CLINICAL TRIAL PROTOCOL

Protocol title:	**Open-label study of tusamitamab ravtansine (SAR408701) in combination with ramucirumab in participants previously treated for advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma with CEACAM5-positive tumors**
Protocol number:	**ACT16444**
Amendment number:	**Not applicable**
Compound number (INN/Trademark):	**SAR408701** **tusamitamab ravtansine/not applicable**
Brief title:	**Tusamitamab ravtansine (SAR408701) in combination with ramucirumab in pretreated participants with gastric cancer** **CARMEN-GC01**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi aventis recherche & développement**
Legal registered address:	**1 avenue Pierre Brossolette,** **91380 Chilly- Mazarin** **FRANCE** **Manufacturer: Same as Sponsor**
Monitoring team's representative name and contact information	Click here and type

Regulatory agency identifier number(s):

IND:	Not applicable
EudraCT:	2021-001967-26
NCT:	Not applicable
WHO:	Not applicable
EUDAMED:	Not applicable
Other:	Not applicable

Date: 19-Apr-2021 Total number of pages: 114

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

Open-label study of tusamitamab ravtansine (SAR408701) in combination with ramucirumab in participants previously treated for advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma with CEACAM5-positive tumors

Brief title: Tusamitamab ravtansine (SAR408701) in combination with ramucirumab in pretreated participants with gastric cancer

Rationale:

Tusamitamab ravtansine monotherapy shows a significant level of activity and a favorable safety profile in heavily pretreated participants with metastatic nonsquamous, non-small-cell lung cancer (NSQ NSCLC) expressing carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5; 1). In participants with gastric cancer (GC) in the main dose escalation part of first-in-human (FIH) study TED13751, 1 partial response (PR) was observed. In the GC FIH expansion cohort, participants received tusamitamab ravtansine as monotherapy at 100 mg/m² administered every 2 weeks (Q2W); in total, 16 participants were treated, and no objective response was reported. Stable disease (SD) was reported for 37.5% of the participants enrolled from this heavily pretreated (median of 3 prior treatments) participant population; 81.3% of these participants had prior taxane therapy. In the FIH "loading dose" escalation cohort, 2 participants with GC were treated at the recommended dosing regimen (170 mg/m² then 100 mg/m² Q2W): a single participant who had been overdosed with twice the loading dose had a nonconfirmed PR, the other participant had SD.

Ramucirumab (a monoclonal antibody antagonist of vascular endothelial growth factor receptor 2 [VEGFR2]) combined with the antitubulin agent paclitaxel provides improved efficacy as compared to single-agent paclitaxel as second-line therapy for GC. This combination therapy was approved as second-line treatment based on the results of the Phase 3 RAINBOW study (2).

Synergy of tusamitamab ravtansine (containing the cytotoxic antitubulin agent DM4) activity in combination with ramucirumab may lead to improved efficacy in treating GC patients with a high unmet need; further the combination of tusamitamab ravtansine and ramucirumab may have a better safety profile compared to the combination of paclitaxel with ramucirumab. Nonclinical evaluations of the combination of tusamitamab ravtansine with a VEGFR2 antagonist were performed in mice with GC patient-derived xenografts (PDXs) to evaluate the substitution of tusamitamab ravtansine for paclitaxel in the combination with ramucirumab. Improved efficacy, optimized treatment duration, and a favorable safety profile were observed for combinations of tusamitamab ravtansine with an anti-VEGFR2 agent as compared to combinations of paclitaxel with an anti-VEGFR2 agent. The positive data from this work support replacing paclitaxel with tusamitamab ravtansine in combination with ramucirumab in a clinical study. Combining ramucirumab with tusamitamab ravtansine rather than with paclitaxel may lead to improved efficacy with a favorable safety profile of the combination in participants with GC.

Objectives and endpoints

Objectives	Endpoints
Primary	
• Part 1: to confirm the recommended tusamitamab ravtansine loading dose Q2W when given in combination with ramucirumab in advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma population • Part 2: To assess the antitumor activity of tusamitamab ravtansine loading dose Q2W in combination with ramucirumab in advanced gastric or GEJ adenocarcinoma	• Part 1: Incidence of study drug related dose-limiting toxicities (DLTs) at Cycle 1 and Cycle 2 (C1D1 to C2D14) • Part 2: Objective Response Rate (ORR), defined as the proportion of participants with confirmed complete response (CR) or partial response (PR) as best overall response (BOR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
Secondary	
• To assess the safety and tolerability of tusamitamab ravtansine loading dose Q2W in combination with ramucirumab	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and laboratory abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V5.0
• To assess the durability of the response to treatment with tusamitamab ravtansine loading dose Q2W in combination with ramucirumab	• Duration of response (DOR), defined as the time from first documented evidence of CR or PR until progressive disease (PD) determined per RECIST 1.1 or death from any cause, whichever occurs first
• To assess progression-free survival (PFS) of tusamitamab ravtansine loading dose Q2W in combination with ramucirumab	• Progression-free survival, defined as the time from the first investigational medicinal product (IMP) administration to the date of the first documented disease progression or death due to any cause, whichever comes first
• To assess the disease control rate (DCR) of tusamitamab ravtansine loading dose Q2W in combination with ramucirumab	• Disease control rate, defined as the proportion of participants with confirmed CR or PR or SD as BOR per RECIST 1.1
• To assess the pharmacokinetics (PK) of tusamitamab ravtansine loading dose Q2W and ramucirumab when given in combination	• Pharmacokinetic parameters of tusamitamab ravtansine and ramucirumab
• To assess the immunogenicity of tusamitamab ravtansine loading dose Q2W when given in combination with ramucirumab	• Incidence of antitherapeutic antibodies (ATAs) against tusamitamab ravtansine

Overall design:

Brief summary:

This is a single group, treatment, Phase 2, open-label, single-arm study to confirm the recommended dose (RD), safety, PK, and preliminary antitumor activity of tusamitamab ravtansine combined with ramucirumab in participants previously treated for gastric or gastroesophageal adenocarcinoma with CEACAM5-positive (defined as CEACAM5 immunohistochemical [IHC] intensity ≥2+ in ≥50% of cells) tumors.

This will be a 2-part study.

Part 1 (safety run-in):

In Part 1, participants will receive ramucirumab 8 mg/kg followed by tusamitamab ravtansine at 170 mg/m^2 (150 mg/m^2) at Day 1 Cycle 1, and ramucirumab 8 mg/kg followed by tusamitamab ravtansine 100 mg/m^2 at Cycle 2 and Q2W in all subsequent cycles. In the case that it is decided to reduce the initial loading dose of tusamitamab ravtansine to DL-1 (Table 1), a tusamitamab ravtansine loading dose of 150 mg/m^2 will be administered to participants on Day 1 of Cycle 1.

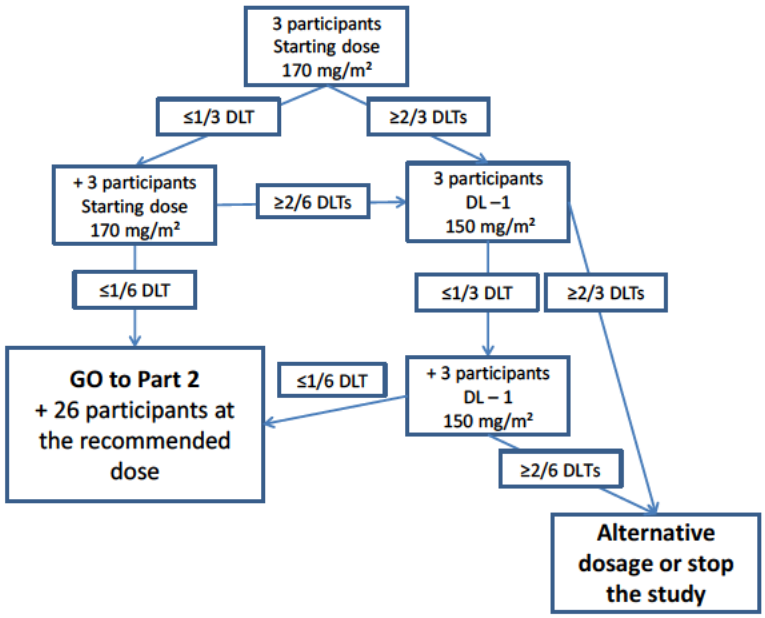
Table 1 - Dose levels for Part 1 (safety run-in)

Dose level (DL)	Tusamitamab ravtansine	Ramucirumab
Starting dose	170 mg/m^2 Q2W Cycle 1; 100 mg/m^2 Q2W Cycle 2 and thereafter	8 mg/kg Q2W
Minus -1 (DL -1)	150 mg/m^2 Q2W Cycle 1; 100 mg/m^2 Q2W Cycle 2 and thereafter	8 mg/kg Q2W

BSA = body surface area; DL -1=dose level -1; Q2W = every 2 weeks.
Infusion of tusamitamab ravtansine will be administered at least 1 hour after the end of ramucirumab infusion for at least the first 2 cycles. For participants with a BSA >2.2 m^2, the tusamitamab ravtansine dose will be calculated based on a BSA of 2.2 m^2.

As no overlap in the safety profiles for ramucirumab and tusamitamab ravtansine is anticipated, the starting dose for tusamitamab ravtansine is selected as the maximum tolerated dose (MTD) used in studies evaluating tusamitamab ravtansine as loading-dose monotherapy. Enough participants will be enrolled in Part 1 to achieve 6 to 12 participants evaluable for DLTs to confirm the recommended dose. The tolerability of the combination is assessed in Part 1 according to the algorithm illustrated in Figure 1. The DLT observation period is the first 2 cycles (approximately 28 days). A DLT-evaluable participant must have completed 2 cycles of treatment or have been discontinued from study treatment because of a DLT; DLT-nonevaluable participants will be replaced. A minimum delay of 1 week is required between the initial dose in the first participant treated in a DL cohort and dosing of the next 2 participants treated at the same DL.

Figure 1 Decision tree for tusamitamab ravtansine loading dose in Part 1



Note: Abbreviations: DL -1 = dose level -1 (150 mg/m2); DLT = dose-limiting toxicity.
In case of 2 or more DLTs at DL-1, an alternative dosage may be considered or the study may be stopped.

In Part 2 of the study, the recommended dose confirmed in Part 1 will be evaluated for activity in 26 additional participants. A total of 32 participants, including participants treated at the recommended dose in Part 1, will be evaluated for activity.

Number of participants:

Approximately 158 participants will be prescreened to achieve up to approximately 38 treated participants, based on an estimated CEACAM5 prescreening failure rate of 70% and an estimated study screening failure rate of 20%.

Intervention groups and duration:

The duration of the study for a participant will include:

- **Screening period:** up to 28 days.
- **Treatment period:** once successfully screened, enrolled participants may receive study intervention until disease progression, unacceptable adverse event (AE), death, initiation of a new anticancer therapy, or the participant's or investigator's decision to stop the treatment. Each cycle of treatment will have a duration of 2 weeks. After discontinuing study intervention, participants will return to the study site approximately 30 days after the last investigational medicinal product (IMP) administration or before the participant receives another anti-cancer therapy, whichever is earlier, for end-of-treatment assessments.
- **Safety follow-up visit**: will be performed approximately 90 days after the last dose of IMP. If any ongoing related AE/SAE is resolved or stabilized, no further follow-up visit is needed.

Participants who stopped treatment before documented progressive disease (PD; ie, achieving SD or CR or PR) should undergo a tumor assessment and an on-site follow-up visit every 8 weeks (±7 days) after the last tumor assessment until radiological disease progression, start of a new anticancer therapy, death, withdrawal of a participant's consent, or cut-off date for secondary efficacy endpoints, whichever comes first. After PD or a start of new anticancer therapy, a participant will be followed until any ongoing related AE/AESI/SAE is resolved or stabilized.

The study cut-off for analysis of the primary endpoint, ORR, corresponds to the date on which all evaluable treated participants have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. This study cut-off can be up to approximately 16 weeks (12 weeks for 2 tumor assessments and 4 weeks for confirmation of response, if needed) after the last participant's first IMP administration.

The final study cut-off date for analysis of the secondary efficacy endpoints, which include DOR and PFS, will be 4 months after the cut-off date for the primary analysis. At that time, the primary analysis of ORR and DCR will also be updated.

After the cut-off date for the analysis of secondary efficacy endpoints, participants still receiving study treatment can continue study treatment, if clinical benefit is observed, until PD, unacceptable toxicity, initiation of a new anticancer therapy, or withdrawal of participants' consent, and will continue to undergo all assessments as per the study flow chart.

The expected duration of study intervention for participants may vary, based on disease progression date; median expected duration of study per participant is estimated as 34 weeks (up to 4 weeks for screening, a median of 18 weeks for treatment, and a median of 12 weeks for end-of-treatment assessments and the safety follow-up visit).

Study interventions

Study interventions include tusamitamab ravtansine and ramucirumab. To prevent hypersensitivity reactions, each administration will be preceded by premedication.

Administration of tusamitamab ravtansine will be initiated after the completion of ramucirumab infusion. As infusion-related reactions (IRRs) may occur during or following ramucirumab administration, a 1 hour observation period following the ramucirumab infusion is mandatory prior to the initiation of tusamitamb ravtansine administration for the first 2 infusions. If the patient shows no evidence of an IRR with the first 2 infusions of ramucirumab, no observation period is required for subsequent infusions. In the event an IRR occurs thereafter, the 1 hour observation should be reinstituted.

Each cycle of treatment will have a duration of 2 weeks.

Investigational medicinal products

Ramucirumab

Ramucirumab will be administered prior to administration of tusamitamab ravtansine.

- Formulation: CYRAMZA® (ramucirumab) is a concentrate for solution for infusion supplied in 10 mL or 50 mL single-use vial. Each vial contains either 100 mg ramucirumab in 10 mL (10 mg/mL) or 500 mg ramucirumab in 50 mL (10 mg/mL).
- Route of administration: IV infusion
- Dose regimen: Ramucirumab will be administered as an 8 mg/kg IV infusion administered over 1 hour on Day 1 of every 2 week cycle.

Tusamitamab ravtansine

- Formulation: tusamitamab ravtansine is supplied as a 25 mL extractable volume of concentrate for solution for infusion of 125 mg contained in a 30 mL Type I glass vial.
- Route of administration: intravenous (IV) infusion.
- Dose regimen: tusamitamab ravtansine loading dose at 170 mg/m² (or RD) will be administered via IV infusion over 1 hour 30 minutes on Day 1 of Cycle 1, followed by 100 mg/m² Q2W from Cycle 2 and in all other cycles.
- For participants with a body surface area (BSA) >2.2 m², the dose will be calculated based on a BSA of 2.2 m².

Noninvestigational medicinal products

Both tusamitamab ravtansine and ramucirumab have potential risk for IRR; therefore, premedication with an IV histamine H1 antagonist (diphenhydramine 50 mg IV or equivalent; eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability) given approximately at least 15 minutes before ramucirumab administration is required for all participants. If a participant previously experienced an IRR following a dose of ramucirumab or tusamitamab ravtansine, premedication for subsequent infusions will also include dexamethasone 10 mg IV and acetominophen (paracetamol). All drugs used as premedication will be entered on the concomitant premedication page.

Posttrial access to study medication:

Not applicable.

Statistical considerations:

- **Analysis of primary endpoint:**
  - Incidence of DLTs during the DLT observation period (Cycle 1 and Cycle 2) will be summarized on the DLT-evaluable population, by DL (if applicable).

- Objective response rate (ORR) will be summarized on the all-treated population using descriptive statistics and 95% exact confidence intervals (CIs) will be provided using the Clopper-Pearson method. As a supplementary analysis, ORR will also be summarized on the activity population.

- **Analysis of secondary efficacy endpoints:**
  - Duration of response will be summarized for the subgroup of participants who achieve confirmed objective response on the all-treated population with descriptive statistics using Kaplan-Meier methods. The median DOR and associated 95% CI will be provided.
  - Progression-free survival will be summarized on the all-treated population using Kaplan-Meier methods. The median PFS times and associated 95% CI will be provided, along with probabilities of being progression-free at different time points.
  - Disease control rate will be summarized on the all-treated population using descriptive statistics and 95% CIs will be provided using the Clopper-Pearson method. As a supplementary analysis, DCR will also be summarized on the activity population.
- **Analysis of safety endpoints:**
  - Number and percentage of participants experiencing TEAEs by primary system organ class (SOC) and preferred term will be summarized by NCI-CTCAE V5.0 Grade (all grades, and Grade ≥3) on the all-treated population. Similar summaries will be prepared for TEAEs related to IMP, TEAEs leading to permanent full/partial intervention discontinuation, TEAEs leading to dose modification or dose interruption, serious TEAEs, TEAEs with fatal outcome, adverse events of special interest (AESIs), and AEs/SAEs occurring during the posttreatment period. In addition, the number (%) of participants with any Grade 5 AE (TEAE and posttreatment) will be summarized.
  - Hematology and clinical chemistry results will be graded according to the NCI-CTCAE V5.0, when applicable. Number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the on-treatment period will be provided on the all-treated population.

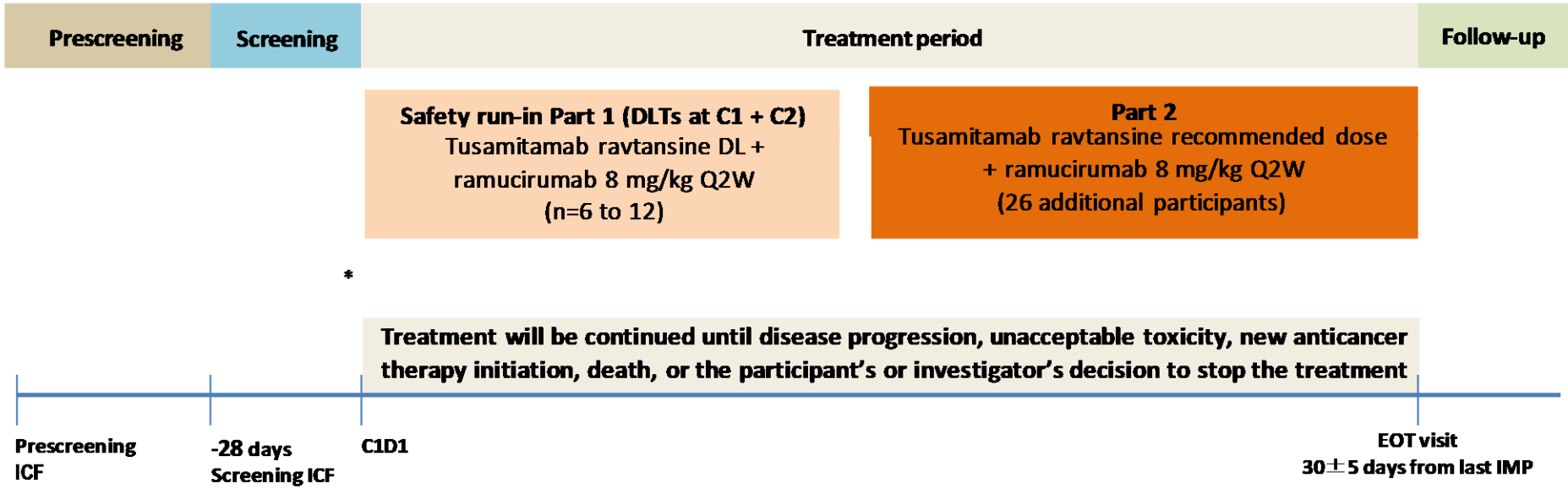
Data Monitoring/Other committee: Yes

Study Committee (SC; Part 1)
The SC includes the Investigators or designees and Sponsor team members and, when appropriate, ad hoc experts. The SC will have regular meetings every 2 weeks during Part 1 (safety run-in phase) of the study.

