a revised informed consent form or an appendix to the original informed consent form (with dated signature of the participant or his/her legally authorized representative).

10.4 Data Protection

Information on data protection and privacy protection will be included (or in some cases, along with the use of separate files) in the ICF.

Preventive measures will be taken to ensure the confidentiality of the document and prevent the identification of the participant. However, under special circumstances, some personnel may have access to a participant's genetic data and personal identification number. For example, in the event of medical emergency, the Sponsor, its physician or the Investigator will have access to participant's identification number and genetic data. In addition, relevant regulatory authorities may require access to relevant documents.

10.5 Protocol Violation

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP requirements, or Manuals of Procedures. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. Corrective actions on the deviations should be developed by the site and implemented promptly.

11 Study Management

11.1 Data Handling and Record Retention

Documents in clinical trials (such as protocol and protocol amendments, completed eCRFs, and signed ICFs) need to be preserved and managed in accordance with GCP requirements. Study sites should keep these documents until 5 years after marketing approval of the investigational drugs. Research documents should be properly preserved for future access or data traceability. Safety and environmental risks should be taken into account regarding document preservation.

No study document may be destroyed without the written permission of the Sponsor and the Investigator. Only after notifying the Sponsor and obtaining its written consent can the Investigator/study site transfer the study documents to other parties who comply with the document preservation requirements or to other locations that meet the requirements.

11.2 Access to Raw Data/Documents

The Investigator agrees that the Sponsor, CRO and relevant authorized regulatory authorities have direct access to all study-related documents, including participants'

medical records.

11.3 Protocol Amendment

Any appropriate changes to the protocol during the course of the study should be discussed between and agreed upon by the Sponsor and the Investigator. The Sponsor should ensure that protocol amendments are submitted to regulatory authorities in a timely manner.

All amendments to the protocol should be preserved as supplements to the protocol. Any amendments to the protocol should be submitted to the EC for approval or filing in accordance with the requirements of the EC. If necessary, protocol amendments should also be submitted to the regulatory authorities for approval and approved by the EC and regulatory authorities (if necessary) before implementation (except for amendments to the protocol to eliminate immediate hazards to trial participants).

11.4 Investigator Responsibilities

The Investigator will conduct this study in accordance with the protocol, ethical principles of Declaration of Helsinki, GCP and relevant laws and regulations.

11.5 Publication Policy

All data generated from this study are confidential information of the Sponsor. The Sponsor has the right to publish the study results. Information regarding the Sponsor's and Investigator's publication policy will be described in the clinical trial agreement.

All information related to this study (not limited to the following documents: protocol, Investigator's Brochure) must be kept strictly confidential. The Investigator should be aware that the scientific or medical information derived from this study may be of commercial value to the Sponsor. The Investigator should keep the information and data related to this trial confidential. In order to publish the information related to this trial or the conclusions drawn from this trial, it is necessary to negotiate with the Sponsor in advance and obtain the written consent of the Sponsor. In order to protect its rights and interests, the Sponsor may require that the Investigator not publish the information about the trial before the investigational product is approved for marketing.

The Sponsor has the right to publish the information or data related to this study or submit the information to the regulatory authorities. If the Sponsor needs to display the name of the Investigator in a publication or advertisement, the Investigator's consent should be obtained.

11.6 Finance and Insurance

The Sponsor will purchase insurance for participants of this study in accordance with local laws and regulations and minimum requirements. The terms of the insurance will be stored in the study folder.

