NCT Number: NCT05245071

CLINICAL TRIAL PROTOCOL

Protocol title:	**Open-label, Phase 2 study, evaluating the efficacy and safety of tusamitamab ravtansine in non-squamous non-small-cell lung cancer (NSQ NSCLC) participants with negative or moderate CEACAM5 expression tumors and high circulating CEA**
Protocol number:	**ACT17241**
Amendment number:	**Not Applicable**
Compound number (INN/Trademark):	**SAR408701** **tusamitamab ravtansine/NA**
Brief title:	**Tusamitamab ravtansine in NSQ NSCLC participants with negative or moderate CEACAM5 expression tumors and high circulating CEA**
Acronym:	**CARMEN-LC06**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi Aventis Recherche & Développement**
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TABLE OF CONTENTS

CLINICAL TRIAL PROTOCOL **1**

TABLE OF CONTENTS **2**

LIST OF TABLES **7**

LIST OF FIGURES **7**

1 PROTOCOL SUMMARY **8**

1.1 SYNOPSIS 8

1.2 SCHEMA 15

1.3 SCHEDULE OF ACTIVITIES (SOA) 16

1.3.1 Study flow chart 16

1.3.2 PK/ATA flow chart 24

2 INTRODUCTION **25**

2.1 STUDY RATIONALE 25

2.2 BACKGROUND 26

2.3 BENEFIT/RISK ASSESSMENT 27

2.3.1 Risk assessment 27

2.3.2 Benefit assessment 32

2.3.3 Overall benefit/risk conclusion 32

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS **33**

3.1 APPROPRIATENESS OF MEASUREMENTS 35

4 STUDY DESIGN **36**

4.1 OVERALL DESIGN 36

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN 37

4.3 JUSTIFICATION FOR DOSE 37

4.4 END OF STUDY DEFINITION 37

5 STUDY POPULATION **38**

5.1 INCLUSION CRITERIA 38
5.2 EXCLUSION CRITERIA 40
5.3 LIFESTYLE CONSIDERATIONS 42
5.4 SCREEN FAILURES 42
5.5 CRITERIA FOR TEMPORARILY DELAYING 43
6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY 44
6.1 STUDY INTERVENTION(S) ADMINISTERED 44
6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY 46
6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING 46
6.4 STUDY INTERVENTION COMPLIANCE 47
6.5 DOSE MODIFICATION 47
6.5.1 Retreatment criteria 48
6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY 48
6.7 TREATMENT OF OVERDOSE 48
6.8 CONCOMITANT THERAPY 49
6.8.1 Rescue medicine 50
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 51
7.1 DISCONTINUATION OF STUDY INTERVENTION 51
7.1.1 Permanent discontinuation 51
7.1.2 Temporary discontinuation 52
7.1.3 Rechallenge 52
7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY 52
7.3 LOST TO FOLLOW UP 53
8 STUDY ASSESSMENTS AND PROCEDURES 54
8.1 EFFICACY ASSESSMENTS 54
8.2 SAFETY ASSESSMENTS 55
8.2.1 Physical examinations 55
8.2.2 Specific ocular tests 55
8.2.3 Vital signs 56

8.2.4 Electrocardiograms 56
8.2.5 Clinical safety laboratory tests 56
8.2.6 Guidelines for management of adverse events 57
8.2.6.1 Hypersensitivity reactions 57
8.2.6.2 Ocular toxicity 57
8.2.6.3 Keratopathy/keratitis management 58
8.2.6.4 Management of anemia 59
8.2.6.5 Management of neutropenia 59
8.2.6.6 Liver function tests 59
8.2.6.7 Peripheral neuropathy 59
8.2.6.8 Colitis (including hemorrhagic) 60
8.2.7 Pregnancy testing 60
8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING 60
8.3.1 Time period and frequency for collecting AE and SAE information 61
8.3.2 Method of detecting AEs and SAEs 61
8.3.3 Follow-up of AEs and SAEs 61
8.3.4 Regulatory reporting requirements for SAEs 61
8.3.5 Pregnancy 62
8.3.6 Cardiovascular and death events 62
8.3.7 Adverse events of special interest 62
8.3.8 Guidelines for reporting product complaints 63
8.4 PHARMACOKINETICS 63
8.5 GENETICS 64
8.5.1 Circulating tumor DNA analysis 64
8.5.2 Tumor DNA and RNA analyses 64
8.6 BIOMARKERS 65
8.7 IMMUNOGENICITY ASSESSMENTS 65
8.8 HEALTH ECONOMICS 66
8.9 PATIENT-REPORTED OUTCOMES 66
8.9.1 NSCLC-SAQ 66
8.9.2 PGIS-LCS and PGIC-LCS 67
8.9.3 FACT-GP5 67
8.10 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH 67
9 STATISTICAL CONSIDERATIONS 69