1.2 SCHEMA

A graphical representation of study design is shown in Figure 2:

Figure 2 - Graphical study design



Abbreviations: C1 = Cycle 1; C2 = Cycle 2; D1 = Day 1; DL = dose level; DLT = dose-limiting toxicity; EOT = end of treatment; ICF = informed consent form; IMP = investigational medicinal product; Q2W = every 2 weeks.

1.3 SCHEDULE OF ACTIVITIES (SOA)

1.3.1 Study flow chart

	Pre-screening[a]	Screening[b]	Treatment Cycle 1		Treatment Cycle 2 and thereafter		End of treatment	90 (±7) day (3 month) Follow-up[d]	Notes
Day		**Days to first infusion**	**D1**		**14 (±2) days from previous infusion**		**30 (±5) days from last infusion**		
			Pre-infusion[c]	**EOI**	**Pre-infusion[c]**	**Every 6 weeks (±7 days)**			
CEACAM5 expression status[a] (archival or fresh tumor tissue) - central IHC/prescreening Informed consent	X								
Informed Consent		X							
Inclusion/exclusion criteria		≤28	X						Section 5.1, Section 5.2
Demography, medical/surgical/disease history[e]		≤28							
Tumor characteristics[f]	X	≤28							
Height		≤7							
Performance status (ECOG)		≤7	X		X		X	X	Section 8.2.1, Section 8.2.3
Physical examination, including vital signs, body weight[g]		≤7	X		X		X	X	Section 8.2.1
Hematology[h]		≤7	X		X		X		Section 8.2.6, Section 10.2 (Appendix 2)
Coagulation[i]		≤7	X		X		X		Section 10.2 (Appendix 2)
Clinical blood chemistry[j]		≤7	X		X		X		Section 8.2.6, Section 10.2 (Appendix 2)
Urinalysis[k]		≤7	X		X				Section 10.2 (Appendix 2)

	Pre-screening[a]	Screening[b]	Treatment Cycle 1		Treatment Cycle 2 and thereafter		End of treatment	90 (±7) day (3 month) Follow-up[d]	Notes
Day		**Days to first infusion**	**D1**		**14 (±2) days from previous infusion**		**30 (±5) days from last infusion**		
			Pre-infusion[c]	**EOI**	**Pre-infusion[c]**	**Every 6 weeks (±7 days)**			
HBsAg & HCV serology and HIV test (only if required at country level)		X							
Urine/serum pregnancy test[l]		≤7			X		X	X	Section 8.2.8; Section 10.2 (Appendix 2)
Left ventricular ejection fraction (MUGA/echocardiogram)[m]		≤28							Section 8.2.5
12-lead ECG[n]		≤7	X	X	X		X		Section 8.2.4
Specific ocular tests[o]		≤28					X		Section 8.2.2
Assessment of ocular/visual symptoms			X		X				Section 8.2.2
Tusamitamab ravtansine/Ramucirumab administration			X		X				Section 6.1
AE assessment[p]	X	Continuously throughout the study period							
Concomitant medication[q]		X	Continuously throughout the study period						Section 6.8
Tumor assessment – RECIST 1.1 - CT/MRI[r]		≤28				X	X	X	Section 8.1, Section 10.13 (Appendix 13)
Circulating CEA[s]	X	≤28				X	X	X	Section 8.6
Plasma and whole blood for future analysis (optional)[t]			X						Section 8.6
IgG			X						
Record further anticancer therapy								X	
Tusamitamab ravtansine and ramucirumab PK			Refer to PK/ATA flowchart, Section 1.3.2						Section 8.4
Tusamitamab ravtansine immunogenicity			Refer to PK/ATA flowchart, Section 1.3.2						Section 8.7

Abbreviations: AE = adverse event; AESI = AE of special interest; ALP = alkaline phosphatase; ALT (SGPT) = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase; ATA = antitherapeutic antibody; BUN = blood urea nitrogen; CEA = carcinoembryonic antigen; CEACAM5 = carcinoembryonic antigen-related cell adhesion molecule 5; CR = complete response; CT = computed tomography; eCRF = electronic case report form; ECOG = Eastern Cooperative Oncology Group (performance status); ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOI = end of infusion; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgG = immunogloubulin G; IHC = immunohistochemistry; IMP = investigational

medicinal product; INR = International Normalized Ratio; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; PD = progressive disease; PD-L1 = programmed death ligand 1; PK = pharmacokinetic; PR = partial response; RBC = red blood cells; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious AE; SD = stable disease; WBC = white blood cells.

a **Prescreening:** a prescreening Informed Consent will be signed by the participant for CEACAM5 assay on archival or fresh tumor tissue and circulating CEA assay.

b **Screening:** Informed consent should be signed before any study-specific procedures. It can be signed more than 28 days prior to initiating study treatment. Screening time indicates the time frame in which exams used to support eligibility must be done prior to initiating therapy. All tests or procedures on D1 should be done at predose time unless otherwise stated. Assessments must be performed prior to first IMP administration: participants must have confirmed CEACAM5 expression as assessed centrally. Baseline evaluations should be completed within 1 week prior to initiation of therapy, except for tumor assessment, circulating CEA, echocardiography, and ocular tests that may be performed within 4 weeks prior to the first IMP administration. The Investigator should review results of these tests prior to initiating therapy.

c **D1 predose**: Cycle 1 D1 refers to the day the participant receives the initial dose of IMP. D1 of Cycle 2 and of each subsequent cycle corresponds to D15 of the previous cycle. During treatment, D1 assessment can be done on the day of infusion (before infusion) or the day before. C1D1 hematology, blood chemistry, coagulation and urinalysis tests may be omitted if baseline test performed within 7 days are normal. If baseline tests are abnormal should be repeated within 2 days of first study intervention.

d **Follow-up visit:** SAEs/AESIs (regardless of relationship with study treatment) and IMP-related AEs ongoing at the end of study treatment, and any new IMP-related AE/SAE/AESI will be followed until resolution or stabilization (defined as an event ongoing without any change for at least 3 months). Date of disease progression and further anticancer treatment will be collected at the follow-up visit. Participants who stopped treatment before documented progressive disease (PD; ie, achieving stable disease [SD] or complete or partial response [CR or PR]) should undergo a tumor assessment and an on-site follow-up visit every 8 weeks (±7 days) after the last tumor assessment until radiological disease progression, death, cut-off date for secondary endpoints, initiation of further anticancer therapy, or withdrawal of the participant's consent, whichever comes first. Participants with documented disease progression should attend an on-site follow-up visit 90 days after the last dose of study medication. If every ongoing related AE/SAE/AESI is resolved or stabilized, no further follow-up visit is needed; otherwise an on-site follow-up visit will be performed every 12 weeks after the End of Treatment visit until resolution of the event.

e **Disease history** includes previous antitumor therapy (type, start and end dates, reason for discontinuation and response to the therapy).

f **Tumor characteristics:** data collected will include histologic types, stage at diagnosis, disease extent at study entry; known specific mutations (*BRAF, KRAS, NRAS, PIK3CA, PTEN, PTP53, CCDN1, NTRK1, NTRK2, NTRK3*), known HER2 and MET status (data collected at screening) and known PD-L1 expression (data to be collected only at prescreening).

g **Physical examination** will include: vital signs (temperature, blood pressure, heart rate) and examination of major body systems. Signs and symptoms will be reported in the electronic case report form (eCRF) as AEs only if they are still present at the time of first IMP administration.

h **Hematology**: Hemoglobin, hematocrit, RBC, WBC with differential, platelet counts. These tests will be done before IMP administration at each cycle. If Grade 4 neutropenia, assess absolute neutrophil count (ANC) every 2-3 days until ANC ≥0.5 x 10^9/L. During first 2 cycles, hematology will be performed weekly.

i **Coagulation:** International normalized ratio (INR), activated partial thromboplastin time (aPTT).

j **Clinical blood chemistry**: Liver function tests: AST (SGOT), ALT (SGPT), total bilirubin, conjugated bilirubin, ALP. Renal function tests: Urea (or BUN) & creatinine; eGFR. Electrolytes: Sodium, potassium, calcium, glucose, Others: LDH, albumin and total proteins. During first 2 cycles, liver function tests will be performed weekly. The liver function tests and renal function tests will be done before IMP administration at each cycle, unless clinically appropriate. In case of Grade ≥3 liver function test abnormal, additional tests will be repeated every 2-3 days until recovery to baseline value.

k **Urinalysis** tests on morning spot will be performed by dipstick at baseline, and at every treatment cycle. In case of proteinuria ≥ ++ (dipstick), proteinuria quantification by proteinuria/24 h should be performed. If proteinuria >500 mg/24 h: blood tests including haptoglobin, LDH, platelet count and schizocytes should be performed systematically.

l **Serum pregnancy test**: women of child-bearing potential must have a negative serum pregnancy test result within 7 days prior to the initial dose of IMP. A pregnancy test (serum/urine) will be repeated every 4 weeks before IMP administration, and a serum test will be repeated at the End of Treatment evaluation (30 ±5 days after the last IMP administration), and at the Follow-up visit (90 ±7 days after last IMP dose).

m **Echocardiogram or MUGA scan:** left ventricular ejection fraction (LVEF) will be evaluated during screening period, and whenever clinically indicated.

n **12-lead ECG** is required at baseline before starting and after completing the first IMP administration (within 30 minutes after the end of tusamitamab ravtansine infusion); before IMP administration at each cycle; and at the End of Treatment evaluation, 30 (±5) days after last IMP administration.

o **Specific ocular tests** will include assessment of ocular/visual symptoms and ocular exams including visual acuity, slit lamp under dilatation, and Schirmer's test at screening and whenever clinically indicated.

p **AE**: For participant who was prescreened and had fresh biopsy, only the AEs related to the fresh biopsy procedure itself should also be reported in eCRF as general requirement of AE/SAE with the reporting time frame interval of 1 month for the prescreening period after fresh biopsy

q **Concomitant** medication will be recorded in the eCRF from 28 days prior to the first study intervention administration, before every cycle during the study treatment period, and for up to 30 days after the final dose of study intervention. Once the participant has withdrawn from study treatment, concomitant medication should only be recorded if used to treat new or unresolved study treatment-related AEs.

r **Tumor assessment:** Chest, abdomen, pelvic CT scan or MRI and any other examinations as clinically indicated will be performed to assess disease status at baseline and then every 6 weeks (±7 days) during the study treatment period until radiological disease progression; initiation of further anticancer therapy; death; or cut-off for secondary endpoints. The scheduled tumor assessment time point will not be modified in case of a cycle delay. Brain CT-scan or MRI should be performed at baseline only for known stable lesions or if clinically indicated and followed during treatment only for participants with brain lesions at baseline.

s **CEA** samples should be collected before IMP infusion, and as close as possible to tumor assessment.
t **Plasma and whole blood samples** to be collected for future use before infusion on Day 1 or the day before (optional).

1.3.2 Pharmacokinetic/Antitherapeutic antibody flow chart for Part 1 and Part 2

Cycle		C1			C2	C3	C4		Subsequent cycles[b,c,d]	EOT
Day		D1		D4	D1	D1	D1		D1	D30 ±5 days after last IMP
Ramucirumab	IV infusion	X---	---X		X	X	X		X	
	Sample RNT (hours) Ref. ramucirumab SOI	SOI	EOI		SOI	SOI	SOI		SOI	
	Sample time window	(-24h, SOI)	±10 min		(-24h, SOI)	(-24h, SOI)	(-24h, SOI)		(-24h, SOI)	
	PK sample ID	S00[a]	S01		S00[a]	S00[a]	S00[a]		S00[a,b]	
Tusamitamab ravtansine	IV infusion	X---	---X		X	X	X		X	
	Sample RNT (hours) Ref. tusamitamab ravtansine SOI	SOI	EOI	72h	SOI	SOI	SOI	EOI+1h	SOI	
	Sample time window	(-24h, SOI)	±10 min	±24 h	(-24h, SOI)	(-24h, SOI)	(-24h, SOI)	±10 min	(-24h, SOI)	
	PK sample ID	P00[a]	P01	P02	P00[a]	P00[a]	P00[a]	P01	P00[a,c]	
	ATA sample ID	AB00[a]			AB00[a]	AB00[a]			AB00[a,d]	ABF00

Abbreviations: AB = antibody; ATA = antitherapeutic antibody; C = cycle; D = Day; EOI = End of infusion; EOT = End of -Treatment; F = final; IMP = investigational medicinal product; IV = intravenous; P = plasma; PK = pharmacokinetic; RNT = relative nominal time; S = serum; SOI = start of infusion.

a Samples collected strictly before start of infusion (SOI), tusamitamab ravtansine and ramucirumab predose samples can be collected at the same time before ramucirumab administration.
b Ramucirumab PK samples will be collected at SOI at Cycle 7 only. After the cut-off date for the primary analysis, no more PK samples will be collected.
c Tusamitamab ravtansine PK samples will be collected at SOI each cycle at Cycles 5, 6 and 7 and thereafter at Cycle 13 only. After the cut-off date for the primary analysis, no more PK samples will be collected.
d Tusamitamab ravtansine ATA samples will be collected at SOI at Cycle 7 and thereafter every 6 cycles (ie, C7, C13, C19…).
Note: The sampling time-points for PK and ATA may be reduced during the course of the study based on the updated knowledge of drug behavior, upon notification from the Sponsor.

2 INTRODUCTION

Tusamitamab ravtansine (SAR408701) is an antibody-drug conjugate (ADC) combining hu769_4D4 (SAR408377), a humanized antibody that recognizes selectively the A3-B3 extracellular domain of CEACAM5, a tumor-associated carcinoembryonic antigen, with the potent cytotoxic maytansinoid derivative, DM4, that inhibits microtubule assembly. Tusamitamab ravtansine is expected to selectively deliver DM4 to cancer cells expressing the CEACAM5 antigen, such as colon, stomach and its signet-ring cell subtype as well as non-squamous NSCLC.

Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) was first described in 1965 as a tumor-associated antigen in human colon cancer tissue extracts (3). High levels of CEACAM5 expression have since been observed in several epithelial tumors while in normal adult tissue, its expression is limited to few tissues (4, 5). Immunostaining of CEACAM5 in a large panel of human tumor tissue microarray samples has shown the highest prevalence of cell surface CEACAM5 expression in adenocarcinoma of the colon, the stomach and its subtype signet ring cell as well as in non-squamous NSCLC.

2.1 STUDY RATIONALE

In the FIH study TED13751, a cohort of participants with NSQ NSCLC tumors that were CEACAM5-positive (at least 50% of the tumor cell population with membrane immunohistochemical intensity ≥2+) was treated with tusamitamab ravtansine at the recommended dose of 100 mg/m² every 2 weeks. Participants were heavily pretreated before enrollment, with a median of 3 prior treatments (1 to 10 lines) for advanced disease, including antitubulin agents (60.9%) and anti-PD1/PD-L1 (70.3%; 1). Tusamitamab ravtansine showed encouraging antitumor activity in the 64 participants treated in this study, with a response rate of 20.3% (95% CI: 12.27% to 31.71%); 28 participants (43.8%) had SD.

Tusamitamab ravtansine is being developed as a treatment for NSQ NSCLC. The randomized Phase 3 study EFC15858 is currently ongoing to evaluate the efficacy and the safety of tusamitamab ravtansine versus docetaxel in participants previously treated for metastatic NSQ NSCLC who have CEACAM5-positive tumors. The use of combination therapy with tusamitamab ravtansine is also currently being studied in 2 Phase 2 trials in participants with NSQ NSCLC: in second or third-line settings (study ACT16525; tusamitamab ravtansine in combination with ramucirumab in participants with CEACAM5-positive tumors previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor), and in a first-line setting (study ACT16146; tusamitamab ravtansine in combination with pembrolizumab, with or without platinum-based therapy, as first-line treatment in participants with CEACAM5-positive and PD-L1-positive tumors).

Other tumor types also express CEACAM5 in tumor cells known to be sensitive to antitubulin agents such as taxanes (eg, paclitaxel, docetaxel). In the “basket” trial, study ACT16432, the efficacy of tusamitamab ravtansine is being evaluated in metastatic breast cancer (10% prevalence of high expression, defined as ≥2+ in intensity involving at least 50% of the tumor cells) and pancreas (15% prevalence of high expression). The prevalence of high CEACAM expression in gastric cancer is 30%.

In the dose escalation phase of FIH study TED13751 evaluating tusamitamab ravtansine monotherapy, 1 PR was observed in 1 participant with GC. In the GC expansion cohort of this FIH study, a total of 16 participants received tusamitamab ravtansine as monotherapy at 100 mg/m^2. No objective response was reported for participants in the GC expansion cohort; SD was reported for 37.5% of heavily pretreated (median of 3 prior treatments) participants; 81.3% of participants had prior taxane therapy. In the "loading dose" escalation cohort, 2 participants with GC were treated at the recommended dose (170 mg/m^2 then 100 mg/m^2 Q2W); a single participant with GC had nonconfirmed PR (overdosed, having received twice the loading dose), and the other participant achieved SD.

Ramucirumab, an antibody antagonist of vascular endothelial growth factor receptor 2 (VEGFR2), was approved by the US Food and Drug Administration (FDA) as monotherapy for second-line gastric cancer in April 2014, based on the results from the Phase 3 REGARD study (6). The REGARD study compared ramucirumab monotherapy (8 mg/kg IV infusion on Days 1 and 15 every 4 weeks) to best supportive care (BSC) in subjects refractory to previous fluoropyrimidine treatment (with or without platinum). Ramucirumab significantly improved OS (5.2 months compared to 3.8 months with BSC, hazard ratio [HR]=0.776, p=0.047) and PFS (2.1 months as compared to1.3 months with BSC, HR 0.483, p <0.0001).

Ramucirumab (anti-VEGFR2) combined with the antitubulin agent paclitaxel leads to improved efficacy as compared to paclitaxel single agent as second-line therapy for the treatment of GC. The combination of ramucirumab plus paclitaxel was approved for second-line treatment of GC by the US FDA in November 2014, based on results from the Phase 3 RAINBOW study (2). This study evaluated paclitaxel (80 mg/m^2 IV on Days 1, 8, and 15 of a 28 day cycle) with or without ramucirumab (8 mg/kg IV infusion on Days 1 and 15 of a 28 day cycle) in subjects with metastatic gastric cancer refractory or progressive after first-line platinum and fluoropyrimidine therapy. Median OS was significantly improved for the combination (9.6 months) compared to paclitaxel alone (7.4 months), with a HR 0.807 (p=0.017). Median PFS was 4.4 months with the combination and 2.9 months with monotherapy, with a HR of 0.635 (p <0.0001) favoring the combination. Adverse events of Grade ≥3 occurring in more than 5% of participants were more frequent with combination treatment as compared to paclitaxel alone; incidences appeared to be elevated with the combination as compared to paclitaxel monotherapy for neutropenia (41% compared to 19%), leukopenia (17% compared to 7%), hypertension (14% compared to 2%), fatigue (12% compared to 5%), anemia (9% compared to 10%), and abdominal pain (6% compared to 3%).