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13 Appendices

Appendix 1 Protocol Amendment History

Version Number	Version Date
V1.0	April 26, 2022
V1.1	June 7, 2022
V1.2	October 21, 2022
V3.0	April 8, 2024
V3.1	April 26, 2024
V4.0	May 30, 2024

Appendix 2 Evaluation Criteria (RECIST v1.1)

1. Measurability of tumor at baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be classified as measurable or non-measurable according to the following definitions:

1.1. 1 Measurable disease

Tumor lesions: at least one diameter that can be accurately measured (to be recorded as the largest diameter) with the following minimum lengths:

10 mm by CT scan (CT scan slice thickness no greater than 5 mm);

10 mm by clinical routine examination (tumor lesions that cannot be accurately measured by calipers should be recorded as non-measurable);

Chest X-ray 20 mm;

Malignant lymph nodes: Pathologically enlarged and measurable, an individual lymph node must be ≥ 15 mm in the short axis by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

1.1. 2 Non-measurable disease

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes ≥ 10 mm to < 15 mm short axis) and non-measurable lesions. Non-measurable lesions include meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, lymphangitic carcinomatosis of the skin/lung, abdominal masses that cannot be confirmed by imaging and followed up, and cystic lesions.

1.1. 3 Special Considerations for Lesion Measurements

Bone lesions, cystic lesions, and lesions previously treated with local therapy need to be specifically noted:

Bone lesions:

1) Bone scan, PET scan or plain film are not suitable for measuring bone lesions, but can be used to confirm the presence or disappearance of bone lesions;

2) Lytic bone lesions or mixed lytic/blastic lesions with defined soft tissue components that meet the definition of measurability described above can be considered as measurable lesions if they can be evaluated with cross-sectional imaging techniques such as CT or MRI;

3) Blastic lesions are non-measurable.

Cystic lesions:

1) Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions because they are simple cysts by definition, neither measurable nor non-measurable;

2) Cystic metastases that meet the definition of measurability described above can be considered as measurable lesions. However, if non-cystic lesions are present in the same participant, they should be preferred as target lesions.

Locally treated lesions:

Lesions located in sites that have been irradiated or other loco-regional therapy are generally considered non-measurable unless there is unequivocal progression in the lesion. The protocol should describe in detail the conditions under which these lesions are measurable.

1.2 Description of measurement method

1.2. 1 Lesion Measurements

All tumor measurements will be recorded in the metric system at the time of clinical evaluation. All baseline assessments of tumor lesion size should be performed as close as possible to the start of treatment and must be completed within 28 days (4 weeks) prior to the start of treatment.

1.2. 2 Evaluation method

The same techniques and methods should be used for baseline and subsequent measurements of lesions. All lesions must be evaluated by imaging, except those that cannot be evaluated by imaging but can only be evaluated by clinical examination.

Clinical lesions: Clinical lesions will be considered measurable only if they are superficial and ≥ 10 mm in diameter when measured (e.g., skin nodules, etc.). For participants with skin lesions, it is recommended that a color photograph containing a ruler to measure the size of the lesion be used for archiving. When lesions are evaluated by both imaging and clinical examination, imaging evaluation should be selected whenever possible because imaging is more objective and can be repeated at the end of the study.

Chest X-ray: Chest CT should be preferred when tumor progression is an important endpoint because CT is more sensitive than X-ray, especially for new lesions. Chest X-ray is indicated only if the lesion being measured is well-defined and the lungs are well ventilated.

CT, MRI: CT is currently the best reproducible method available for response assessment. The definition of measurability in this guideline is based on CT scan slice thickness ≤ 5 mm. If CT slice thickness is greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI may also be acceptable in

some cases (e.g., full body scans).

Ultrasound: Ultrasound should not be used as a method of measurement to measure lesion size. Ultrasonography is not repeatable after the end of the measurement due to its operational dependency and does not guarantee the identity of the technique and measurement between different measurements. If a new lesion is identified by ultrasound during the trial, it should be confirmed by CT or MRI. If radiation exposure from CT is considered, MRI may be used instead.

Endoscopy, laparoscopy: The use of these techniques for objective tumor assessment is not recommended, but they can be used to confirm CR when biopsies are obtained and to confirm recurrence in trials where recurrence after CR or surgical resection is an endpoint.

2. Assessment of tumor response

2.1 Target Lesion Assessment

Complete Response (CR): Disappearance of all target lesions and reduction in short axis of all pathological lymph nodes (both target and non-target) to < 10 mm.

Partial Response (PR): at least a 30% decrease from baseline in the sum of diameters of target lesions.