9.1 POPULATIONS FOR ANALYSES 69
9.2 STATISTICAL ANALYSES 70
9.2.1 General considerations 70
9.2.2 Primary endpoint analyses 71
9.2.3 Secondary endpoints analyses 71
9.2.3.1 Progression-free survival 72
9.2.3.2 Disease control rate 73
9.2.3.3 Duration of response 73
9.2.4 Tertiary/exploratory endpoint(s) analyses 74
9.2.5 Safety analyses 74
9.2.5.1 Adverse events 74
9.2.5.2 Laboratory variables, vital signs and electrocardiograms (ECGs) 75
9.2.6 Other analyses 76
9.3 INTERIM ANALYSES 76
9.4 SAMPLE SIZE DETERMINATION 77
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 78
10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS 78
10.1.1 Regulatory and ethical considerations 78
10.1.2 Financial disclosure 79
10.1.3 Informed consent process 79
10.1.4 Data protection 80
10.1.5 Committees structure 82
10.1.6 Dissemination of clinical study data 82
10.1.7 Data quality assurance 83
10.1.8 Source documents 84
10.1.9 Study and site start and closure 84
10.1.10 Publication policy 85
10.2 APPENDIX 2: CLINICAL LABORATORY TESTS 85
10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING 87
10.3.1 Definition of AE 87
10.3.2 Definition of SAE 89
10.3.3 Recording and follow-up of AE and/or SAE 90
10.3.4 Reporting of SAEs 92
10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE 93

10.4.1 Definitions 93
10.4.2 Contraception guidance 93
10.5 APPENDIX 5: GENETICS 94
10.6 APPENDIX 6: RECOMMENDED SUPPORTIVE CARE AND/OR DOSE MODIFICATION GUIDELINES FOR DRUG-RELATED ADVERSE EVENTS 95
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 98
10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS 98
10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY 98
10.9.1 Remote pre-screening process 99
10.9.2 Screening procedures 100
10.9.3 Study intervention 100
10.9.4 Study procedures 100
10.9.5 Statistical analyses and deviation 101
10.9.6 Informed consent process 101
10.10 APPENDIX 10: DEFINITION OF WELL CONTROLLED HUMAN IMMUNODEFICIENCY VIRUS INFECTION 101
10.11 APPENDIX 11: CYP SUBSTRATES WITH NARROW THERAPEUTIC RANGE AND STRONG CYP3A INHIBITORS 102
10.12 APPENDIX 12: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1 104
10.12.1 Measurability of tumor at baseline 104
10.12.2 Special considerations regarding lesion measurability 104
10.13 APPENDIX 13: ABBREVIATIONS 111
10.14 APPENDIX 14: PROTOCOL AMENDMENT HISTORY 113
11 REFERENCES 114

LIST OF TABLES

Table 1 - Risk assessment 28
Table 2 - Objectives and endpoints 33
Table 3 - Summary of primary estimands for main endpoints 34
Table 4 - Study intervention(s) administered 44
Table 5 - Study arm(s) 45
Table 6 - Individual tusamitamab ravtansine dose reduction 48
Table 7 - Population for analyses 69
Table 8 - [redacted] 77
Table 9 - Protocol-required laboratory tests 86
Table 10 - Recommended Dose Modification or Discontinuation for SAR40870 95
Table 11 - List of CYP substrates with narrow therapeutic range 102
Table 12 - List of strong CYP3A inhibitors 102
Table 13 - Response criteria 107
Table 14 - Response in participants with target disease 109
Table 15 - Response in participants with non-target disease only 110

LIST OF FIGURES

Figure 1 - Graphical study design 15

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

Open-label, Phase 2 study, evaluating the efficacy and safety of tusamitamab ravtansine in non-squamous non-small-cell lung cancer (NSQ NSCLC) participants with negative or moderate CEACAM5 expression tumors and high circulating CEAOpen-label, Phase 2 study, evaluating the efficacy and safety of tusamitamab ravtansine in non-squamous non-small-cell lung cancer (NSQ NSCLC) participants with negative or moderate CEACAM5 expression tumors and high circulating CEA

Brief title:

Tusamitamab ravtansine in NSQ NSCLC participants with negative or moderate CEACAM5 expression tumors and high circulating CEA

Rationale:

Tusamitamab ravtansine is an antibody (anti-CEACAM5) conjugate to the cytotoxic maytansinoid agent DM4. In the first in human (FIH) TED13751 study, a cohort of 64 participants with heavily pretreated non-squamous non-small-cell-lung-cancer (NSQ NSCLC) with high carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) expression using immunohistochemistry (IHC) method applied at pre-screening on archived tumor sample (defined as ≥2+ in intensity in at least 50% of the tumor cells) have been treated with tusamitamab ravtansine at 100 mg/m² every 2 weeks (Q2W). Tusamitamab ravtansine has shown encouraging anti-tumor activity which was associated with an overall response rate of 20.3% (13 participants who had partial response [PR]) per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (95% CI: 12.27%–31.71%), warranting further development of tusamitamab ravtansine to treat this patient population.

CEACAM5 is one of the 7 members of the carcinoembryonic antigen (CEA) family and circulating CEA is the shed form of membranous proteins.