Synergy of the activity of tusamitamab ravtansine (containing the cytotoxic antitubulin agent DM4) in combination with ramucirumab may lead to improved efficacy in the treatment of GC patients with a high unmet need; furthermore, this combination may have a better safety profile as compared to the combination of paclitaxel with ramucirumab. Nonclinical evaluations of the combination of tusamitamab ravtansine with a VEGFR2 antagonist were conducted in mice with GC PDX to evaluate substitution of paclitaxel with tusamitamab ravtansine in combination with ramucirumab. The results of these evaluations support clinical investigation of tusamitamab ravtansine in combination with ramucirumab: more extensive and sustained regression observed in evaluations of tusamitamab ravtansine in combination with the VEGFR2 antagonist as compared with paclitaxel in combination with anti-VEGF2 agent in GC PDX. Additionally, the observed safety profile for the tusamitamab ravtansine and anti-VEGFR2 combination in PDX

mice compared favorably to that observed for the taxol and anti-VEGFR2 combination. Replacing paclitaxel with tusamitamab ravtansine in combination treatment with ramucirumab may improve efficacy and optimize DOR, as well as safety in participants with CEACAM5-positive, antitubulin-agent-sensitive GC, who represent a patient population with a high unmet need.

2.2 BACKGROUND

Gastric cancer is the fifth most common cancer worldwide (7, 8), with 1 089 103 new cases diagnosed in 2020 (9). It is the third most common cause of cancer death, and incidence varies geographically, with approximately half of all cases occurring in east Asia (10). In the United States, an estimated 22 280 cases of gastric cancer were diagnosed and 11 430 participants died from this disease in 2006 (11). Although treatment for participants with unresectable or metastatic disease remains palliative, chemotherapy improves survival and quality of life when compared to BSC. Currently, platinum-based and fluoropyrimidine-based combinations are accepted worldwide as established first-line drug regimens (12). Trastuzumab is a HER2-targeted humanized monoclonal antibody that, in combination with chemotherapy, has also been approved as a first-line treatment for participants with HER2-positive advanced gastric cancer. Ramucirumab (anti-VEGFR2 agent) combined with paclitaxel is a standard-of-care option for second-line treatment.

2.3 BENEFIT/RISK ASSESSMENT

Detailed information regarding known risks and precautions for patients receiving ramucirumab may be found in the Cyramza® prescribing information.

2.3.1 Risk assessment

Risk assessment for tusamitamab ravtansine

Based on available safety data, the main identified risk to participants is corneal toxicity presenting as microcystic keratopathy, which is reversible and manageable with dose delay and dose reduction in some participants. Peripheral neuropathy is an identified risk in participants previously exposed to neurotoxic drugs.

Among the 16 participants in the GC cohort treated in FIH study TED13751, the most common TEAEs (reported in >10% of participants) were Asthenia (37.5%), Decreased appetite (31.3%), Fatigue (25%), Dyspnea, Nausea, Abdominal pain, Back pain, Dyspepsia, Disease progression (each in 18.8%), Anemia, Dizziness, Dry eye, Constipation, Vomiting, Ascites, and Edema peripheral (each in 12.5%).

In the loading-dose escalation phase from the FIH study, among the 28 participants treated, the most common TEAEs were: Nausea and Asthenia (each in 21.4%), Keratopathy and Abdominal pain (each in 17.9%), Peripheral sensory neuropathy, Keratitis, Dry eye, Dyspnea, and Diarrhea (each in 14.3%), and Cough, Decreased appetite, and Fatigue (each in 10.7%).

Among the 13 participants treated at the dose of 170 mg/m^2 at Cycle 1 followed by 100 mg/m^2 for subsequent cycles Q2W, preferred terms reported as TEAEs (all grades) for at least 2 participants were: Keratopathy, Keratitis, Asthenia, and Nausea (each reported for 4 participants); Decreased appetite, Peripheral sensory neuropathy, Gastroesophageal reflux disease, Proctalgia, Accidental overdose, and Dry eye (each reported for 2 participants). Grade 3 keratopathy was reported for 2 participants. No Grade 4 event was reported. Overall, the safety profile was consistent with what is reported in the main escalation phase of the study; refer to the Investigator's Brochure for SAR408701 for details of safety data for study TED13751.

Other potential risks were observed in a limited number of patients, and clinical pictures were consistent with a presentation in patients with underlying relevant risk factors. These potential risks include Colitis ([including hemorrhagic], mainly in participants with a known history of colitis or gastrointestinal tract conditions), Cardiotoxicity (myocardial or conduction abnormalities), Hematologic cytopenias, and Hepatotoxicity, as well as Systemic acute hypersensitivity reactions (including anaphylaxis; 1). More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of tusamitamab ravtansine may be found in the Investigator's Brochure.

Potential risks for tusamitamab ravtansine and mitigation strategies to be employed in the study are summarized in Table 2.

Table 2 - Risk assessment for tusamitab ravtanisine

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study interventions: tusamitamab ravtansine		
Microcystic keratopathy	**Nonclinical**: Mitotic arrest/single cell necrosis in the cornea of the eye in mice and monkeys. In addition, brown discoloration of the cornea associated, microscopically, with minimal dark pigmentation in cornea epithelial cells in monkeys. Findings considered related to the cytotoxic properties of DM4. **Clinical**: Main DLT in the dose escalation part of study TED13751. In study TED13751 pooled data: among the 160 patients treated at a dose level of 100 mg/m^2 Q2W, 51 patients (31.9%) had a corneal TEAE; of these, 13 patients (8.1%) had events ≥ Grade 3. In study TCD15054, of the 6 patients treated at a dose level of 100 mg/m^2 Q2W, 3 patients (50%) reported a corneal TEAE.	Careful collection of medical history and physical examination. Assessment of ocular/visual symptoms at each visit before IMP administration. Specific ocular tests at screening, whenever clinically indicated and at EOT. Wearing of contact lenses is forbidden. Preventive instillation of artificial tears or hyaluronic ophthalmic gel drops. Curative action: dose delay and reduction; artificial tears, corticosteroid eye drops and symptomatic treatment; ophthalmologist follow-up.
Peripheral neuropathy	**Nonclinical**: Nerve fiber degeneration in the peripheral nervous system and spinal cord in mice and monkeys. Effects attributed to the tubulin binding properties of DM4 and inhibition of microtubule assembly. **Clinical**: In study TED13751 at dose level of 100 mg/m^2 Q2W, 43 patients (26.9%) had at least 1 peripheral neuropathy TEAE. In study TCD15054, 1 patient (16.7%) had peripheral sensory neuropathy.	Close surveillance of any signs and symptoms of peripheral neuropathies. This AE is managed by dose delay/reduction as well as treatment discontinuation in case of Grade 3-4.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Colitis (including hemorrhagic) in patients with a known history of colitis or gastrointestinal tract conditions	**Preclinical**: mitotic arrest/single cell necrosis observed in the GI tract (tongue, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon and/or rectum). Therefore, degeneration and villous atrophy was noted in the intestinal mucosa as well as mucosal erosions and/or ulcers. Findings related to the cytotoxic properties of DM4. **Clinical**: no cases observed in study TCD15054, and very limited occurrence in study TED13751: • 1 patient developed Grade 3 colitis (pooled data among the 160 patients treated at 100 mg/m^2 Q2W). • 2 additional patients with colitis in the main dose escalation phase at 120 mg/m^2 and 150 mg/m^2 dose levels.	Exclusion criterion (see Section 5.2). Close surveillance of any diarrhea event and further investigation when clinically indicated.
Hematologic cytopenias	**Nonclinical**: Following a single or a weekly IV administration for 5 weeks of tusamitamab ravtansine in mice and/or cynomolgus monkeys, transient decreases in RBC and WBC, decreases/increases in reticulocytes and decreases/increases in platelets. In addition, mitotic arrest/single cell necrosis associated with a decreased cellularity in the bone marrow and lymphoid tissues. Findings considered related to the cytotoxic properties of DM4. **Clinical**: no cases observed in study TCD15054, and very limited occurrence in study TED13751: • Laboratory data showed anemia Grade 3 in 8 patients (5.1%), platelet count decreased Grade 3 in 1 patient (0.6%), and Grade 4 in 3 patients (1.9%).	Exclusion criterion (see Section 5.2). Close surveillance of any signs and symptoms. Routine blood hematology workup, Hemoglobin, hematocrit, WBC with differential, platelet counts. These tests will be performed before IMP administration at each visit. During the first 2 cycles, they will performed on weekly basis. If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC ≥0.5 x 10^9/L.
Cardiotoxicity (myocardial or conduction abnormalities)	**Nonclinical**: Occasional minimal or mild degeneration/necrosis in the heart observed in single- and repeat-dose weekly for 5 weeks toxicity studies in monkeys. In the weekly for 5 weeks toxicity study in monkeys, compound-related effects on ECG parameters observed in some monkeys at the top dose (7 mg/kg/adm) using an external telemetric methodology (reversible marked increase in HR and non-reversible long-lasting episodes of bundle branch block suggesting an alteration in ventricular conduction which could nevertheless not be evidenced quantitatively (no widening of QRS complex duration) in the present experimental conditions. **Clinical**: • In study TCD15054 no case was observed • In study TED13751 pooled data, the following AEs were each reported for 1 patient: angina pectoris, atrioventricu ar block first degree, bundle branch block right, Electrocardiogram QT prolonged.	Exclusion criterion (see Section 5.2). Cardiovascular examination. Monitoring of potential cardiac conduction defects by regular ECG.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Hepatotoxicity	**Nonclinical**: Following a single IV administration of tusasmitamab ravtansine in mice and/or cynomolgus monkeys, increased aspartate AST, alanine ALT, ALP and/or GLDH have been noted. In addition, this was associated with mitotic arrest/single cell necrosis observed in the liver. These findings are considered related to the cytotoxic properties of DM4. **Clinical**: • In study TED13751 pooled data under hepatobiliary disorders SOC, 3 patients (1.9%) had hepatocellular injury events including 1 patient (1.3%) with Grade 4, 1 patient with a hepatic function abnormal event, and 1 patient with hypertransaminasaemia. Clinical laboratory data showed ALT increased Grade 3 in 2 patients (1.3%) and Grade 4 in 2 patients (1.3%); AST increased Grade 3 in 6 patients (3.8%) and Grade 4 in 3 patients (1.9%); ALP increased Grade 3 in 14 patients (8.9%; none with Grade 4), and blood bilirubin increased Grade 3 in 6 patients (3.8%; none with Grade 4). • In study TCD15054, AST increased was reported for 1 patient (16.7%). • No “Hy's law" cases have been observed.	Exclusion criterion (see Section 5.2). Close surveillance of any signs and symptoms of hepatotoxicities. Liver function tests will be performed before IMP administration at each visit. During the first 2 cycles, they will be performed on a weekly basis. In case of Grade ≥3 liver function abnormal tests, additional tests will be repeated every 2-3 days until recovery to baseline value.
Systemic acute hypersensitivity reactions (including anaphylaxis)	**Nonclinical:** Not observed. **Clinical:** • in study TED13751 pooled data, 2 patients, including 1 patient (0.6%) with Grade 3 hypersensitivity and 1 patient had Grade 1 infusion-related reaction. • in study TCD15054, 1 patient (33.3%) developed rash.	Premedication with histamine H1 antagonist. If a patient has previously experienced an infusion-related reaction in a previous tusamitamab ravtansine administration, premedication will also include dexamethasone 10 mg IV for future infusions. Target infusion time is 1.5 h. In case of an IRR, the flow rate can be decreased; minimum authorized f ow rate is 33 mL/h. Recommended curative action: In case of infusion reaction ≥ Grade 2, tusamitamab ravtansine administration will be interrupted. The infusion may be resumed at half of the previous infusion rate after the recovery.

Abrreviations: ALT = alanine aminotransferase; ALP = alkaline phosphatase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DLT = dose-limiting toxicity; ECG = electrocardiogram; EOT = end of treatment; GLDH = glutamate dehydrogenase; IMP = investigational medicinal product; IRR = infusion-related reaction; IV = intravenous; SOC = system organ class; TEAE = treatment-emergent adverse event; Q2W = every 2 weeks; RBC = red blood cell count; WBC = white blood cell count.

Ramucirumab

Ramucirumab, a human IgG1 monoclonal antibody that inhibits VEGFR-2, in combination with paclitaxel, has been approved in for the treatment of patients with gastric cancer. Potential and identified risks associated with ramucirumab in gastric cancer are summarized here; more detailed information about the known and expected benefits and risks and reasonably expected adverse effects of ramucirumab and recommended mitigation measures may be found in the US Package Insert or Summary of Product Characteristics/SmPC for Cyramza®.

The most common serious adverse drug reactions (ADRs) associated with ramucirumab were: anemia (3.8%) and intestinal obstruction (2.1%).

The most common ADRs (all grades) observed in ramucirumab-treated patients at a rate of ≥10% and ≥2% higher than placebo were hypertension and diarrhea (6).

In Ramucirumab Administered in Combination with Paclitaxel (RAINBOW), the most common serious adverse reactions in patients who received ramucirumab with paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%; 2). The most common adverse reactions (all grades) observed in patients who received ramucirumab with paclitaxel at a rate of ≥30% and ≥2% higher than placebo with paclitaxel were fatigue/asthenia, neutropenia, diarrhea, and epistaxis.

Safety profile for the combination

No overlap in the safety profiles for tusamitamab ravtansine and ramucirumab is anticipated. Given the risks of adverse effects including neutropenia, anemia, and infection associated with paclitaxel, the combination of tusamitamab ravtansine with ramucirumab may represent a treatment regimen with an improved safety profile as compared to the approved combination of paclitaxel and ramucirumab.

2.3.2 Benefit assessment

Based on the current data obtained in the ongoing monotherapy studies of tusamitamab ravtansine (TED13751 and TCD15054), anticipated benefits in the treatment of advanced malignancies support the continued clinical development of the agent for treatment in other indications. Such indications include GC in which tumor cells express CEACAM5 and are known to be sensitive to antitubulin agents, which are associated with significant toxicity.

Ramucirumab, a human IgG1 monoclonal antibody that inhibits VEGFR-2, is approved in combination with paclitaxel for the treatment of patients with advanced or metastatic gastric or gastroesophageal cancer with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

Nonclinical investigations of the efficacy of combination of tusamitamab ravtansine with a surrogate for ramucirumab for use in the murine model context, a rat IgG1 monoclonal antibody directed against the murine VEGFR, were performed in gastric cancer PDXs. In a set of 3 gastric cancer PDXs, synergy for the combination of tusamitamab ravtansine and anti-VEGFR2 was observed in PDXs resistant to paclitaxel (Taxol®) or tusamitamab ravtanisine alone. Efficacy for the tusamitamab ravtansine and anti-VEGFR2 combination was the same or better as compared

to combination of taxol and anti-VEGFR2, even in PDX resistant to single-agent tusamitamab ravtanisine. Additionally, the observed safety profile for the tusamitamab ravtansine and anti-VEGFR2 combination in PDX mice compared favorably to that observed for the paclitaxel and anti-VEGFR2 combination.

Given the risks of adverse effects including neutropenia, anemia, and infection associated with paclitaxel, the combination of tusamitamab ravtansine with ramucirumab may represent a treatment regimen with an improved safety profile as compared to the approved combination of paclitaxel and ramucirumab. Replacing paclitaxel with tusamitamab ravtansine in combination treatment with ramucirumab may improve efficacy in participants with CEACAM5-positive in gastric cancer, who represent a patient population with a high unmet need.

2.3.3 Overall benefit-risk conclusion

To date, efficacy and safety data from ongoing studies of tusamitamab ravtansine (TED13751, and TCD15054) support its continued clinical development. The combination of tusamitamab ravtansine with ramucirumab may represent a treatment regimen with improved efficacy and a better safety profile as compared to the combination of paclitaxel with ramucirumab approved as second-line treatment for gastric or gastroesophageal adenocarcinoma.

3 OBJECTIVES AND ENDPOINTS

Table 3 - Objectives and endpoints

Objectives	Endpoints
Primary	
• Part 1: to confirm the recommended tusamitamab ravtansine loading dose Q2W when given in combination with ramucirumab in advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma population • Part 2: To assess the antitumor activity of tusamitamab ravtansine loading dose Q2W in combination with ramucirumab in advanced gastric or GEJ adenocarcinoma	• Part 1: Incidence of study drug related dose-limiting toxicities (DLTs) at Cycle 1 and Cycle 2 (C1D1 to C2D14) • Part 2: Objective response rate (ORR), defined as the proportion of participants with confirmed complete response (CR) or partial response (PR) as best overall response (BOR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
Secondary	
• To assess the safety and tolerability of tusamitamab ravtansine loading dose Q2W in combination with ramucirumab	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and laboratory abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V5.0
• To assess the durability of the response to treatment with tusamitamab ravtansine loading dose Q2W in combination with ramucirumab	• Duration of response (DOR), defined as the time from first documented evidence of CR or PR until progressive disease (PD) determined per RECIST 1.1 or death from any cause, whichever occurs first
• To assess progression-free survival (PFS) of tusamitamab ravtansine loading dose Q2W in combination with ramucirumab	• Progression-free survival, defined as the time from the first investigational medicinal product (IMP) administration to the date of the first documented disease progression or death due to any cause, whichever comes first
• To assess the disease control rate (DCR) of tusamitamab ravtansine loading dose Q2W in combination with ramucirumab	• Disease control rate, defined as the proportion of participants with confirmed CR or PR or SD as BOR per RECIST 1.1
• To assess the pharmacokinetics (PK) of tusamitamab ravtansine loading dose Q2W and ramucirumab when given in combination	• Pharmacokinetic parameters of tusamitamab ravtansine and ramucirumab
• To assess the immunogenicity of tusamitamab ravtansine loading dose Q2W when given in combination with ramucirumab	• Incidence of antitherapeutic antibodies (ATAs) against tusamitamab ravtansine
Exploratory	
• To explore circulating carcinoembryonic antigen (CEA) as a potential biomarker for activity and to evaluate circulating CEA levels at prescreening	• Circulating CEA at prescreening, screening, during the treatment period and during the follow-up period

Abbreviations: ATAs = antitherapeutic antibodies; BOR = best overall response; C1D1 = Cycle 1, Day 1; C2D14 = Cycle 2, Day 14; CEA = carcinoembryonic antigen; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DLT = dose-limiting toxicity; DOR = duration of response; GEJ = gastroesophageal junction; IMP = investigational medicinal product; NCI = National Cancer Institute; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; TEAEs = treatment-emergent adverse events, SAEs = serious adverse events.

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy and safety assessments chosen for use in this study is considered well established and relevant in an oncology study setting. In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy and to minimize any risks to participant safety.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2, open-label, multicenter, single-arm study to confirm the recommended dose, safety, efficacy (antitumor activity), and PK of of tusamitamab ravtansine combined with ramucirumab in participants previously treated for gastric or gastroesophageal adenocarcinoma with CEACAM5-positive tumors.

In the prescreening phase, patients with gastric or gastroesophageal adenocarnioma will have tumor tissue tested centrally to assess proportions of CEACAM5-positive cells and intensity of expression, with a prospective analysis of CEACAM5 expression on most recent archival tumor tissue. For this analysis, at least 5 fresh-cut slides of formalin-fixed, paraffin embedded (FFPE) archival tumor tissue sectioned at a thickness of 4 to 5 µm are required to be sent to the central laboratory designated by the Sponsor.