Progressive disease (PD): at least a 20% relative increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters of all target lesions measured throughout the study (the baseline value will be taken as reference if the baseline value is the smallest); In addition, the absolute increase in the sum of diameters must be at least 5 mm (the appearance of one or more new lesions is also considered PD).

Stable disease (SD): Neither a decrease to the level of PR nor an increase to the level of PD in target lesions, taking as reference the smallest sum diameters on study.

2.2 Considerations for Target Lesion Assessment

Lymph nodes: Even if lymph nodes identified as target lesions decrease to within 10 mm, the actual short axis value corresponding to baseline should be recorded at each measurement (in the same anatomical plane as the baseline measurement). This means that if a lymph node is a target lesion, it cannot be said that the lesion has completely disappeared even if the criteria for CR are met, since a normal lymph node is defined as < 10 mm in short axis. Target nodal lesions should be recorded in a specific location in the CRF or other recording methods: for CR, all nodal short axis must be < 10 mm; For PR, SD and PD, the actual short axis measurement of target nodes will be included in the sum of the diameters of target lesions.

Target lesions that are too small to measure: in clinical studies, all lesions (nodal or

non-nodal) recorded at baseline should have their actual measurements recorded again at subsequent assessments, even if they are very small (e.g., 2 mm). But sometimes it may be too small to make the CT scan so blurry that the radiologist has difficulty defining the exact value and may report it as "too small to measure." When this occurs, it is important to record the previous value on the eCRF form. If in the opinion of the radiologist, the lesion may have disappeared, it should also be recorded as 0 mm. If a lesion is present but blurry and cannot be accurately measured, the default value is 5 mm. (Note: Lymph nodes are unlikely to be present because they typically have a measurable size under normal conditions or are often surrounded by adipose tissue as they are in the retroperitoneum; however, if such a situation does not allow measurement, the default value is 5 mm). The default value of 5 mm is derived from the cut thickness of the CT scan (this value does not change according to the different cut thickness values of CT). Providing this default value will reduce the risk of erroneous evaluation since the same measurement is not likely to be repeated. However, it should be reiterated that if the radiologist is able to provide an exact value for the size of the lesion, the actual value must be recorded even if the lesion is less than 5 mm in diameter.

Separated or Combined Lesions: When a non-nodal lesion splits into fragments, the longest diameters of the separate portions are added together to calculate the sum of the diameters of the lesions. Similarly, for coalescent lesions, the planes between the coalescent segments can be used to distinguish them, and the respective maximum diameter can be calculated. However, if the combination is inseparable, the longest diameter should take the longest diameter of the whole coalescing lesion.

2.3 Assessment of Non-Target Lesions

This section defines tumor response criteria for non-target lesions. Although some non-target lesions are actually measurable, they do not need to be measured and only need to be assessed qualitatively immediately at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes are non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesions and/or persistence of tumor marker level above normal.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. Note: The appearance of one or more new lesions is also considered PD.

2.4 Special Considerations for Assessment of Progression of Non-Target Lesions

The definition of progression of non-target disease is supplemented with the following explanation: When a participant has measurable non-target disease, to define unequivocal progression on the basis of non-target disease, even if the target disease

assessment is SD or PR, the overall worsening in non-target disease must be sufficient to warrant discontinuation of therapy. A general increase in the size of one or more non-target lesions is often not sufficient to meet the criteria for progression, and therefore, in the presence of SD or PR in target lesions, it is almost rare for a change in non-target disease alone to define overall tumor progression.

When a participant has non-measurable non-target disease: This occurs in some Phase 3 trials when the inclusion criteria do not specify that measurable disease must be present. The overall assessment will also refer to the above criteria, but in this case, there is no measurable disease. Worsening in non-target disease cannot be easily assessed (by definition: all non-target lesions must be truly non-measurable), and therefore a valid test is needed to assess unequivocal progression in non-target disease when the increase in overall disease burden due to the change in non-target disease is comparable to PD in target disease. This is described as an increase in tumor burden corresponding to an additional 73% increase in volume (corresponding to a 20% increase in diameter of a measurable lesion). Another example is peritoneal exudation from "trace" to "large"; Lymphangiopathy from "local" to "widespread"; Or described in the protocol as "sufficient to change treatment". Examples include pleural effusion ranging from trace to large, lymphatic involvement spreading from the primary site to distant sites, or may be described in protocols as "warranting a change in therapy". If unequivocal progression is found, the participant should be considered PD overall at that time point. It is preferable to have objective criteria applicable to the assessment of non-measurable disease, note that the added criteria must be reliable.

2.5 New lesions

The appearance of new malignant lesions predicts disease progression; Therefore, some evaluation of new lesions is very important. There are no specific criteria for radiographic detection of lesions, however the finding of a new lesion should be unequivocal. For example, progression cannot be attributed to differences in imaging techniques, changes in imaging modality, or lesions other than tumor (e.g., some so-called new bone lesions are simply healing of the original lesion, or recurrence of the original lesion). This is important when a participant has a partial or complete response of baseline lesions, e.g. Necrosis of a liver lesion may be identified as a new cystic lesion on the CT report when it is not.

Lesions detected at follow-up but not at baseline will be considered new lesions and indicate PD. For example, a participant with visceral disease at baseline who has metastases on CT or MRI of the brain will be considered as evidence of PD, even if he did not have a brain examination at baseline.

If a new lesion is equivocal, for example due to its small size, further treatment and follow-up evaluation are required to confirm whether it is a new lesion. If repeat testing

confirms that it is a new lesion, the time of PD should be counted from the time of its initial finding.

^{18}F-FDG-PET assessment of lesions generally requires additional testing for confirmation, and it is reasonable to combine ^{18}F-FDG-PET with CT to assess progression (especially for new suspected disease). New lesions can be identified by ^{18}F-FDG-PET using the following procedures:

A negative ^{18}F-FDG-PET at baseline followed by a positive ^{18}F-FDG-PET at follow-up indicates disease progression.

No baseline ^{18}F-FDG-PET and positive follow-up 18F-FDG-PET:

PD is documented if the positive ^{18}F-FDG-PET at follow-up identifies a new lesion consistent with the CT findings.

If a positive ^{18}F-FDG-PET at follow-up is not confirmed by CT, additional CT scans will be used to confirm new lesions (if confirmed, PD will begin with the previous abnormal ^{18}F-FDG-PET scan).

If a positive ^{18}F-FDG-PET at follow-up is consistent with a pre-existing lesion on CT that does not progress radiographically, there is no progression.

2.6 Description of Missing Assessments and Not Evaluable

If a lesion cannot be imaged or measured at a particular time point, the participant is not evaluable at that time point. If only a subset of lesions can be evaluated at an assessment, this is generally considered not evaluable at that timepoint unless there is evidence that the missing lesions do not affect the response assessment at the given timepoint.

2.7 Special Notes for Efficacy Assessment

When nodal lesions are included in the overall target lesion assessment and the nodes decrease in size to "normal" size (< 10 mm), they will still have a lesion size scan report. In order to avoid overestimating what is reflected by an increase in nodal size, measurements will be recorded even if the node is normal. As already mentioned, this means that participants with a response of CR will not be recorded as 0 on the eCRF.

If confirmation of response is required during the course of the trial, repeated "non-measurable" time points will complicate the best response assessment. The analysis plan for the trial must specify that these missing data/assessments can be accounted for when determining efficacy. For example, in most trials, a participant's response of PR-NE-PR can be considered a confirmed response.

Symptomatic progression should be reported when a participant experiences a global deterioration in his/her health condition requiring discontinuation of treatment without objective evidence. Every effort should be made to assess objective progression even

after treatment discontinuation. Symptomatic deterioration is not an assessment description of an objective response, it is a reason for discontinuation of treatment. The objective response of such participants will be evaluated by target and non-target lesions as shown in Table 2-1 ~ 2-3.

Conditions defined as early progression, early death, and non-evaluability are study specific and should be clearly described in each protocol (depending on treatment interval and treatment cycle).