If less material is available, a participant will be eligible only after discussion with the Sponsor confirming that available material is sufficient for key CEACAM5 expression analyses. In case of unavailable archival tissue, a fresh biopsy can be considered in participants who have reachable lesion that is suitable for biopsy. This prescreening activity can be performed in advance, when a participant may be on prior anticancer therapy.

Once the results for CEACAM5 become available, only participants with positive results (defined as CEACAM5 expression of ≥2+ in intensity involving at least 50% of the tumor cell population), in archival tumor sample (or if not available fresh biopsy sample) will enter the screening phase. During the screening phase, all inclusion/exclusion criteria will be checked to confirm the participants' eligibility for treatment part.

Treatment allocation will be performed using interactive response technology (IRT). After being screened, eligible participants will receive tusamitamab ravtansine combined with ramucirumab until documented disease progression, unacceptable toxicity, new anticancer therapy initiation, death, or the participant's or Investigator's decision to stop the treatment.

This will be a 2-part study.

Part 1 (Safety Run-In):

In Part 1, participants will receive ramucirumab at 8 mg/kg followed by tusamitamab ravtansine loading dose at 170 mg/m² (150 mg/ m²) on Day 1 of Cycle 1; and ramucirumab 8 mg/kg followed by tusamitamab ravtansine 100 mg/m² every 2 weeks (Q2W) at Cycle 2 and all subsequent cycles.

The DLT observation period is the first 2 cycles (approximately 28 days). A DLT-evaluable participant must have completed 2 cycles of treatment or have been discontinued from study treatment because of a DLT; DLT nonevaluable participants will be replaced.

Part 2:

In Part 2 of the study, the recommended dose confirmed in Part 1 will be evaluated for activity in 26 additional participants. Refer to Section 1.1 for an overview of study design, and Section 6 for details of administration of study intervention.

The expected duration of study intervention for participants may vary, based on the disease progression date; the median expected duration of the study per participant is estimated as 34 weeks (up to 4 weeks for screening, a median of 18 weeks for treatment, and a median of 12 weeks for end-of-treatment assessments and the safety follow-up visit).

Serious adverse events/AESIs (regardless of relationship with study treatment) and IMP-related AEs ongoing at the end of study treatment, and any new IMP-related AEs/SAEs/AESIs will be followed until resolution or stabilization (defined as an event ongoing without any change for at least 3 months). A safety follow-up visit will be performed 90 days after the last IMP administration. If all ongoing IMP related AEs/SAEs/AESIs are resolved or stabilized, no further safety follow-up visit will be needed; otherwise, an on-site follow-up visit will be performed every 12 weeks.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The efficacy and the safety of tusamitamab ravtansine is being explored in indications for which the tumor expresses CEACAM5 and which are also known to be sensitive to antitubulin agents. The prevalence of high CEACAM5 expression (defined as ≥2+ in intensity involving at least 50% of the tumor cells) is 30% in gastric cancer.

Assuming a prescreening failure rate of 70% and a screening failure rate of 20%, approximately 158 participants will be prescreened to achieve up to approximately 38 treated participants in whom the safety and antitumor activity of tusamitamab ravtansine in combination with ramucirumab can be evaluated in this Phase 2, single-arm study.

Ramucirumab (an anti-VEGFR2 agent) combined with paclitaxel (an antitubulin agent) leads to improved efficacy as compared to single-agent paclitaxel in gastric cancer second-line therapy, based on results of the the Phase 3 RAINBOW study (2). Based on nonclinical data (Section 2.1), replacing paclitaxel with tusamitumab ravtansine in combination treatment with ramucirumab may improve efficacy with an optimized DOR, as well as achieve better safety as compared to the combination of paclitaxel with ramucirumab.

4.3 JUSTIFICATION FOR DOSE

The main escalation phase of first-in-human study TED13751 showed that the MTD using a Q2W schedule of administration is 100 mg/m². Of 28 DLT-evaluable participants, 5 experienced a DLT during the evaluation period: 3 of 8 participants dosed at 120 mg/m², and 2 of 3 participants dosed at 150 mg/m². All DLTs were reversible microcystic keratopathies occurring at the end of Cycle 2. Confirmed objective response was induced in 2 of 6 participants (1 with colorectal cancer and 1 with gastric cancer) treated at the MTD (100 mg/m² Q2W). Additional responses

were documented in 2 participants with colorectal cancer treated in the 120 mg/m² cohort after having received only 2 infusions at 120 mg/m², followed by a dose delay and reduction to 100 mg/m² for occurrence of corneal DLT at the end of Cycle 2. Even with dose delay and dose reduction, instances of near-maximum tumor shrinkage were documented at the first tumor assessment (Cycle 4), indicating that the initial dosing is important. Although a small data set and a heterogeneous population does not permit PK/PD correlations to be established, preliminary exposure data for tusamitamab ravtansine based on C_{max} and $AUC_{0\text{-}14d}$ at Cycle 1 suggest exposures in participants in whom a response was induced tended to be higher relative to nonresponding participants treated in the same cohort. Therefore, increasing the exposure at the beginning of the Q2W schedule may permit pharmacologically active concentrations to be attained more quickly, potentially increasing the efficacy without increasing the occurrence of ocular toxicity. A new "loading dose schedule" cohort was added in order to determine the recommended dose and to evaluate the safety.

At the cut-off date of 17 June 2020, 28 participants were treated in the dose-escalation phase using the loading-dose schedule (loading dose at Cycle 1 followed by 100 mg/m² starting at Cycle 2). Three participants were treated at the intended loading DL 120 mg/m², 4 participants at DL 135 mg/m², 8 participants at DL 150 mg/m², and 13 participants at DL 170 mg/m². No DLT was observed at DLs 120, 135, or 150 mg/m². In the first 6 evaluable participants treated at 170 mg/m², 2 DLTs were reported (in both cases, treatment delay due to keratopathy, Grade 2). The 3 following participants treated at 150 mg/m² showed no DLT. The study committee decided (supported by the Bayesian modeling) to treat 3 more participants at 170 mg/m², and no DLT was reported. The MTD was identified to be 170 mg/m² at Cycle 1 followed by 100 mg/m² starting at Cycle 2. Based on supportive PK, clinical data, and the Bayesian model, the Study Committee decided 170 mg/m² as the recommended loading dose at Cycle 1 to be followed by 100 mg/m² Q2W administration starting at Cycle 2 as a dosing regimen for further studies; thus, this recommended loading dose will be used as the starting dose in this study.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

A participant is considered to have completed the study if he/she has completed all phases of the study including the EOT and the Follow-Up visit approximately 90 days after the last IMP administration.

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all the following criteria apply:

Age

I 01. At least 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Histologically or cytologically confirmed diagnosis of gastric or GEJ adenocarcinoma.

I 03. Metastatic disease or locally advanced, unresectable disease.

I 04. Measurable disease by RECIST 1.1, as determined by the Investigator.

At least 1 measurable lesion is required. A previously irradiated tumor lesion is considered measurable if progression has been demonstrated in the lesion. The lesion must be ≥10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥15 mm) as imaged in computed tomography (CT; preferred) or magnetic resonance imaging (MRI) scans.

I 05. Documented disease progression during or after first-line therapy containing platinum and/or fluoropyrimidine agents, and if appropriate, HER2 therapy.

No more than 1 previous line of chemotherapy is allowed. Previous treatment with an immune checkpoint inhibitor is allowed. Adjuvant/neoadjuvant treatment for a participant who had disease progression during or within 6 months of completing platinum and/or fluoropyrimidine treatment will be considered as first-line treatment.

I 06. Expression of CEACAM5 as demonstrated prospectively by a centrally assessed IHC assay of ≥2+ in intensity involving at least 50% of the tumor cell population in an archival tumor sample (or, if not available, a fresh biopsy sample).

At least 5 fresh-cut slides of formalin-fixed, paraffin embedded (FFPE) tumor tissue sectioned at a thickness of 4 to 5 µm are required. If less material is available, the participant could still be considered eligible after discussion with the Sponsor, who may assess and confirm that the available material is sufficient for key evaluations.

I 07. Eastern Cooperative Oncology Group (ECOG) performance status 0-1.

Sex, contraceptive/barrier method and pregnancy testing requirements

I 08. All participants (male and female)

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants
Male participants are eligible to participate if they agree to the following during the intervention period and for at least 4 months after the last dose of study intervention:

- Refrain from donating sperm
- Plus either:
  - Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

    OR
  - Must agree to use contraception/barrier as detailed below:

    Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person

b) Female participants
A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP)

  OR
- Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4 of the protocol during the intervention period and for at least 7 months after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.

  A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) before the first dose of study intervention. Additional requirements for pregnancy testing during and after study intervention are located in Appendix 4 (Section 10.4) of the protocol. The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

I 09. Capable of giving signed informed consent as described in Appendix 1 of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Untreated brain metastases, leptomeningeal disease, or uncontrolled spinal cord compression. Participants with previously treated and stable brain metastases may participate. The participant must not require any systemic corticosteroids to manage brain metastases within 3 weeks prior to the first dose of study intervention.

E 02. Significant concomitant illness, including any severe medical condition that, in the opinion of the investigator or Sponsor, would impair the participant's participation in the study or interpretation of the results.

E 03. History within the last 3 years of an invasive malignancy other than that treated in this study, with the exception of resected/ablated basal or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix, or other local tumors considered cured by local treatment.

E 04. Known uncontrolled infection with human immunodeficiency virus (HIV). Participants with well controlled HIV infection/disease (Appendix 10; Section 10.10) must be on antiretroviral therapy (ART) to be eligible.

E 05. Active infection with hepatitis A, B (defined as either positive HBs antigen or positive hepatitis B viral DNA test above the lower limit of detection of the assay), or C (defined as known positive result for antibodies to hepatitis C and known quantitative hepatitis C virus [HCV] RNA results greater than the lower limit of detection of the assay).

E 06. Nonresolution of any prior treatment-related toxicity to < Grade 2 according to NCI CTCAE v5.0, with the exception of alopecia, vitiligo, or active thyroiditis controlled with hormone replacement therapy (HRT).

E 07. Unresolved corneal disorder or any previous corneal disorder considered by an ophthalmologist to predict higher risk of drug-induced keratopathy.

E 08. Use of contact lenses that the participant is unwilling to stop for the duration of the study intervention. The use of contact lenses is not permitted.

E 09. Radiographic evidence of major airway or blood vessel invasion or intratumor cavitation, regardless of tumor histology.

E 10. History of uncontrolled hereditary or acquired thrombotic disorder or history of aneurysm.

E 11. Major surgery within 28 days prior to Day 1/first IMP infusion; subcutaneous venous access device placement within 7 days prior to Day 1; or postoperative bleeding complications or wound complications from a surgical procedure performed in the last 2 months.

E 12. History of gross hemoptysis (defined as bright red blood or ≥1/2 teaspoon) within 2 months before the first administration of study intervention.

E 13. Any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months before the first administration of study intervention.

E 14. Uncontrolled arterial hypertension (systolic ≥150 mmHg or diastolic ≥90 mmHg) despite standard medical management. A participant with systolic pressure >150 mmHg or diastolic pressure >90 mmHg is ineligible for the study.

E 15. Serious or nonhealing wound, skin ulcer, or bone fracture within 28 days before the first administration of study intervention.

E 16. Gastrointestinal (GI) perforation and/or fistulae within 6 months prior to first administration of study intervention.

E 17. Significant bleeding disorders, vasculitis, or Grade 3-4 gastrointestinal (GI) bleeding within 3 months before the first administration of study intervention.

E 18. Bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection Crohn's disease, ulcerative colitis, or chronic diarrhea.

E 19. Medical condition requiring concomitant administration of a medication with a narrow therapeutic window and metabolized by CYP_{450} (Appendix 11; Section 10.11); and for which a dose reduction cannot be considered.

E 20. Medical conditions requiring concomitant administration of a strong CYP3A inhibitor (see Appendix 12; Section 10.12), unless it can be discontinued at least 2 weeks before first administration of study intervention.

Prior/concomitant therapy

E 21. Any previous systemic therapy with taxane or targeting VEGF or the VEGFR signaling pathways (including investigational agents). Other previous targeted therapies are permitted, if stopped at least 3 weeks prior to enrollment.

E 22. Concurrent treatment with any other anticancer therapy.

E 23. Prior therapy targeting CEACAM5.

E 24. Prior maytansinoid treatment (DM1 or DM4 ADC).

E 25. Washout period before the first administration of study intervention of less than 3 weeks or less than 5 times the half-life, whichever is shorter, for prior antitumor therapy (chemotherapy, targeted agents, immunotherapy and radiotherapy, or any investigational treatment).

E 26. Poor coagulation as defined by International Normalized Ratio (INR) ≥1.5 or prothrombin time (PT) ≥1.5 × upper limit of normal (ULN) and partial thromboplastin time/activated partial thromboplastin time (PTT/aPTT) ≥1.5 × ULN, unless the participant is receiving anticoagulation therapy. Participants receiving warfarin must be switched to low-molecular-weight heparin and must achieve a stable coagulation profile prior to the first IMP administration.

Prior/concurrent clinical study experience

E 27. Previous enrollment in this study, current participation in any other clinical study involving an investigational study treatment, or any other type of medical research.

Diagnostic assessments

E 28. Poor organ function as defined by any one of the following prior to IMP administration:

a) Serum creatinine >1.5 × ULN or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 as estimated using a Modification of Diet in Renal Disease (MDRD) formula.

b) Total bilirubin >1.0 × ULN (excluding congenital conjugation disorders [Gilberts], for whom total bilirubin ≤3.0 × ULN, with direct bilirubin ≤1.5 × ULN, is allowed).
or
aspartate aminotransferase (AST), alanine aminotransferase (ALT) >2.5 × ULN (In case of documented liver metastasis, AST, ALT <5 × ULN is allowed).

c) Neutrophils <1.5 × 10^9/L, platelet count <100 × 10^9/L, or hemoglobin <9 g/dL (blood infusion-free for at least 2 weeks).

E 29. Urine dipstick or routine analysis indicating proteinuria of 2+ or higher, unless a 24 hour urine collection demonstrates <1000 mg of protein.

Other exclusions

E 30. Accommodation in an institution because of regulatory or legal order (eg, prisoners or participants who are legally institutionalized).

E 31. Any country-related specific regulation that would prevent the participant from entering the study - see Appendix 8 (Section 10.8) of the protocol (country-specific requirements).

E 32. Unsuitability for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or potential risk for noncompliance with study procedures.

E 33. Employment by the clinical study site or direct involvement in the conduct of the study, or having an immediate family member with this status (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6).

E 34. Any specific situation during study implementation/course that may raise ethics concerns.

E 35. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

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

For individuals who do not meet the criteria for participation in this study (screen failure) and for whom resolution of the screen failure may not be expected within a reasonable time frame, the screen failure will be recorded.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a participant number different from that for the initial screening, and all the screening procedures will be repeated and entered in the screening visit pages.

In case the participant is a temporary screen failure, there is no need to have participant reconsent (ie, new ICF signed) if the participant finally participates in the trial. However, if the reason for the temporary screen failure might have altered the participant's initial given agreement to participate, the Investigator should ask the participant and confirm the participant's willingness to continue or redo some screening procedures and participate in the trial. This oral agreement should be documented in the participant's chart. All the tests outside protocol-specified window should be repeated and entered to the additional pages.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT

During a regional or national emergency declared by a governmental agency, the Investigator/site should assess the site's capacity to conduct procedures for a new participant to be enrolled into the study before initiating any screening procedures. Site capacity also should be ensured before enrollment of a participant. If the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Appendix 9 (Section 10.9) should be applicable to prescreening/screening/enrollment/administration of study treatment.

6 STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study intervention is defined as any investigational interventions, marketed products, placebo, or medical devices intended to be administered to a study participant according to the study protocol. Treatment preparation and administration (including compatible materials), handling, storage and accountability will be further detailed in the Pharmacy Manual.

6.1 STUDY INTERVENTIONS ADMINISTERED

Table 4 - Overview of study interventions administered

Intervention label	Tusamitamab ravtansine	Ramucirumab
Intervention name	tusamitamab ravtansine	ramucirumab
Type	Drug	Drug
Dose formulation	concentrated solution for IV	concentrated solution for IV
Unit dose strength(s)	5 mg/mL	10 mg/mL
Dosage levels[a]	170 (150) mg/m² Cycle 1 then 100 mg/m² Q2W	8 mg/kg Q2W
Route of administration	IV infusion	IV infusion
Use	experimental	experimental
IMP or NIMP	IMP	IMP
Packaging and labeling	Supplied in a 30 mL glass vial with a white plastic flip-off cap, containing 125 mg/25 mL tusamitamab ravtansine, and labelled with a multilingual booklet	Supplied in a single-dose vial (100 mg/10 mL or 500 mg/50 mL), labeled with a multilingual booklet, and individually packaged in a carton
Current/Former names or aliases	tusamitamab ravtansine/SAR408701	Cyramza®

Abbreviations: DL -1 = dose level -1; IMP = investigational medicinal product; IV = intravenous; NIMP = noninvestigational medicinal product; Q2W = every 2 weeks.

a The tusamitamab ravtansine starting dose is 170 mg/m²; the dose may be decreased to 150 mg/m² (DL -1)

Table 5 - Single arm interventions

Arm name	Tusamitamab ravtansine/ramucirumab (single arm)
Associated interventions	tusamitamab ravtansine, ramucirumab

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9: Contingency Measures for a regional or national emergency that is declared by a governmental agency (Section 10.9).

Study medication infusion:

Infusion via a central line is preferred, if available. Prior to dosing, each participant's dose will be individually prepared by the study pharmacist and labeled with protocol number, participant number, and treatment description.

On Day 1 of each treatment cycle, the patient's BSA will be determined using the most recent weight available on the day of the infusion preparation: the weight on the day of the infusion or the most recent weight, assuming it was assessed in a reasonable time frame according to Investigator assessment. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, this will not prevent assessment of weight on D1 of each cycle, which must be recorded in the eCRF. The dose needs to be adjusted if change in body weight is >5% of weight at the previous cycle.

Investigational medicinal products:

Ramucirumab: Ramucirumab should be administered prior to tusamitamab ravtansine infusion. Using a controlled infusion pump, ramucirumab will be administered by IV infusion over 1 hour on Day 1 of each cycle. If the first infusion is tolerated, all subsequent ramucirumab infusions may be administered over 30 minutes. In case of IRR, Grade 1 or 2, the infusion rate of ramucirumab will be reduced by 50%.

Tusamitamab ravtansine: Infusion of tusamitamab ravtansine should be initiated after the end of ramucirumab infusion. As IRRs may occur during or following ramucirumab administration, a 1 hour observation period following the ramucirumab infusion is mandatory prior the initiation of tusamitamb ravtansine administration for the first 2 infusions. If the patient shows no evidence of an IRR with the first 2 infusions of ramucirumab, no observation period is required for subsequent infusions. In the event an IRR occurs thereafter, the 1 hour observation should be reinstituted.

Using a controlled infusion pump, tusamitamab ravtansine will be administered by IV infusion over 1 hour 30 minutes. For a participant with a BSA >2.2 m^2, the calculated dose of tusamitamab ravtansine will be based on a BSA of 2.2 m^2. After the first administration of tusamitamab ravtansine, participants should be observed for acute reactions on site for up to 4 hours depending on any sign of IRR. In case of a Grade 1-2 IRR, tusamitamab ravtansine must be interrupted and may be resumed only after patient recovery, at half of the previous infusion rate, with a minimum authorized flow rate at 33 mL/h. Detailed instructions for dilution and administration of the IMP is provided in Pharmacy Manual.

Noninvestigational medicinal products:

Premedication:

Both tusamitamab ravtansine and ramucirumab have potential risk of IRR; thus, premedication with an IV histamine-1 receptor antagonist (diphenhydramine 50 mg IV or equivalent; eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability) will be given approximately at least 15 minutes before ramucirumab administration. If a participant previously experienced an IRR following a dose of ramucirumab or tusamitamab

ravtansine, premedication will also include corticosteroids equivalent to 10 mg IV dexamethasone, and acetaminophen/paracetamol for future infusions. All drugs used as premedication will be entered on the concomitant premedication page.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Partially used and used study treatments will be destroyed at the study site according to the standard practices of the site after an accurate accountability has been performed and signed by the Investigator (or the pharmacist). A detailed treatment log form of the destroyed study treatment will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team. The Investigator must not destroy the unused IMP unless Sanofi provides written authorization.

Further guidance and information for the final disposition of used and unused study interventions are provided in the pharmacy manual and/or monitoring plan.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly reported to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.8).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable; this is a single-arm, nonrandomized, open-label study.

6.4 STUDY INTERVENTION COMPLIANCE

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

Participants are dosed at the site and will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of eaceh dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

A record of the quantity of tusamitamab ravtansine and ramucirumab administered to each participant must be maintained and reconciled with study intervention and compliance records. These records (eg, drug movement form) include the date the IMPs are received from the Sponsor, dispensed to the participant and destroyed or returned to the Sponsor. The packaging batch number (IP number) and the treatment number on the vial must be recorded on the drug accountability form.Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5 DOSE MODIFICATION

Part 1 (Safety Run-In):

During Part 1, recommended dose of tusamitamab ravtansine in combination with ramucirumab will be determined according to the DLTs observed in participants according to the algorithm shown in Figure 1.

Dose limiting toxicity definition

All AEs specified in Table 6 occurring during the first 2 cycles of treatment, unless due to disease progression or to a cause obviously unrelated to IMP, will be considered DLTs. The duration of the DLT observation period will be longer for a participant who delays initiation of Cycle 2 due to a treatment-related AE for which the event's duration would determine whether the AE meets the definition of a DLT. The NCI CTCAE Version 5.0 will be used to assess the severity of AEs. Causal relationships are to be determined by the Investigator. The DLTs will be confirmed by the SC.

Table 6 - Dose-limiting toxicities

Hematological abnormalities
Grade 4 neutropenia for 7 or more consecutive days.
Grade 3 to 4 neutropenia complicated by fever (temperature ≥38.5°C on more than 1 occasion) or microbiologically or radiographically documented infection
Grade ≥3 thrombocytopenia associated with clinically significant bleeding requiring clinical intervention
Nonhematological abnormalities
Grade 4 non-hematologic AE
Grade ≥3 keratopathy
In addition, any other AE that the recruiting Investigators and Sponsor deem to be dose limiting, regardless of its grade, may also be considered as DLT.

Abbreviations: AE = adverse event; DLT = dose-limiting toxicity.

In the case that it is decided to reduce the initial loading dose of tusamitamab ravtansine to DL -1 (Table 1), a tusamitamab ravtansine loading dose of 150 mg/m^2 will be administered to participants on Day 1 of Cycle 1.

Individual dose adjustment/dose delay: Part 1 and Part 2

Dose adjustment and/or cycle delay are permitted in case of AEs. In case of toxicity, cycle delays and dose modifications should be implemented according Appendix 6 (Section 10.6). Every effort will be made to administer the full dose regimen and maximize dose intensity.

Dose adjustments will be made according to the worst grade of AE observed within a cycle. If a participant experiences several adverse events and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed.

Administration of the study treatment will be discontinued in the event of a TEAE that persists despite appropriate dose modifications or any other AE that, in the opinion of the Investigator, warrants discontinuation.

Ramucirumab or tusamitamab ravtansine can be discontinued prematurely. The patient will remain on study treatment until the last IMP can be discontinued for disease progression, unacceptable AE, or the participant's or investigator's decision to stop the treatment. The reason for premature discontinuation will be captured in the appropriate eCRF page.

Dose modifications different from those stated in the protocol should be made only in consultation with the Sponsor unless required for immediate participant safety.

All changes to study treatment administration must be recorded in the eCRF.

In the event of neutropenia or febrile neutropenia, therapeutic G-CSF should be administered according to the current American Society of Clinical Oncology (ASCO) guidelines (13); for specific recommendations for this study, refer to Appendix 6 (Section 10.6).

The acceptable treatment window for tusamitamab ravtansine and ramucirumab administration is ±2 days.

See Appendix 6 in Section 10.6 for further guidance for dose modification or discontinuation. Approved product labels for ramucirumab should be followed for supportive care and dose modification requirement due AEs not listed in Section 10.6. During the conduct of the study, a second dose reduction may be needed; such an action must be decided in a case-by-case discussion with the Sponsor. In case a dose reduction is necessary for Cycle 2 and subsequent cycles, the study intervention will be administered as follows in Table 7.

Table 7 - Dose modification for toxicity

Drug name	Dose	1st dose reduction[a]	2nd dose reduction[a]
tusamitamab ravtansine	100 mg/m^2 Q2W	80 mg/m^2 Q2W	(not permitted)
ramucirumab	8 mg/kg Q2W	6 mg/kg Q2W	5 mg/kg Q2W

a Dose modification is applicable from Cycle 2. At Cycle 1 the dose will remain the recommended dose (170 mg/m^2 or 150 mg/m^2).

Any participant who requires a tusamitamab ravtansine or ramucirumab dose reduction will continue to receive a reduced dose until discontinuation from tusamitamab ravtansine/ramucirumab or discontinuation from the study.

Any patient who has had 1 tusamitamab ravtansine dose reduction or 2 ramucirumab dose reductions and who experiences an event that would cause an additional dose reduction must be discontinued from tusamitamab ravtansine/ramucirumab.

If 1 of the 2 drugs (tusamitamab ravtansine or ramucirumab) is prematurely permanently discontinued, the other drug can be continued until disease progression.

Retreatment of a patient requiring a dose delay of more than 1 month will need to be justified by an individual case risk-benefit assessment.

6.5.1 Retreatment criteria: Part 1 and Part 2

All participants entered into the study will be treated at Day 1. A participant may receive additional study interventions if he/she meets retreatment criteria as determined by the Investigator and agrees to be retreated.

At Day 1, the participant must meet all of the following criteria to be eligible for retreatment:

- Neutrophil count ≥1.5 × 10^9/L.
- Platelets ≥100 × 10^9/L.
- Total bilirubin ≤1.5 × ULN.
- AST, ALT ≤2.5 × ULN or ≤5 × ULN in case of documented liver metastasis.
- No IMP-related toxicity Grade >1 (except for alopecia) or baseline severity.

- Urine protein:
  - <2+ on dipstick or urinalysis for C1D1
  - ≤2+ on dipstick or urinalysis for subsequent infusions

  OR

  - <2 g on 24 hour urine collection.
- Hypertension is controlled. Every attempt should be made to control blood pressure (<150 mmHg systolic and <90 mmHg diastolic).
- Wound healing: any wound is fully healed.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Not applicable.

6.7 TREATMENT OF OVERDOSE

For this study, any dose of tusamitamab ravtansine or ramucirumab greater than at least 30% above the intended administered dose at each cycle, expressed in unit per BSA or weight, respectively, will be considered an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor immediately.
2. Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted or whether the dose should be reduced.
3. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
4. Obtain a plasma sample for PK analysis if requested by the Sponsor or Sponsor representative(s) (determined on a case-by-case basis).
5. Document appropriately in the CRF.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Concomitant medication may be considered on a case-by-case basis by the Investigator, in accordance with the following guidelines:

- Participants with well controlled HIV infection must receive a stable ART regimen containing no antiretroviral medication other than the following: abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, rilpivirine, and/or tenofovir.
- Palliative radiotherapy may be given for control of pain (for palliative intent). If palliative radiotherapy is being considered, the Sponsor should be contacted for approval prior to initiating treatment, and prior to resuming therapy on the study.

  The irradiated area should be as small as possible and should involve no more than 20% of the bone-marrow in any given 3 week period. In all such cases, the possibility of tumor progression should be ruled out by physical and radiological assessments of the tumor. The irradiated area cannot be used as a parameter for response assessment. If the only evaluable lesions are to be irradiated, the participant will stop the study intervention.
- Any background therapy taken by the participant for concomitant illnesses other than cancer (eg, HRT, statin, antihypertensive medication) is allowed.
- Supportive treatment as medically indicated for the participant's well-being may be prescribed at the Investigator's discretion. Every medication or treatment taken by the participant during the trial and the reason for its administration must be recorded on the eCRF.

The following treatments are not permitted during this study:

- Concurrent treatment with other investigational drugs.
- Concurrent treatment with any other anticancer therapy not specified in the protocol, including immunotherapy, hormonal therapy, targeted therapy or biological therapies.
- The primary prophylactic use of Granulocyte-Colony Stimulating Factor is not allowed during the DLT observation period. Secondary prophylaxis or therapeutic administration are allowed as detailed in Appendix 6 (Section 10.6).
- Use of prophylactic erythropoietin during the first 2 cycles.
- Participants treated or intended to be treated with drugs identified as CYP_{450} substrates with narrow therapeutic range (NTR) should be carefully monitored (See Section 10.11 [Appendix 11]).
- Concomitant use of strong CYP3A inhibitors should be avoided from 2 weeks before tusamitamab ravtansine administration up to the last tusamitamab ravtansine administration (See Section 10.12 [Appendix 12]).

- The use of contact lenses will not be permitted during the study treatment period.
- Participants receiving a stable ART regimen must receive no antiretroviral medication other than the following: abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, rilpivirine, and/or tenofovir.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and disease progression status, when applicable. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation within 1 week before making a decision of permanent discontinuation of the IMP for the concerned participant.

Handling of participants after permanent intervention discontinuation

Participants will be followed according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP, including blood samples for PK and immunogenicity assessments.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency; Section 10.9). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of

study discontinuation and follow-up and for any further evaluations that need to be completed.

- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for 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 must 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 (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

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

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count, urine tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Tumor CEACAM5 expression, PD-L1 expression status, and circulating CEA will be collected during the prescreening visit.
- In participants who fail prescreening, limited information will be collected as detailed in Section 1.3.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency (Section 10.9).

8.1 EFFICACY ASSESSMENTS

Planned time points for all efficacy assessments are provided in the SoA.

The assessment of antitumor activity of tusamitamab ravtansine combined with ramucirumab with regard to ORR per RECIST 1.1 is the primary efficacy objective.

All participants treated must have at least one measurable lesion as per RECIST 1.1 for inclusion based on tumor assessment defined in the SOA, Section 1.3.

Tumor assessment will be made every 6 weeks (±7 day window), and a scheduled assessment time point will not be modified in case of a cycle delay. Thoracic-abdominal-pelvic CT-scan or MRI and any other examinations as clinically indicated will be performed to assess disease status at baseline; then every 6 weeks during the study treatment period until radiological disease progression, initiation of further anticancer therapy, death, or study cut-off for secondary endpoints, whichever comes first; and at the end of study treatment, except if already done at last cycle. Confirmatory radiological evaluation will be performed at least 4 weeks after initial documentation of response. After IMP discontinuation, tumor assessment should be performed at EOT for patients without imaging performed within past 4 weeks, and every 8 weeks (±7 days) after the last tumor assessment until disease progression or initiation of a new anticancer treatment, death, or the study cut-off for secondary endpoints, whichever comes first. Brain

CT-scan or MRI should be performed at baseline and followed only for patients with brain lesions at baseline. Imaging assessments during the on-treatment period are to be scheduled using the Cycle 1, Day 1 date as the reference date for all time points, and are not to be scheduled based on the date of the previous imaging time point. Delay of an imaging assessment to conform to treatment delay is not permitted. The same tumor assessment technique must be used throughout the study for a given lesion/participant.

Secondary efficacy endpoints will include DOR, PFS, and DCR.

The RECIST 1.1 criteria will be followed for assessment of tumor response; see Appendix 13 (Section 10.13) for details.

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than AE assessments (Section 8.3).

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the major body systems, including Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height (only at screening) and weight will also be measured and recorded.
- ECOG performance status should be assessed at baseline, before each IMP administration, at EOT, and at the follow-up visit. Performance status will be evaluated using ECOG scale (14).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new AE.

8.2.2 Specific ocular tests

Specific complete ocular tests at baseline and EOT will include: assessment of ocular/visual symptoms and ocular exams including visual acuity, slit lamp under dilatation, and Schirmer's test.

Standard specific ocular tests include:

- Assessment of ocular/visual symptoms, (ie, blurred vision, photophobia, dry eye, etc) at each visit before each study intervention. Start and end dates of symptoms will be collected.
- Visual acuity at baseline and whenever clinically indicated.
- Slit lamp under dilatation at screening and whenever clinically indicated.
- Schirmer's test at baseline and whenever clinically indicated.

In participants with any ocular/visual symptom (eg, blurred vision, photophobia), complete ocular tests will be repeated at the time of the occurrence of the ocular toxicity, if any, regardless of the grade. Thereafter, visual acuity, slit lamp examination under dilatation, and Schirmer's test will be repeated once weekly (if not recommended to have less frequent assessment by ophthalmologist based on lesion characteristics) until resolution to Grade 1. In case of recurrent ocular toxicity observed in subsequent cycles, visual acuity and slit lamp examination under dilatation, and Schirmer's test will be performed at the time of the event onset, then weekly until resolution to Grade 1.

8.2.3 Vital signs

- Temperature, pulse rate, and blood pressure will be assessed during each physical examination.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded.

8.2.4 Electrocardiograms

- Single 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals.
- ECG is required at screening within 7 days prior IMP administration, at baseline before starting and after completing the first IMP administration (within 30 minutes after the end of tusamitamab ravtansine infusion); before IMP administration at each cycle; and at the End of treatment evaluation, 30 (±5) days after last IMP administration. This test can be performed on the same day before the study intervention administration, or on the day before. An ECG is to be repeated as clinically indicated.
- ECGs will be interpreted by a qualified physician at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, should additional ECGs be performed or for immediate patient management should any clinically relevant findings be identified.

8.2.5 Echocardiogram or MUGA scan

An echocardiogram or multigated acquisition (MUGA) scan to evaluate left ventricular ejection fraction (LVEF) will be evaluated during screening period, and whenever clinically indicated.

8.2.6 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency. These tests will be done at each cycle; during the first 2 cycles, hematology and liver function tests will be assessed weekly.
- If Grade 4 neutropenia occurs, assess ANC every 2 to 3 days until ANC $\geq 0.5 \times 10^9$/L.
- In case of Grade ≥3 abnormal liver function tests, additional tests will be done every 2 to 3 days until recovery to the baseline value. Additional tests will be performed when clinically appropriate. This test can be performed before the study intervention administration on the same day or the day before.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3.).
  - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.2.7 Guidelines for management of adverse events

Management of AEs related to tusamitamab ravtansine and ramucirumab is summarized in Appendix 6 (Section 10.6); for specific AE related to ramucirumab intake, please refer to the current prescribing information leaflet; the most relevant reported events are summarized in this section as reminder.

8.2.7.1 Hypersensitivity reactions

Premedication treatments provided as prophylactic treatment for hypersensitivity reactions are detailed in Section 6.1.

In case of an event of hypersensitivity reaction, please refer to the recommended dose modification or discontinuation table in Appendix 6 (Section 10.6).

As with other monoclonal antibodies, IRRs may occur during or following ramucirumab or tusamitamab ravtansine administration. Patients should be closely monitored for signs and symptoms indicative of an IRR from the initiation of the infusion in an area where resuscitation equipment and other agents (such as epinephrine and corticosteroids) are readily available.

A 1 hour observation period following the ramucirumab infusion is mandatory for the first 2 infusions. If the patient shows no evidence of an IRR with the first 2 infusions of ramucirumab, no observation period is required for subsequent infusions. In the event an IRR occurs thereafter, the 1 hour observation should be reinstituted. Symptoms of IRRs include rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms include bronchospasm, supraventricular tachycardia, and hypotension. If the patient experiences a Grade 1 or Grade 2 IRR, interrupt the infusion and treat the patient with anti-allergic medication. If symptoms resolve, resume the infusion at a reduced rate (50%).

8.2.7.2 Ocular toxicity

It is recommended that topical artificial tears (and/or hyaluronic ophthalmic gel) are used regularly in all patients treated with tusamitamab ravtansine during the study treatment period.

The patient should be asked about ocular/visual symptoms at each visit, and ocular evaluation including visual acuity, slit lamp examination under dilatation, and Schirmer's test should be carried on according to Study Procedures (Section 8.2.2). Ocular evaluation will be performed at baseline (during the screening period), as required during the treatment (ie, on occurrence of ocular symptoms such as blurred vision, photophobia, pain), at the EOT visit, and when relevant at follow-up visit(s). The outcome of the examination should be available before infusion of the next cycle. If ocular symptoms are present, then a formal ocular examination should be performed. In patients with any ocular/visual symptom(s) (eg, blurred vision, photophobia), the ocular evaluation should be repeated once weekly, unless less frequent assessment is recommended by an ophthalmologist, until resolution to Grade 1. Subsequently, the participant should be followed with ocular exam (slit lamp and visual acuity) at each cycle until total resolution of the event.

Photographs of the cornea are recommended to be taken at the site, if possible, when ocular findings are first documented, and to follow progression when relevant. Tonometry and additional ocular assessment can be performed at discretion of an ophthalmologist when applicable.

8.2.7.2.1 Keratopathy/keratitis management

Reversible non-inflammatory, microcystic keratopathy was identified as the DLT during the dose escalation process in study TED13751with tusamitamab ravtansine. At slit-lamp examination, it presents as lesions consisting of 100s to 1000s microcysts and/or deposits that are initially observed at the periphery of the cornea, the limbus being preserved. The lesions have a centripetal distribution and evolve towards the center of the corneal upon resolution, following the natural keratinocyte regeneration process.

For standardization of AE verbatim, keratopathy should be preferred term unless otherwise specified by an ophthalmologist due to inflammatory findings on eye exams leading to diagnosis of keratitis.

The potential ocular/visual toxicity symptoms could include, but are not limited to, blurred vision, dry eye, and photophobia. Curative treatment may be used as recommended by an ophthalmologist.

No primary prophylaxis other than prevention of dry eye with artificial tears and/or hyaluronic ophthalmic gel is recommended; the use of contact lenses is not permitted during the treatment period. Corticosteroid-containing ocular drugs are recommended for the management of keratopathy/keratitis in the case that ocular symptoms occur, and treatment will be performed based on discretion of ophthalmologist. Dose modification and recommendations are further described in Appendix 6 (Section 10.6).