In some cases, it is difficult to distinguish a local lesion from normal tissue. When the assessment of CR is based on this definition, it is recommended that a biopsy be performed prior to the response assessment of CR of local lesions. In some participants, 18F-FDG-PET was used as a similar assessment to biopsy for response confirmation of CR when abnormal radiographic findings in local lesions were considered to represent fibrosis or scarring of the lesion. In such cases, the use of 18F-FDG-PET should be prospectively described in the protocol, supported by reports from the specialized medical literature for this condition. However, it must be recognized that the limitations of 18F-FDG-PET and biopsy itself, including their resolution and sensitivity, may lead to false-positive results in the assessment of CR.

Attached Table 2-1 Time Point Response-Participants with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall response
CR	CR	None	CR
CR	Non-CR/Non-PD	None	PR
CR	Not evaluable	None	PR
PR	Non-progressive or not fully evaluable	None	PR
SD	Non-progressive or not fully evaluable	None	SD
Not fully assessed	Non-Progressive	None	NE
PD	Any condition	Yes or No	PD
Any condition	PD	Yes or No	PD
Any condition	Any condition	Yes	PD

Note: CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable.

Attached Table 2-2 Time Point Response-Participants with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall response
CR	None	CR
Non-CR or Non-PD	None	Non-CR or Non-PD
Not fully assessed	None	Not evaluable
Indeterminate PD	Yes or No	PD
Any condition	Yes	PD

Note: For non-target lesions, "non-CR/non-PD" is defined as a response superior to SD. As SD is increasingly used as an endpoint to evaluate response, a non-CR/non-PD response was developed to address the non-specified absence of measurable disease.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic or necrotic lesions in pre-existing lesions), treatment may continue until the next assessment. If PD is confirmed at the next assessment, the date of progression should be the previous date of suspected progression.

Attached Tables 2-3 Best overall response requiring confirmation of CR and PR

First Time Point Overall Response	Overall Response at Subsequent Timepoints	Best overall response
CR	CR	CR
CR	PR	SD, PD or PRa
CR	SD	SD if SD lasts for sufficient time, otherwise PD
CR	PD	SD if SD lasts for sufficient time, otherwise PD
CR	NE	SD if SD lasts sufficient time, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD if SD lasts for sufficient time, otherwise PD
PR	NE	SD if SD lasts sufficient time, otherwise NE
NE	NE	NE

Note: CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable.
a: If a CR truly occurs at the first timepoint, any disease that occurs at a subsequent timepoint will remain PD at a subsequent timepoint even if the participant meets the criteria for PR relative to baseline (since disease will reappear after CR). Best response is determined by the occurrence of SD within the shortest treatment interval. However, sometimes the first assessment is CR, but subsequent time point scans suggest that small lesions still appear to be present, so that the participant's response should actually be PR rather than CR at the first time point. In this case, the initial CR determination should be revised to PR and the best response is PR.

2.8 Response Assessment/Confirmation of Response Duration

2.8. 1 Confirmation of response

For non-randomized clinical studies where tumor response is the primary endpoint, confirmation of PR and CR is mandatory to ensure that response is not the result of misevaluation. In studies with SD or PD as the primary endpoint, confirmation of response is no longer required because it is not valuable for the interpretation of trial results. In the case of SD, at least one measurement met the SD criteria specified in the protocol at the shortest interval after the start of the trial (generally not less than 6 to 8 weeks).

2.8. 2 Overall Response

The duration of overall response is measured from the time the measurement first meets the criteria for CR or PR (whichever is first measured) to the first true documentation of recurrent or progressive disease (taking the smallest measurement recorded on the trial as reference for PD). The time to overall complete response is the time from the time the measurement first meets the criteria for CR to the first true documentation of disease recurrence or progression.

2.8. 3 Stable Disease

The time from the start of treatment to PD (in randomised trials, from the time of randomisation), taking as reference the smallest sum in the trial (if the baseline sum is the smallest, this is the reference for the calculation of PD). The clinical relevance of stable disease varies from study to study and from disease to disease. If the proportion of participants who maintain a minimum duration of stabilization is used as an endpoint in a particular trial, the protocol should specifically specify the minimum time interval between two measurements in the definition of SD.