After resuming study treatment, a patient who had Grade ≥2 keratopathy/keratitis should be followed with standard ocular exams (ie, slit lamp examination under dilatation and visual acuity) every 2 cycles, even if symptoms are no longer reported. If no event recurs during the next 4 cycles, then regular follow-up (ie, symptom assessment at each visit with standard ocular exam in case of any ocular sign/symptom) is applied.

8.2.7.3 Management of anemia

Close surveillance of any signs and symptoms is required: a routine blood hematology workup, including red blood cell (RBC) counts, hemoglobin, hematocrit, WBC with differential, and platelet counts will be done weekly during the first 2 cycles, and thereafter each treatment cycle before IMP administration. Patients should not start Cycle 1 treatment if hemoglobin is <9.0 g/dL. To be eligible for the study and to receive the first study treatment, the participant must have been transfusion-free for 2 weeks. During the treatment period, erythrocyte transfusion can be given, upon Investigator decision. Erythropoietin can be given at the discretion of the Investigator, except during Screening and the first 2 cycles. Cycle delays or modifications should be compliant with Appendix 6 (Section 10.6).

8.2.7.4 Management of neutropenia

In patients who experienced either Grade 3 or 4 febrile neutropenia or Grade 4 decreased neutrophil count (<500 cells/mm^3) for more than 1 week during study intervention, prophylactic G-CSF should be implemented per ASCO guidelines (13) to ensure dose intensity (Appendix 6, Section 10.6). Doses of tusamitamab ravtansine should be reduced in case of recurrent events even after prophylactic G-CSF use.

If the patient continues to experience these reactions at a lowered dose, the treatment should be discontinued (Section 7.1).

8.2.7.5 Liver function tests

Hepatic enzyme increase has been reported with tusamitamab ravtansine administration as monotherapy or ramucirumab. Patients should be carefully followed and in case of Grade ≥3 abnormal liver function tests, additional liver function tests will be done every 2 to 3 days until recovery to baseline value. tusamitamab ravtansine should be permanently discontinued in case of drug-induced Grade 4 liver enzyme increase. For stopping rules for ramucirumab administration, the current product leaflet should be followed.

Grade ≥3 (ie, >5 × ULN) increased liver enzyme events should be reported as AESIs.

8.2.7.6 Hypertension

An increased incidence of severe hypertension (CTCAE Grade 3) has been reported in patients receiving ramucirumab as compared with placebo. In most cases, hypertension was controlled using standard antihypertensive treatment. Preexisting hypertension should be controlled before starting ramucirumab treatment. Monitoring of blood pressure is required during ramucirumab therapy. Every attempt should be made to control blood pressure to systolic <140 mmHg and diastolic <90 mmHg prior to starting treatment with ramucirumab. Routine clinical and laboratory monitoring is required in patients who again develop hypertension or experience a deterioration in previous hypertension.

Withhold ramucirumab for severe hypertension until medically controlled. Permanently discontinue ramucirumab for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

8.2.7.7 Proteinuria

Proteinuria is an adverse effect for all therapies targeting the vascular endothelial growth factor (VEGF)/VEGFR-2 pathway, including ramucirumab. Proteinuria has been associated with ramucirumab in clinical studies; the majority of events were Grade 1 or 2.

Monitor proteinuria by urine dipstick or routine urinalysis. If the result of the urine dipstick is 2+ or greater, perform a 24 hour urine collection for protein measurement.

Withhold ramucirumab for urine protein levels of 2 or more grams collected over 24 hours. Reinitiate ramucirumab at a reduced dose once the urine protein level returns to less than 2 grams over 24 hours. Permanently discontinue ramucirumab for urine protein levels greater than 3 grams over 24 hours, or in the setting of nephrotic syndrome.

8.2.7.8 Bleeding/hemorrhage

Ramucirumab is an antiangiogenic therapy and has the potential to increase the risk of severe bleeding. Permanently discontinue ramucirumab in patients who experience severe (Grade 3 or Grade 4) bleeding.

8.2.7.9 Arterial thromboembolic events

Serious, sometimes fatal, arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials. Permanently discontinue ramucirumab in patients who experience an ATE.

8.2.7.10 Peripheral neuropathy

Participants with a known history of peripheral neuropathies and/or patients having received medications known to cause peripheral neuropathies (eg, prior antitubulin, platinum and/or taxanes) are at high risk of developing neuropathy. Peripheral neuropathies potentially present as signs and symptoms of sensory (paresthesia, dysesthesias, pain, and change in proprioception), motor (weakness), and neural dysfunctions.

There is no further recommendation beyond routine guidance on prevention and treatment of peripheral neuropathy. Cycle delays or modifications should be compliant with Appendix 6 (Section 10.6).

8.2.7.11 Colitis (including hemorrhagic)

In study TED13751 evaluating tusamitamab ravtansine in patients with several cancer types, a limited number of participants developed colitis. Based on clinical observations, patients with known underlying colitis or gastrointestinal tract conditions are noted to be at highest risk for such events. The monitoring of patients for GI toxicities will rely on careful evaluation by routine history, physical examination, and standard laboratory examination. Close surveillance of any signs and symptoms is required, with additional routine hematology workup (hemoglobin, hematocrit, and WBC with differential and platelet counts) whenever indicated. As 1 Grade 4 case of colitis erosive has been reported, it is recommended to conduct close surveillance of any diarrhea event, with further exams when clinically indicated. Treatment is per patient condition, based on Investigator discretion.

8.2.8 Pregnancy testing

Refer to Section 5.1 for pregnancy testing criteria. The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk of including a female participant with an early undetected pregnancy.

- Pregnancy testing (urine or serum as required by local regulations) should be conducted every 4 weeks during intervention (at study visits and if needed, at home in between visits).
- Pregnancy testing (urine or serum as required by local regulations) must be conducted corresponding with the time frame for female participant contraception in Section 5.1.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.7.

An AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue study intervention (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the ICF until at least 30 days after the last study intervention at the time points specified in the SoA (Section 1.3). For a participant who was prescreened and had fresh biopsy, only the AEs in the prescreening period related to the fresh biopsy procedure itself and within the reporting time frame interval of 1 month after fresh biopsy should also be reported in eCRF according to general requirements of AE/SAE.

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3). Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and AEs of special interest (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected for tusamitamab ravtansine will be specified in the reference safety information in the Investigator Brochure.
- Suspected unexpected serious adverse reactions (SUSARs) are reported to regulatory authorities, Investigators, and IRBs/IECs as follows:
  - For SUSARs that are life-threatening or result in death, reporting is no later than 7 days after first knowledge by the Sponsor, with all relevant follow-up information subsequently reported within an additional 8 days.
  - For SUSARs, other than those that are life-threatening or result in death, reporting is no later than 15 days after first knowledge by the Sponsor.
  - Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR, or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure for tusamitamab ravtansine and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 7 months after the last intervention.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy.
  - Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants' pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

Prior to continuation of study intervention following pregnancy, the following must occur:

- The Sponsor and the relevant IRB/IEC give written approval.
- The participant gives signed informed consent.
- The Investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

8.3.6 Cardiovascular and death events

Cardiovascular and death events will be treated as regular events.

8.3.7 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor’s product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP;
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Section 8.3.5).
- Symptomatic overdose (serious or nonserious) with IMP

  Symptomatic overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as an increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.

- Grade ≥3 keratopathy
- Bundle branch blocks or any conduction defects
- Grade ≥3 liver enzyme increased (symptomatic or asymptomatic)
- All protocol-defined DLTs (Section 6.5)

8.3.8 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 PHARMACOKINETICS

Blood samples will be collected for the measurement of tusamitamab ravtansine and ramucirumab concentrations as described in the PK/ATA flow charts (Section 1.3.2). The actual date and time of each sample will be recorded. Instructions for the collection and handling of PK samples will be provided by the Sponsor in a separate laboratory manual. These samples will be tested by the Sponsor's designee. Pharmacokinetic samples could be used for testing analytical method performance such as comparability and incurred sample reproducibility.

8.4.1 Tusamitamab ravtansine

Data from plasma concentrations of tusamitamab ravtansine will be used for population PK analysis by nonlinear mixed-effects modeling. Empirical Bayesian estimation of individual exposure parameters such as maximum concentration (C_{max}), trough concentration (C_{trough}), and area under the concentration-time curve (AUC) will be derived.

8.4.2 Ramucirumab

Ramucirumab concentration data will be summarized by descriptive statistics.

8.5 GENETICS

A 20 mL blood sample corresponding to about 10 mL of plasma and an additional 2 mL blood sample for germline DNA will be collected for future use at pre-infusion of Cycle 1, Day 1. These samples may be used for but not restricted to tumor circulating free deoxyribonucleic acid (cfDNA) and germline DNA isolation respectively. Other blood and plasma components as circulating proteins or RNA may be also evaluated.

Participants who do not wish to participate in the genetic research may still participate in the study.

In case of cfDNA/DNA isolation, samples are planned to be transferred to a central laboratory for extraction and mutational profiling of key cancer genes to understand the significance of existing mutation during tusamitamab ravtansine treatment.

Fragmented circulating tumor DNA or cfDNA is released from the tumor in the plasma and can readily be extracted and analyzed for mutation of common cancer genes. Subtractive mutation analysis will be performed with germline DNA data to identify tumor specific somatic genetic aberrations. The list (not exhaustive) of the genes that could be mutated/translocated is: *AKT1, ALK, BRAF, CDKN1B,CDKN2A, CDKN2D, EGFR, ESR1, FGFR4, HER2, HRAS, KRAS, MDM2, MED1, MET, NRAS, PIK3CA, PTEN, RB1, RET, ROS1*, and *TP53*.

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection, shipment and destruction of these samples can be found in the study laboratory manual.

As new knowledge is acquired about the disease and/or tusamitamab ravtansine, other techniques could be implemented to evaluate other analytes such as circulating proteins or RNA.

8.6 BIOMARKERS

Collection of biological samples for other biomarker research is also part of this study. Samples collected for biomarker analyses and their derivatives will be stored for a period of up to 15 years after last participant, last visit for potential re-analysis.

- The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:
  - Tumor tissue samples will be collected and assayed for CEACAM5 expression to determine eligibility for this study.

    The level of CEACAM5 expression in tumor tissues will be determined by a central laboratory using a specific anti-CEACAM5 antibody (clone 769).
  - Blood samples for circulating CEA will be collected to assess correlation with CEACAM5 expression in tumor samples and to explore modulations of circulating CEA as a potential pharmacodynamics biomarker of response to tusamitamab ravtansine treatment.

    Blood samples for circulating CEA levels will be collected at prescreening for all participants, at baseline for screened participants, every 6 weeks during the treatment period, at the EOT visit, and in the follow-up period at the time of laboratory assessment (as close as possible to and no more than 2 weeks from the tumor assessment) until disease progression. Circulating CEA will be assessed using local testing. Venous blood samples of approximately 3 mL (volume may change depending on local laboratory assay) will be collected for measurement at the local laboratory.
  - Blood samples will be collected for measurement of IgG to explore impact of IgG level on PK of tusamitamab ravtansine.

The level of IgG in blood at pre-infusion of Cycle 1, Day 1 will be determined by a central laboratory. For this test 2 mL of blood, corresponding to 1 mL of serum, will be collected.

- Blood and plasma samples will be collected for future analyses (as optional).

  For future use, a 20 mL blood sample corresponding to about 10 mL of plasma and an additional 2 mL blood will be collected at baseline. Samples will be stored and analysis may be performed for research to develop methods, assays, prognostics and/or companion diagnostics related to tusamitamab ravtansine, disease process, pathways associated with disease state, and/or mechanism of action of tusamitamab ravtansine. Analytes to be evaluated may include but not limited to DNA, RNA, or serum analytes to evaluate their association with observed clinical responses to tusamitamab ravtansine.

8.7 IMMUNOGENICITY ASSESSMENTS

Blood samples will be collected for assessing the presence of ATA against tusamitamab ravtansine in plasma from all participants as described in the PK/ATA flowcharts (Section 1.3.2). These samples will be tested by the Sponsor's designee.

Refer to the laboratory manual for details regarding sample collection, processing, storage, and shipment.

Plasma samples will be screened for antibodies binding to tusamitamab ravtansine and the titer of confirmed positive samples will be reported.

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the

purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects.

Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research).

All study participant data and samples will be coded such that no participant direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

The samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

The safety run-in (Part 1) aims to confirm the recommended dose of tusamitamab ravtansine loading dose Q2W in combination with ramucirumab according to DLTs observed.

Part 2 of this study is designed to obtain preliminary efficacy, safety, and PK data on tusamitamab ravtansine loading dose Q2W administered in combination with ramucirumab to participants with gastric or GEJ adenocarcinoma. As Part 2 is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design.

9.1 SAMPLE SIZE DETERMINATION

Assuming a prescreening failure rate of 70% and a study screening failure rate of 20%, approximately 158 participants will be prescreened to achieve up to approximately 38 treated participants in the safety run-in (Part 1) and Part 2.

Sample size for the safety run-in (Part 1):

The actual sample size is expected to vary depending on DLTs observed. It is anticipated that around 6 to 12 DLT-evaluable participants will be enrolled in the safety run-in part of the study.

Sample size for Part 2:

The initial plan is to treat a total of 32 participants evaluable for activity (at least 1 postbaseline evaluable tumor assessment, early clinical progression, or death due to disease progression). The 6 participants treated at the recommended DL in the safety run-in part will also be evaluable for the second part of the study.

Estimated ORR and 95% exact CIs by number of responders from a sample size of 32 evaluable participants for activity are listed in Table 8:

Table 8 - Estimated objective response rate (ORR) depending on number of responders

Number of responders (N=32)	Objective response rate in percent (Clopper-Pearson 95% CI)
[redacted]	

Abbreviation: CI = confidence interval

9.2 POPULATIONS FOR ANALYSES

The following populations for analyses are defined in Table 9:

Table 9 - Populations for analyses

Population	Description
Prescreened	All participants who signed the prescreening informed consent for CEACAM5 assessment of their biopsy.
Screened	All participants who signed screening informed consent for study participation.
Enrolled	Participants from screened population who have been allocated to intervention regardless of whether the intervention was received or not.
All-treated	All enrolled participants exposed to the study treatment, regardless of the amount of treatment administered. This population is the primary population for all efficacy parameters.
DLT-Evaluable (Part1)	All enrolled participants who received 2 cycles with at least 80% of the intended dose for both tusamitamab ravtansine and ramucirumab at each of the first 2 infusions unless they discontinued the study intervention before the end of Cycle 2 due to a DLT.
Activity	All treated participants who have measurable disease at study entry and at least 1 postbaseline evaluable tumor assessment. Participants with no postbaseline evaluable tumor assessment but with an early clinical progression or who died from disease progression will also be included in this set. This population is the secondary population for all efficacy parameters.
PK	All participants from the all-treated population with at least 1 postbaseline PK concentration (whatever the cycle and even if dosing is incomplete) with adequate documentation of dosing and sampling dates and times.
ATA	All participants from the all-treated population with at least 1 postbaseline ATA result (negative, positive or inconclusive).

Abbreviations: ATA = antitherapeutic antibody; CEACAM5 = carcinoembryonic antigen-related cell adhesion molecule 5; DLT = dose-limiting toxicity; PK = pharmacokinetic.

Participants exposed to study intervention before or without being enrolled will not be considered enrolled and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Enrolled participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population.

For any participant enrolled more than once, only the data associated with the first enrollment will be used in any analysis population. The safety experience associated with any later enrollment will be reported separately.

9.3 STATISTICAL ANALYSES

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.3.1 General considerations

This study is not intended to explicitly test a hypothesis. For primary and secondary efficacy endpoints, 95% CIs will be provided.

All efficacy endpoints based on radiological assessments of tumor burden (ie, ORR, DOR, PFS, and DCR) will be derived using the local radiologist's/Investigator's assessment.

In general, continuous data will be summarized using the number of observations available, mean, standard deviation, median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before the first dose of investigational medicinal product (IMP).

The study cut-off for analysis of the primary endpoint for the study, ORR, corresponds to the date on which all evaluable treated participants have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. This study cut-off can be up to approximately 16 weeks (12 weeks for 2 tumor assessments and 4 weeks for confirmation of response, if needed) after the last participant's first IMP administration.

The final study cut-off date for analysis of the secondary efficacy endpoints, which include DOR and PFS, will be 4 months after the cut-off date for the primary analysis. At that time, the primary analysis of ORR and DCR will also be updated.

Observation period

The observation period will be divided into 4 segments:

- The **pretreatment period** is defined as the period up to first IMP administration.
  - The **prescreening period** is defined as the period from the prescreening informed consent to the day before the screening informed consent.
  - The **screening period** is defined as the period from the screening informed consent up to the first IMP administration.
- The **on-treatment period** (ie, treatment-emergent (TE) period) is defined as the period from the first IMP administration to the last IMP administration +30 days.
- The **posttreatment** period is defined as the period from the end of the on-treatment period.

9.3.2 Primary endpoints

As it is a 2-part study, there are 2 primary endpoints: incidence of study-drug related DLTs at Cycle 1 and Cycle 2 in Part 1 and ORR as per RECIST 1.1 in Part 2.

9.3.2.1 Incidence of study-drug related DLT at Cycle 1 and Cycle 2

The primary safety analysis will be based on a principal stratum estimand defined according to the following attributes:

- The primary safety endpoint is study-drug related DLT during the DLT observation period (ie, from Cycle 1 Day 1 to Cycle 2 Day 14).
- The treatment condition of interest is tusamitamab ravtansine loading dose Q2W in combination with ramucirumab, by DL (if applicable).
- The analysis population is the DLT-evaluable population (defined in Section 9.2 Populations for analyses).
- There is no defined strategy for handling intercurrent events due to the definition of the analysis population. Indeed, participants from the DLT-evaluable population will not experience any anticipated intercurrent events (intervention discontinuation, study discontinuation, start of an anticancer therapy and death) before experiencing a DLT at Cycle 1 or Cycle 2, or before completing the Cycle 2, whichever is earlier.
- The population-level summary will include the incidence of DLTs at Cycle 1 and Cycle 2, defined as number and percentage of participants experiencing at least 1 study-drug-related DLT. There will be no missing data in the analysis population.

9.3.2.2 Objective response rate

The primary efficacy analysis will be based on a treatment policy and composite variable estimand defined according to the following attributes:

- The primary efficacy endpoint is confirmed objective response (confirmed CR or PR as BOR) as per RECIST 1.1. The BOR will be derived according to RECIST 1.1 definitions based on the investigator's assessment. The BOR is the best overall response observed from the date of the first administration of IMP until documented disease progression, death, start of an anticancer therapy, or analysis cut-off date, whichever occurs first.
- The treatment condition of interest is tusamitamab ravtansine loading dose Q2W in combination with ramucirumab.
- The analysis population is the subgroup of participants from all-treated population (defined in Section 9.2 Populations for analyses) treated at the recommended dose of tusamitamab ravtansine loading dose Q2W (ie, excluding participants treated at the starting dose if this differs from the recommended dose).

- Intercurrent events:
  - The study intervention discontinuation intercurrent event will be handled with the treatment policy strategy. Confirmed objective response will be assessed based on tumor assessments regardless of study intervention discontinuation.
  - The other anticipated intercurrent events will be handled with the composite strategy. Participants who discontinue the study, start an anticancer therapy, experience PD, or die prior to a confirmed objective response will be considered nonresponders.
- The population-level summary will be the ORR, defined as the rate of participants with confirmed objective response and 2-sided 95% CIs using the Clopper-Pearson method. In the absence of confirmed objective response, participants will be considered as nonresponders, whatever the reason (including participants with missing or nonevaluable BOR).

  As a supplementary analysis, ORR as per RECIST 1.1 will also be summarized on the subgroup of participants from activity population (defined in Section 9.2 Populations for analyses) treated at the recommended dose for tusamitamab ravtansine in a loading-dose Q2W regimen (ie, excluding participants treated at the starting dose if this differs from the recommended dose). The same analytical approach as described above will be used.

9.3.3 Secondary endpoints

The secondary efficacy endpoints detailed in this section are DOR, PFS, and DCR. Analyses of other secondary endpoints are described separately with other safety analyses (adverse events and laboratory variables, vital signs and electrocardiograms) or other analyses (pharmacokinetic, immunogenicity).

9.3.3.1 Duration of response

Analysis of the DOR will be based on a treatment policy and composite variable estimand defined according to the following attributes:

- The endpoint is DOR, defined as the time from the date of first initial occurrence of the confirmed CR or PR to the date of first radiological documentation of PD according to RECIST 1.1 or death due to any cause, whichever occurs first.

  In the absence of disease progression or death before the analysis cut-off date, DOR will be censored at the date of the last evaluable tumor assessment (not showing documented disease progression) performed before the analysis cut-off date.
- The treatment condition of interest is tusamitamab ravtansine loading dose Q2W in combination with ramucirumab.
- The analysis population is the subgroup of participants from all-treated population (defined in Section 9.2 Populations for analyses) treated at the recommended dose of tusamitamab ravtansine in a loading-dose Q2W regimen (ie, excluding participants treated at the starting dose if this differs from the recommended dose) who achieved a confirmed objective response (PR or CR).

- Intercurrent events:
  - The study intervention discontinuation intercurrent event will be handled with the treatment policy strategy. DOR will be assessed based on tumor assessments regardless of study intervention discontinuation.
  - The other anticipated intercurrent events will be handled with the composite strategy. For participants who discontinue the study or start an anticancer therapy prior to observing PD or death, DOR will be censored at the date of the last evaluable tumor assessment (not showing PD) performed prior to the intercurrent event.
- The population-level summary will include the median DOR and associated 95% CI using Kaplan-Meier methods. In the absence of confirmed objective response, DOR will not be derived.

9.3.3.2 Progression-free survival

Analysis of the PFS will be based on a treatment policy and composite variable estimand defined according to the following attributes:

- The endpoint is PFS, defined as the time from the date of the first administration of IMP to the first documentation of objective PD according to RECIST 1.1 definitions or death due to any cause, whichever comes first.

  If progression or death is not observed before the analysis cut-off date, then PFS will be censored at the date of the last evaluable tumor assessment performed before the analysis cut-off date. A participant without PFS event (death or documented disease progression) and without any evaluable postbaseline tumor assessment will be censored at the date of the first administration of IMP (Day 1).
- The treatment condition of interest is tusamitamab ravtansine loading dose Q2W in combination with ramucirumab.
- The analysis population is the subgroup of participants from all-treated population (defined in Section 9.2 Populations for analyses) treated at the recommended dose of a tusamitamab ravtansine loading-dose Q2W regimen (ie, excluding participants treated at the starting dose, if this differs from the recommended dose).
- Intercurrent events:
  - The study intervention discontinuation intercurrent event will be handled with the treatment policy strategy. PFS will be assessed based on tumor assessments regardless of study intervention discontinuation.
  - The other anticipated intercurrent events will be handled with the composite strategy. For participants who discontinue the study or start an anticancer therapy prior to observing a PFS event (death or documented disease progression), PFS will be censored at the date of the last evaluable tumor assessment (not showing PD) performed prior to observing the intercurrent event. A participant without a PFS event and without any evaluable postbaseline tumor assessment will be censored at the date of the first administration of IMP (Day 1).

- The population-level summary will include:
  - Kaplan-Meier estimates of the 25th, 50th, and 75th percentiles and their associated 95% CIs. The method of Brookmeyer and Crowley and a log-log transformation of the survival function will be used to construct 95% CIs.
  - Number (%) of participants at risk as well as the probabilities of being event-free at least at 2, 4, 6, 8, and 10 months with 95% CIs using the Kaplan-Meier method and a log-log approach based on a normal approximation following Greenwood's formula.
  - Kaplan-Meier curves including the number of participants at risk at key time points.
  - Number (%) of participants with an event and the type of event (documented disease progression or death).
  - Number (%) of censored participants and reason for censoring (no baseline tumor assessment, no evaluable postbaseline tumor assessment, ongoing without documented progression, event occurred after 2 or more non-evaluable tumor assessments or initiation of further anticancer therapy).

9.3.3.3 Disease control rate

Analysis of the DCR will be based on a treatment policy and composite variable estimand defined according to the following attributes:

- The endpoint is disease control response (confirmed CR or PR, or SD as BOR) as per RECIST 1.1.
- The treatment condition of interest is tusamitamab ravtansine loading dose Q2W in combination with ramucirumab.
- The analysis population is the subgroup of participants from all-treated population (defined in Section 9.2 Population for analyses) treated at the recommended dose of tusamitamab ravtansine in a loading-dose Q2W regimen (ie, excluding participants treated at the starting dose, if this differs from the recommended dose).
- Intercurrent events:
  - The study intervention discontinuation intercurrent event will be handled with the treatment policy strategy. Disease control response will be assessed based on tumor assessments regardless of study intervention discontinuation.
  - The other anticipated intercurrent events will be handled with the composite strategy. Participants who discontinue the study, start an anticancer therapy, experience PD, or die prior to observing a disease control response will be considered nonresponders.
- The population-level summary will be the disease control rate (DCR), defined as the rate of participants with disease control response and two-sided 95% CIs using the Clopper-Pearson method. In the absence of a disease control response, participants will be considered as nonresponders, whatever the reason (including participants with missing or nonevaluable BOR).

As a supplementary analysis, DCR as per RECIST 1.1 will also be summarized on the subgroup of participants from activity population (defined in Section 9.2 Population for analyses) treated at the recommended dose of tusamitamab ravtansine in a loading-dose Q2W regimen (ie, excluding participants treated at the starting dose if this differs from the recommended dose). The same analytical approach as described above will be used.

9.3.4 Exploratory endpoints

Analyses of circulating CEA will be described in the SAP.

9.3.5 Other safety analyses

Except if otherwise mentioned, all safety analyses will be conducted in the all-treated population.

9.3.5.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 3 categories:

- Pretreatment AEs: AEs that developed, worsened or became serious during the pretreatment period.
- TEAEs: AEs that developed, worsened or became serious during the treatment-emergent period.
- Posttreatment AEs: AEs that developed, worsened or became serious during the posttreatment period.

Similarly, the deaths will be analyzed in the pretreatment, treatment-emergent and posttreatment periods.

Summaries will be provided for all grades combined and for Grade ≥3 (including Grade 5). Missing grades, if any, will be included in the "all grades" category.

Analysis of all adverse events

Adverse event incidence table will be provided for all types of TEAEs: all TEAEs, all treatment-emergent AESI (defined with a preferred term or a prespecified grouping), all treatment-emergent SAEs, all TEAEs related to IMP, all TEAEs leading to permanent full/partial intervention discontinuation and all TEAEs leading to dose modification or dose interruption.

The AE summaries will be generated with number (%) of participants experiencing at least one event.

Deaths will also be analyzed.

9.3.5.2 Laboratory variables, vital signs and electrocardiograms (ECGs)

Quantitative analyses

For vital signs and ECG variables, descriptive statistics for results and changes from baseline will be provided for each planned visit, and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using local measurements.

Analyses according to Potentially Clinically Significant Abnormalities (PCSA) and NCI grading

For laboratory variables, analyses according to NCI grading will be made based on NCI-CTCAE version 5.0. In addition, for laboratory variables for which NCI-CTCAE scale is not applicable, vital signs and ECG variables, PCSA analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

Analyses according to PCSA and NCI grading will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, vital signs and ECG variables, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For laboratory variables graded by NCI-CTCAE v5.0.

- The number (%) of participants with abnormal laboratory tests at baseline will be presented by grade.
- The number (%) of participants with abnormal laboratory tests during the treatment-emergent period will be summarized by grade. When appropriate, the number (%) of participants with abnormality of any grade and with Grade 3-4 abnormalities will be provided.

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal

9.3.6 Other analyses

Pharmacokinetic

The population PK analyses will be described in a specific document and the results will be presented separately from the clinical study report.

Immunogenicity

Immunogenicity analyses and the potential impact on PK, safety and efficacy will be described in the SAP and will be performed on the ATA population.

Other

For a regional or national emergency declared by a governmental agency (eg, COVID-19), contingency measures are included in Section 10.9.

9.4 INTERIM ANALYSES

No interim analysis is planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, Investigator Brochure, [IDFU] and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding.
- The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
- The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.

- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s) during their participation in the

study. Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).

- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- A participant who requires prolongation of the screening period (temporary screen failure) is not required to sign another ICF. However, if the reason for the temporary screen failure is a reason that might have altered the participant's initial given agreement to participate, the Investigator should ask the participant to confirm willingness to continue or repeat some screening procedures and to participate in the trial. This oral agreement should be documented in the participant's chart. Participants who screen failed and then rescreen need to re-sign a new screening ICF.
- A participant who has CEACAM5 results available from a prior study must sign an addendum to the informed consent; no additional prescreening informed consent will be required.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because they are expected to modify the drug response/because they are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.

- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study.
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

10.1.5.1 Study committee

The SC includes the Investigators or designees and Sponsor team members and, when appropriate, ad hoc experts. Decisions to continue the enrollment at a DL or to reduce the dose to be tested will be made after the appropriate data are collected and reviewed by the SC. The SC will convene regularly (eg, every 2 weeks) during Part 1 of the study (run-in); and may meet ad hoc for specific discussions. Meeting minutes will be documented.

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the “EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations”.

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF completion instructions.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined in the list of predefined potential deviations to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the eCRF completion instructions.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

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

Study/Site termination

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

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

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 10 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing will be performed in all WOCBP at baseline, at End of treatment visit, and the 3 month follow-up, as detailed in the SOA (Section 1.3). Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to the initial intervention; at the End of treatment evaluation (30 ±5 days after the last IMP administration); and at the Follow-up (90 ±7 days after the last IMP administration). Additionally, during the treatment period, serum/urine pregnancy tests will be performed at the beginning of the visit every 4 weeks (ie, every 2 cycles/every other cycle).
- Investigators must document their review of each laboratory safety report.

Table 10 - Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Hematology	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical blood chemistry[a]	Urea/blood urea nitrogen (BUN)
	Creatinine
	Glucose
	Potassium
	Sodium
	Calcium
	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase
	Total and conjugated bilirubin
	Total protein
	Albumin
	LDH
Coagulation	Coagulation parameters (INR, aPTT)

Laboratory assessments	Parameters
Urinalysis	Urine dipstick or routine urinalysis If urine dipstick or routine urinalysis inticates proteinuria ≥2+, a 24 hour urine collection for protein measurement must be obtained.
Serum/urine pregnancy[b]	
Serology[c]	human immunodeficiency virus (HIV) hepatitis B virus surface antigen (HBsAg) hepatitis C virus (HCV)

Abbreviations: aPTT = activated partial thromboplastin time; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = International Normalized Ratio; LDH = tactate dehydrogenase; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase (AST); SGPT = serum glutamic-pyruvic transaminase (ALT); WBC = white blood cell count.
NOTES:

a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Appendix 6 (Section 10.6) All events of Grade 4 AST/ALT increase must be reported as an SAE. Investigators must document their review of each laboratory safety report.

b Only for WOCBP.

c Serological testing for specific viral infections may not be required at all sites. Local authorities may require testing for human immunodeficiency virus (HIV), hepatitis B viral antigen (HBsAg), and/or hepatitis C virus (HCV); please refer to Appendix 8 (Section 10.8) for details of any locally required testing for these or other viruses.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with participant and by review of available medical records at the next visit.

- Solicited AEs are pre-defined local and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Is a suspected transmission of any infectious agent via an authorized medicinal product

g) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the monotoring team.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the Investigator study file.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator study file.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry eligibility.

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

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

10.4.2 Contraception guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)
  Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
  Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - oral
  - injectable
- Sexual abstinence
  Sexual abstinence is considered *a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

10.4.3 Statistical analyses and deviation

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

10.5 APPENDIX 5: GENETICS

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA/RNA analysis from consenting participants.
- DNA samples will be used for research related to tusamitamab ravtansine or advanced solid tumors and related diseases. They may also be used to develop tests/assays including diagnostic tests related to CEACAM5-targeting drugs and advanced solid tumors. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed for determination of tumor mutation profiles of plasma cfDNA and tumor DNA. Subtractive mutation analysis will be performed with germline DNA data to identify tumor-specific somatic genetic aberrations. Additional analyses such as RNA analysis may be conducted if it is hypothesized that these may help further explain the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to tusamitamab ravtansine or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples may be retained while research on tusamitamab ravtansine or advanced solid tumors and related diseases continues, but no longer than 15 years or other period, as per local requirements.

10.6 APPENDIX 6: RECOMMENDED SUPPORTIVE CARE AND/OR DOSE MODIFICATION GUIDELINES FOR DRUG-RELATED ADVERSE EVENTS

Event	Symptoms severity (Nadir) (NCI CTCAE v5)	Management of IMP dosing (ramucirumab)	Management of IMP dosing (tusamitamab ravtansine)	Supportive care guidelines
Infusion-related reactions	Grade 1-2 Mild-moderate Eg, Grade ≤2 nausea, headache, tachycardia, hypotension, rash, shortness of breath.	Interrupt ramucirumab infusion and start appropriate treatment. Reduce infusion rate by 50%	Interrupt tusamitamab ravtansine infusion. Tusamitamab ravtansine may be resumed only after patient recovery, at half the previous infusion rate[a].	Give diphenhydramine 50 mg IV and/or dexamethasone 10 mg IV. ramucirumab label should be followed Dexamethasone can be added as premedication for upcoming cycles for tusamitamab ravtansine
	Grade 3-4 Severe Eg, symptomatic bronchospasm, urticaria lesions covering >30% BSA, hypotension, angioedema.	Interrupt ramucirumab infusion and definitively discontinue ramucirumab	Interrupt tusamitamab ravtansine infusion and definitively discontinue tusamitamab ravtansine and consider infusion delay.	Give diphenhydramine 50 mg IV and/or dexamethasone 10 mg IV and/or epinephrine and any required treatment per investigator judgement.
Ocular toxicity: Keratopathy/keratitis[b] associated with tusamitamab ravtansine	Grade 1 - Asymptomatic Corneal lesions only observed on routine ocular examination and not requiring topical treatment.	Administer ramucirumab at same dose, and same day as tusamitamab ravtansine	Next infusion of tusamitamab ravtansine at the same dose, with or without cycle delay, depending on the recommendation from the ophthalmologist (nature and extent of the lesion).	Standard ocular examination is planned as recommended by the ophthalmologist.
	Grade 2 Symptomatic or requiring topical treatment (curative) or limiting instrumental activity of daily life. Moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Administer ramucirumab at same dose, and same day as tusamitamab ravtansine or administer ramucirumab as planned if definitive discontinuation of tusamitamab ravtansine	1st episode: Omit tusamitamab ravtansine until resolution to Grade 1 (asymptomatic) and restart tusamitamab ravtansine at the same dose. 2nd episode: Omit tusamitamab ravtansine until resolution to Grade 1 (asymptomatic) and tusamitamab ravtansine dose reduction. 3rd episode: depending on benefit risk, definitive discontinuation of tusamitamab ravtansine may be envisaged	Standard ocular examination weekly until resolution[c, d]. Start curative treatment per ophthalmologist recommendation. After resuming study treatment, participant should be followed with standard ocular examination every 2 cycles, even if asymptomatic during next 4 cycles. If no recurrence is observed, the standard process with follow-up of the ocular symptom should be resumed. Management of study drug upon recurrence to be discussed according to Grade of the event at recurrence, clinical benefit from study drug and recommendation from the ophthalmologist.

Event	Symptoms severity (Nadir) (NCI CTCAE v5)	Management of IMP dosing (ramucirumab)	Management of IMP dosing (tusamitamab ravtansine)	Supportive care guidelines
Ocular toxicity *(continued)*	Grade 3 Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); corneal ulcer; limiting selfcare activity of daily life	Administer ramucirumab at same dose, and same day as tusamitamab ravtansine or administer ramucirumab as planned if definitive discontinuation of tusamitamab ravtansine	1st episode: Omit tusamitamab ravtansine until resolution (asymptomatic), and restart tusamitamab ravtansine with dose reduction. 2nd episode: definitive discontinuation of tusamitamab ravtansine.	Standard ocular examination weekly until resolution[c, d] Start curative treatment per ophthalmologist recommendation. After resuming study treatment, participant should be followed with standard ocular examination by every 2 cycles, e en asymptomatic during next four cycles. If no recurrence, standard process with follow-up with ocular symptom is resumed Management of study drug upon recurrence to be discussed according to Grade of the event at recurrence, clinical benefit from study drug and recommendation from the ophthalmologist
	Grade 4 Perforation or best corrected visual acuity of 20/200 or worse in the affected eye.	Administer ramucirumab as planned.	Definitive discontinuation of tusamitamab ravtansine.	Complete the corneal examination as recommended by ophthalmologist. Repeat the standard ocular examination weekly[c] until resolution[d]. Start curative treatment per ophthalmologist recommendation.
Conduction disorder associated with tusamitamab ravtansine	Grade 1 Mild symptoms	Administer ramucirumab as planned.	tusamitamab ravtansine administration to be continued upon decision by the Investigator and Sponsor, depending on the nature of the conduction disorder.	ECG performed once weekly until event resolution. Additional evaluations such as LVEF and Holter monitoring should be performed when relevant.
	Grade ≥2	Administer ramucirumab as planned.	Definitive discontinuation of tusamitamab ravtansine.	ECG to be repeated twice weekly until event resolution. Prompt cardiology consultation Additional evaluations such LVEF and Holter monitoring should be performed when relevant.

Event	Symptoms severity (Nadir) (NCI CTCAE v5)	Management of IMP dosing (ramucirumab)	Management of IMP dosing (tusamitamab ravtansine)	Supportive care guidelines
Peripheral neuropathy	Grade 1: Asymptomatic	Administer ramucirumab as planned.	Administer tusamitamab ravtansine as planned,	Patient who has ongoing Grade 1 neuropathy has high risk of worsening of his/her symptoms and should be closely followed.
	Grade 2: Moderate symptoms; limiting instrumental Activities of Daily Living	Delay cycle until recovery to ≤ Grade 1; at next cycle, administer ramucirumab the same day as tusamitamab ravtansine	Delay cycle until recovery to ≤ Grade 1 and dose reduction if no improvement with dose delay	
	Grade 3: Severe symptoms; limiting self care Activities of Daily Living	Administer ramucirumab as planned.	Definitive discontinuation of tusamitamab ravtansine	
	Grade 4: Life-threatening consequences; urgent intervention indicated	Administer ramucirumab as planned.	Definitive discontinuation of tusamitamab ravtansine	
Neutrophil count decreased	Grade 1 <LLN - 1500/mm^3 ; <LLN - 1.5 × 10^9/L	No change in IMPs administration.	No change in IMPs administration	No intervention.
	Grade 2 <1500 - 1000/mm^3; <1.5 - 1.0 × 10^9/L	Delay the cycle until recovery of absolute neutrophil count >1500/mm^3. Restart at the same dose.	Delay the cycle until recovery of absolute neutrophil count >1500/mm^3. Restart at the same dose.	No intervention.
	Grade 3 <1000 - 500/mm^3; <1.0 - 0.5 × 10^9/L Or Grade 4 <500/mm^3; <0.5 × 10^9/L	Delay the cycle until recovery of absolute neutrophil count >1500/mm^3. Restart when absolute neutrophil count >1500/mm^3 at the same dose. Prophylactic G-CSF can be considered in all subsequent cycles	Delay the cycle. Restart the treatment when absolute neutrophil count >1500/mm^3 at the same dose; prophylactic G-CSF can be considered in all subsequent cycles	Follow ASCO guidelines on usage of G-CSF and antibiotherapy (13). Repeat test every 3 days.