Note: The duration of response, stable disease, and PFS are influenced by the frequency of follow-up after baseline evaluation. Defining a standard follow-up frequency is outside the scope of this guideline. The frequency of follow-up should take into account many factors, such as type and stage of disease, duration of treatment, and standard practices. However, limitations in the accuracy of these measured endpoints should be taken into account if comparisons between trials are necessary.

Appendix 3 List of Causal Relationship between Adverse Events and Study Drug

<table>
<tr><td>Relationship to Sponsor's Product</td><td colspan="2">Did the study drug cauase the AE? The medically qualified Investigator is required to provide a causal assessment between the study drug and the AE. The Investigator will sign/date (initials) the source document or worksheet to support the causality assessment on the AE form to ensure a medically qualified causality assessment. This signed document must be preserved for the timeframe per relevant regulatory requirement. The following criteria aim to serve as a guide to assist the Investigator in assessing the relationship between the investigational product and the occurrence of an AE based on the available information.
The following factors are used to assess the relationship between the study drug and the AE; The stronger (in terms of number and/or intensity) the asscoiation between each item and their corresponding factor, the greater the likelihood that the study drug caused the AE;</td></tr>
<tr><td rowspan="4"></td><td>Exposure</td><td>Is there evidence that the participant was indeed exposed to the trial drug, e.g., a credible medical history, acceptable compliance assessments (drug counts, logs, etc.), expected pharmacological effects, measurement of drug/metabolites in samples collected from the participant?</td></tr>
<tr><td>Time course</td><td>Is there a reasonable temporal sequence between the AE and treatment with the trial drug?
Did the AE occur within a timeframe consistent with an induced by the study drug?</td></tr>
<tr><td>Reasons other than study drug</td><td>Is there an alternative etiology for the AE, such as underlying disease, other drugs/vaccines, or other host or environmental factors</td></tr>
<tr><td>Dechallenge</td><td>Was study drug discontinued or dose/exposure/frequency reduced?
If yes, did the AE resolve or improve?
If yes, a positive dechallenge is indicated.
If not, a negative dechallenge is indicated.
Note: This criterion does not apply if: (1) the AE results in death or permanent disability; (2) AE recovered/improved despite continued use of study drug; (3) the trial used a single-dose design; (4) only dose of the study drug was used.</td></tr>
</table>

	Rechallenge	Has the participant been exposed again to the study drug in this trial? If yes, did the AE reappear or worsen? ? If yes, a positive rechallenge is indicated. If not, a negative rechallenge is indicated. Note: This criterion does not apply if: (1) the initial AE resulted in death or permanent disability, (2) the trial used a single-dose design; (3) only dose of the study drug was used. Note: If a rechallenge is planned for an AE that is serious and may be caused by the investigational product, or if re-exposure to the tiral study drug may pose a serious potential risk to the participant, rechallenge is not recommended unless it is considered that continued treatment with the study drug may benefit participant and no alternative treatment is available, and may be conducted only after approval by the Sponsor.
	Consistency with trial treatment characteristics	Is the clinical/pathological presentation of the AE consistent with information on the pharmacology and toxicology studies of the study drug or drugs of the same class?
The medically qualified Investigator will record the causality assessment based on his/her best clinical judgment that takes into consideration the causality factors above. The causality assessment of the AE to the study drug will be recorded as “related” and “not related”.		
Causality Record		**The table below may be used for causality assessment (not all criteria need to be met)**
Related		There is generally evidence of exposure to study drug. There is a reasonable temporal sequence between occurrence of the AE and treatment with the Sponsor’s product. The occurrence of the AE is more likely to be explained by the study drug than by other causes.
Not related		Generally, the participant was not administered the study drug. There is an unreasonable temporal sequence between occurrence of the AE and treatment with the Sponsor’s product or there are other causes reasonably managed. The occurrence of the AE is more likely to be explained by causes other than the study drug.