Event	Symptoms severity (Nadir) (NCI CTCAE v5)	Management of IMP dosing (ramucirumab)	Management of IMP dosing (tusamitamab ravtansine)	Supportive care guidelines
Neutrophil count decreased *(continued)*	Grade 4 >7 days <500/mm^3; <0.5 × 10^9/L	Delay the cycle until absolute neutrophil count >1500/mm^3. 1st episode administer next cycle with ramucirumab at the same dose and administer growth factors 2nd episode: administer ramucirumab at the same dose 3rd episode: definitive discontinuation of IMPs	Delay the cycle until absolute neutrophil count >1500/mm^3. 1st episode administer tusamitamab ravtansine next cycle at the same dose and administer growth factors 2nd episode: administer tusamitamab ravtansine at reduced dose 3rd episode: definitive discontinuation	Follow ASCO guidelines on G-CSF usage and antibiotherapy (13). Repeat test every 3 days.
Febrile neutropenia	Grade 3 Absolute neutrophil count <1000/mm^3 with a single temperature of >38.3ºC (101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than 1 hour	Delay cycle until absolute neutrophil count >1500/mm^3. 1st episode administer next cycle at the same dose and administer G-CSF 2nd episode: administer ramucirumab at reduce dose 3rd episode: definitive discontinuation	Delay cycle until absolute neutrophil count >1500/mm^3. 1st episode administer next cycle at the same dose and administer G-CSF 2nd episode: administer tusamitamab ravtansine at reduce dose 3rd episode: definitive discontinuation	To ensure relative dose intensity, G-CSF is recommended as secondary prophylaxis in all patients with Grade 3 febrile neutropenia ASCO guideline is recommended for supportive treatment if there are no defined clinical standards (13).
	Grade 4 Life-threatening consequences	Administration changes to be decided at the Investigator's discretion per product label	Administration changes to be decided at the Investigator's discretion. 1st episode: administer next cycle at reduced dose and administer G-CSF 2nd episode: definitive discontinuation	
Hypertension	Grade 3 Severe hypertension	Withhold ramucirumab until controlled with medical management, and restart at same dose	Administer tusamitamab ravtansine the same day as ramucirumab	
	Grade 4 Severe hypertension that cannot be controlled with antihypertensive therapy	Definitively discontinue ramucirumab	Administer tusamitamab ravtansine as planned	

Event	Symptoms severity (Nadir) (NCI CTCAE v5)	Management of IMP dosing (ramucirumab)	Management of IMP dosing (tusamitamab ravtansine)	Supportive care guidelines
Proteinuria	First occurrence of increased urine protein levels greater than or equal to 2 g per 24 hours	Omit ramucirumab until urine protein level is <2 g per 24 hours; then resume ramucirumab at a reduced dose of 6 mg/kg	Administer tusamitamab ravtansine as planned	
	Reoccurrence of urine protein level greater than 2 g per 24 hours following initial dose reduction	Omit ramucirumab until protein level is <2 g per 24 hours; then resume ramucirumab at a reduced dose of 5 mg/kg)	Administer tusamitamab ravtansine as planned	
	Urine protein level greater than 3 g per 24 hours or in the setting of nephrotic syndrome	Definitvely discontinue ramucirumab	Consider benefit/risk for the patient to continue or delay tusamitamab ravtansine infusion	
Hemorrhage	Grade 3 or 4	Definitively discontinue ramucirumab	Definitive discontinuation of tusamitamab ravtansine	
Gastrointestinal Perforation	All Grades	Definitively discontinue ramucirumab	Consider benefit/risk for the patient to continue or delay tusamitamab ravtansine infusion	
Arterial Thromboembolic Events	All Grades	Definitively discontinue ramucirumab	Administer tusamitamab ravtansine as planned	
Wound Healing Complications	All Grades	Definitively discontinue ramucirumab for wound healing complications requiring medical intervention	Consider benefit/risk for the patient to continue or delay tusamitamab ravtansine infusion	

a Tusamitamab ravtansine is stable at least 7.5 hours in the infusion bag at room temperature. If necessary, a new infusion should be prepared with the remaining dose to be administered.

b The NCI CTCAE V5.0 grading is to be applied to keratopathy.

c Standard ocular examination per protocol includes visual acuity, slit lamp examination, Schirmer's test, and enquiring for ocular/visual symptoms.

d When possible at the site, photographs should be done when findings are first documented and to follow progression when relevant. Any additional relevant ocular examination can be done if indicated.

Abbreviations: ASCO = American Society of Clinical Oncology, ASOCT = Anterior segment optical coherence, BSA = Body surface area, ECG = Electrocardiogram, G-CSF = Granulocyte colony-stimulating factor, Hb = Hemoglobin, IMP = Investigational medicinal product, IV = Intravenous; LLN = Lower limit of normal, LVEF = Left ventricular ejection fraction, NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, RBC = Red blood cell.

10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

Serology for HBsAg, HCV, or HIV will be performed at screening only if required at the country level.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, and terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and prescreening/screening/enrollment/administration of study intervention may be temporarily delayed/halted.

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Contingencies implemented due to emergency will be documented.

10.9.1 Remote prescreening process

If there is no other way to conduct prescreening procedures during a regional or national emergency declared by a governmental agency (eg, due to a COVID-19 pandemic), the site may consider implementing a remote prescreening ICF process compliant with country/site requirements for only those participants who have sufficient archival samples.

The process should be compliant with accepted principals of patients' rights and global, national, and local regulatory requirements. Required protection of personal data (including security of e-mail interactions) and confidentiality of study data should be ensured.

If remote prescreening is planned to be implemented at site:

- The Investigator/delegate should contact each participant to inquire regarding the participant's willingness to participate in the prescreening process.
- If participant agrees to pre-screening, the Investigator/delegate should send the pre-screening ICF via e-mail to the participant's personal e-mail address (as allowed by local regulation) or by postal mail. The Investigator/delegate should provide an overview of the study (eg, tusamitamab ravtansine mechanism of action; design of the study in terms of treatment groups, visits, and pre-screening procedures; and rationale for assessment of CEACAM5 expression). The Investigator/delegate should respond to any question raised by a participant, and this correspondence should be documented in detail in the participant's source file.
- If a participant agrees to participate in the pre-screening phase, the participant should print out, sign, and date 2 copies of the ICF. A scan of a signed ICF should be sent via secured e-mail (if available), and 1 of the signed original ICFs to be filed in the Investigator Study File should be sent via postal mail.
- The Investigator/delegate should review each received signed ICF (or a printout of an electronically submitted, scanned copy), sign and date it, and archive it in the Investigator Study File. It is mandatory for the Investigator to ensure the collection of the original signed ICF sent by mail; the signed original should be attached to any previously filed signed printout of an electronically submitted signed ICF. After properly documenting this consent process, the site may proceed to prepare and send the slides for CEACAM5 assessment.

10.9.2 Screening procedures

The Investigator/site should assess the site's capacity to conduct study procedures throughout the study for each participant before starting any screening procedure. If the site cannot guarantee an accurate follow-up in the context of the trial, alternative treatment outside the clinical trial should be proposed. This assessment, per the Investigator's medical judgement and depending on the country/site status, should be communicated to the participant. The participant should satisfy all eligibility criteria before enrolling to the study; and no protocol waiver is acceptable. Remote signature of main study ICF is not acceptable in any circumstance.

10.9.3 Study intervention

During a regional or national emergency declared by a governmental agency, all contingency plans should be implemented to ensure compliance to study treatment, based on a case-by-case benefit-risk assessment. Administration (or, in case of temporary interruption, reinitiation) of the IMP can occur only once the Investigator has determined, according to his/her best judgement, that the contribution of the IMP(s) to the occurrence of the epidemic event (eg, COVID-19) was unlikely.

Any further safety measure (eg, interim laboratory assessment such as neutrophil count monitoring; regular contact with site staff) to follow the safety of patients during the regional or national emergency period can be considered.

10.9.4 Study procedures

All efforts should be made to ensure that measurements of key parameters for efficacy endpoints can be performed at the site. If the Investigator is unable to guarantee that the protocol-required efficacy assessments can be conducted, no participant should be screened until the site confirms its capacity to perform the assessments.

As part of a site's contingency plan, a back-up site should be identified in advance in the case that the site delegated to perform the radiological tumor assessment is prevented from performing the assessment by a regional or national emergency situation (eg, COVID-19 outbreak). The Investigator should ensure that the back-up site conducts the RECIST assessment in same manner as that used for baseline tumor assessments.

In the case that the primary tumor assessment site is incapacitated, ongoing patients would then be referred to the back-up site for tumor assessment. The Investigator/delegate should ensure the information on baseline assessment methods is shared with the back-up site's radiologist to ensure same method is followed for scans.

Depending on site status, if needed, Cycle 1 and Cycle 2 weekly safety laboratory assessment (hematology [hemoglobin, hematocrit, RBC, WBC with differential, and platelet counts] and liver function tests [AST, ALT, total and conjugated bilirubin, ALP]) can be arranged to be performed either at a laboratory certified to perform these tests that is close to the patient's home, or via sampling at the patient's home.

10.9.5 Informed consent process

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or legally authorized representative should be informed verbally prior to initiating any change that is to be implemented for the duration of the emergency (eg, study visit delays, use of back-up sites for safety laboratory or tumor assessment).

10.10 APPENDIX 10: DEFINITION OF WELL CONTROLLED HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Well controlled HIV infection is defined as meeting *all* of the following criteria:

- CD4+ T-cell count >350 cells/mm^3 at time of screening.
- Virologic suppression, defined as confirmed HIV RNA level <50 copies/mL or the lower limit of quantification (below the limit of detection) using a locally available assay, achieved and maintained for at least 12 weeks prior to screening.

- On a stable ART regimen, without changes in drugs or dose modification, for at least 4 weeks prior to study entry (Day 1).
- On a combination ART regimen containing no antiretroviral medication other than the following: abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, rilpivirine, and/or tenofovir.

10.11 APPENDIX 11: CYP450 SUBSTRATES WITH NARROW THERAPEUTIC INDICES

Table 11 - List of CYP substrates with narrow therapeutic range

***In vivo* CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A Narrow Therapeutic Range (NTR) Substrates**	
CYP enzyme	NTR Substrates[a]
CYP1A2	Theophylline, tizanidine
CYP2C8	Paclitaxel
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin
CYP2D6	Thioridazine
CYP3A	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, quinidine, sirolimus, tacrolimus, cisapride, astemizole, terfenadine, pimozide

a CYP Substrates with a Narrow Therapeutic Range - drugs with an exposure-response relationship that indicates that relatively small increases in their exposure levels by co-administered CYP inhibitors may lead to safety concerns

10.12 APPENDIX 12: STRONG CYP3A INHIBITORS

Table 12 - List of strong CYP3A inhibitors

CYP3A inhibitors	Precipitant Therapeutic Class	Victim (oral, unless otherwise specified)	AUC Ratio
Potent CYP3A Inhibitors (yielding substrate AUC ratio >5)			
VIEKIRA PAK	Antivirals	Tacrolimus	55.76
Telaprevir	Antivirals	Midazolam	13.5
Indinavir/RIT	Protease inhibitors	Alfentanil	36.50
Tipranavir/RIT	Protease inhibitors	Midazolam	26.91
Ritonavir	Protease inhibitors	Midazolam	26.41
Cobicistat (GS-9350)	none	Midazolam	19.03
Indinavir	Protease inhibitors	Vardenafil	9.67
Ketoconazole	Antifungals	Midazolam	17.08
Troleandomycin	Antibiotics	Midazolam	14.80
Saquinavir/RIT	Protease inhibitors	Midazolam	12.48
Itraconazole	Antifungals	Midazolam	10.80
Voriconazole	Antifungals	Midazolam	9.63
Mibefradil	Calcium Channel Blockers	Midazolam	8.86
Clarithromycin	Antibiotics	Midazolam	8.39
Danoprevir/RIT	Antivirals	Midazolam	13.42
Lopinavir/RIT	Protease inhibitors	Alfentanil	11.47
Elvitegravir/RIT	Treatments of AIDS	Midazolam	12.8
Posaconazole	Antifungals	Midazolam	6.23
Telithromycin	Antibiotics	Midazolam	6.2
Conivaptan	Diuretics	Midazolam	5.76
Nefazodone	Antidepressants	Midazolam	5.44
Nelfinavir	Protease inhibitors	Midazolam	5.29
Saquinavir	Protease inhibitors	Midazolam	5.18
Boceprevir	Antivirals	Midazolam	5.05
Idelalisib	Kinase inhibitors	Midazolam	5.15
LCL161	Cancer treatments	Midazolam	8.80
Mifepristone	Antiprogestins	Simvastatin	9.55
Ceritinib	Kinase Inhibitors	Midazolam	5.84
Ribociclib	Kinase Inhibitors	Midazolam	5.17
Josamycin	Antibiotics	Ivabradine	7.70
Tucatinib	Kinase Inhibitors	Midazolam	5.74

Abbreviations: AIDS = Acquired immune deficiency syndrome; AUC = Area under the curve; CYP = Cytochrome P450; RIT = Ritonavir.
List extracted from the Drug Interaction Database from the University of Washington, updated January 2021 (https://didb.druginteractionsolutions.org/resources/list-of-substrates-inhibitors-and-inducers/?Oid=1130) and from FDA, updated June 2020 (https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm).

10.13 APPENDIX 13: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1

Details provided in bibliographic reference (15).

10.13.1 Measurability of tumor at baseline

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows.

Measurable lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT-scan (CT-scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

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

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

10.13.2 Special considerations regarding lesion measurability

- **Bone lesions:**

1. Bone scan, positron emission tomography scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
2. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
3. Blastic bone lesions are non-measurable.

- **Cystic lesions**:

1. Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
2. "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

- **Lesions with prior local treatment:**

1. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Method of assessment

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

- **Clinical lesions:** Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.
- **Chest X-ray:** Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- **CT, MRI:** CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT-scan is based on the assumption that CT slice thickness is 5 mm or less. When CT-scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- **Ultrasound:** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.
- **Endoscopy, laparoscopy:** The utilization of these techniques for objective tumor evaluation is not advised.

- **Tumor markers:** Tumor markers alone cannot be used to assess objective tumor response.
- **Cytology, histology:** These techniques can be used to differentiate between PR and CR in rare cases if required by protocol.

Baseline documentation of "target" and "non-target" lesions

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT-scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should not be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent", or "unequivocal progression". In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response criteria

Response criteria are described in Table 13.

Table 13 - Response criteria

Response criteria	Evaluation of target lesions
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
SD	Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Special notes on the assessment of target lesions

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to <10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure": All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT-scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease: Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

The concept of progression of non-target disease requires additional explanation as follows:

When the participant also has measurable disease; in this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

When the participant has only non-measurable disease; to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the participant should be considered to have had overall PD at that point.

New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the participant's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT-scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the participant who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The participant's brain metastases are considered to be constitute PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

While fluorodeoxyglucose-positron emission tomography (FDG-PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT-scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up.

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT-scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of best overall response

Time point response: At each protocol-specified time point, a response assessment should occur. Table 14 provides a summary of the overall response status calculation at each time point for participants who have measurable disease at baseline.

Table 14 - Response in participants with target disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

When participants have non-measurable (therefore non-target) disease only, Table 15 is to be used.

Table 15 - Response in participants with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	Inevaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PD = progressive disease.

Missing assessments and inevaluable designation: When no imaging/measurement is done at all at a particular time point, the participant is not evaluable (NE) at that time point.

If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of "zero" on the CRF.

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a participant with time point responses of PR-NE-PR as a confirmed response.

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

The objective response status of such participants is to be determined by evaluation of target and non-target disease. For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Duration of response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

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

10.14 APPENDIX 14: ABBREVIATIONS AND DEFINITIONS

ADC:	antibody-drug conjugate
ADR:	adverse drug reaction
AESI:	adverse event of special interest
ALT:	alanine aminotransferase (SGPT)
ANC:	absolute neutrophil count
aPTT:	activated partial thromboplastin time
ART:	antiretroviral therapy
AST:	aspartate aminotransferase (SGOT)
ATA:	antitherapeutic antibody
ATE:	arterial thromboembolic event
BOR:	best overall response
BSA:	body surface area
BSC:	best supportive care
CEACAM5:	carcinoembryonic antigen cell adhesion molecule 5
CI:	confidence interval
CR:	complete response
CSICF:	Core Study Informed Consent Form
CT:	computed tomography
CTCAE:	Common Terminology Criteria for Adverse Events
DCR:	disease control rate
DL:	dose level
DLT:	dose limiting toxicity
DOR:	duration of response

ECOG:	Eastern Cooperative Oncology Group
eGFR:	estimated glomerular filtration rate
FDA:	United States Food and Drug Administration
FDG-PET:	fluorodeoxyglucose-positron emission tomography
FFPE:	formalin-fixed, paraffin embedded
FIH:	first-in-human
GC:	gastric cancer
GEJ:	gastroesophageal junction
HBsAg:	hepatitis B virus surface antigen
HCV:	hepatitis C virus
HIV:	human immunodeficiency virus
HR:	hazard ratio
HRT:	hormone replacement therapy
ICF:	informed consent form
IEC:	independent ethics committee
IHC:	immunohistochemistry
IMP:	investigational medicinal product
INR:	International Normalized Ratio
IRB:	institutional review boards
IRR:	infusion-related reaction
IRT:	interactive response technology
IV:	intravenous
MRI:	magnetic resonance imaging
MTD:	maximum tolerated dose
NCI:	National Cancer Institute
NE:	not evaluable
NSQ NSCLC:	nonsquamous, non-small-cell lung cancer
NTR:	narrow therapeutic range
ORR:	objective response rate
PCSA:	potentially clinically significant abnormalities
PD:	progressive disease
PDX:	patient-derived xenograft
PFS:	progression-free survival
PK:	pharmacokinetic
PR:	partial response
PT:	prothrombin time
PTT:	partial thromboplastin time
Q2W:	every 2 weeks
RD:	Recommended Dose
RECIST:	Response Evaluation Criteria in Solid Tumors
SAE:	serious adverse event
SD:	stable disease
SUSAR:	suspected unexpected serious adverse reaction
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
VEGF:	vascular endothelial growth factor

VEGFR2: vascular endothelial growth factor 2
WOCBP: woman of childbearing potential

10.15 APPENDIX 15: PROTOCOL AMENDMENT HISTORY

Not applicable.

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