In this cohort of NSQ NSCLC participants with high CEACAM5 expression on tumor (≥2+ in intensity in ≥50% of tumor cells), 10 out of the 13 responding participants had high baseline circulating CEA (≥100 ng/mL). Potential responses to tusamitamab ravtansine have also been evaluated in a cohort of NSQ NSCLC participants with moderate CEACAM5 expression on tumor (≥2+ in intensity in ≥1% and <50% of tumor cells) but only a limited number of participants (7 out of 28 participants) presented high circulating CEA levels at baseline.

No anti-tumor activity response data are available from the negative CEACAM5 expression on tumor by IHC (intensity 1+ whatever the percentage of stained tumor cells or <1% of tumor cells) with high circulating CEA level (≥100 ng/mL) cohort.

The CEACAM5 expression status may differ between the initial tumor at diagnosis and the tumor at the time of the enrollment in the clinical trial.

Even though a correlation is expected between circulating CEA and CEACAM5 expression status on tumor, there are no available data on concomitant CEACAM5 expression on fresh tumor biopsy and circulating CEA.

The aim of this study is to evaluate, if participants with high circulating CEA level at baseline could benefit from tusamitamab ravtansine treatment despite negative or moderate CEACAM5 expression on archival biopsy, assuming that a high circulating CEA level reflects a high CEACAM5 expression on tumor at the time of the enrollment. To this end, the anti-tumor activity will be assessed in participants with NSQ NSCLC with high circulating CEA levels despite negative or moderate CEACAM5 expression on tumor by IHC testing on archived biopsy in third- or fourth-line treatment.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To assess the anti-tumor activity of tusamitamab ravtansine when given every 2 weeks (Q2W) in non-squamous non-small-cell-lung-cancer (NSQ NSCLC) participants with negative or moderate CEACAM5 expression tumors and high circulating carcinoembryonic antigen (CEA) levels	• Objective Response Rate (ORR) of tusamitamab ravtansine, defined as the proportion of participants who have a confirmed complete response (CR) or partial response (PR) as best overall response (BOR) per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1
Secondary	
• To assess the safety and tolerability of tusamitamab ravtansine	• Incidence of participants with 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 other efficacy parameters of tusamitamab ravtansine	• Progression-free survival (PFS), defined as the time from the date of first tusamitamab ravtansine administration to the date of the first documented disease progression or death due to any cause, whichever comes first. • Disease control rate (DCR), defined as the percentage of participants who have achieved confirmed CR or PR, or stable disease as BOR per RECIST v1.1 • Duration of response (DOR), defined as the time from first documented evidence of CR or PR until progressive disease (PD) determined per RECIST v1.1 or death from any cause, whichever occurs first
• To evaluate the immunogenicity of tusamitamab ravtansine	• Incidence of participants with anti-therapeutic antibodies (ATAs) against tusamitamab ravtansine
• To document the pharmacokinetics (PK) of tusamitamab ravtansine	• Tusamitamab ravtansine concentrations

Overall design:

This is a Phase 2, open-label, multi-center study assessing efficacy (anti-tumor activity), safety, and pharmacokinetic (PK) of tusamitamab ravtansine single agent in NSQ NSCLC participants with negative or moderate CEACAM5 expression tumors and high circulating CEA (≥100 ng/mL) at screening.

Moderate CEACAM5 expression is defined as intensity ≥2+ in ≥1% and <50% of tumor cells.

Negative CEACAM5 expression is defined as intensity 1+ whatever the percentage of stained tumor cells or <1% of tumor cells.

During the pre-screening phase, participants who were pre-screen failed in EFC15858 Phase 3 trial with available CEACAM5 status (central assessment by IHC) as negative or moderate expression on archival tumor tissue can be pre-screened. Participants with high circulating CEA (≥100 ng/mL) will be screened and will go through protocol screening procedures.

After being screened, the eligible participants will receive tusamitamab ravtansine as single agent treatment at the dose of 100 mg/m² Q2W.

Brief summary:

This is an open label single group, Phase 2, one-arm study for treatment to evaluate efficacy, safety, and PK of tusamitamab ravtansine in NSQ NSCLC participants with negative or moderate CEACAM5 expression tumors and high circulating CEA.

Participants who will be enrolled, will receive tusamitamab ravtansine as monotherapy at 100 mg/m^2 Q2W until disease progression, unacceptable adverse event (AE), initiation of a new anticancer therapy, or the participant's or Investigator's decision to stop the treatment, whichever comes first. A total of approximately 38 participants are planned to be treated. An interim analysis is planned after 20 participants treated are evaluable for anti-tumor activity. If at least 2 confirmed objective responses are reported, the recruitment will continue to achieve a total of 38 evaluable treated participants.

Number of participants:

Approximately 285 participants will be pre-screened to achieve approximately 38 treated participants, based on an estimated pre-screening failure rate of 84% and an estimated study screening failure rate of 15%.

Intervention groups and duration:

- Pre-screening period: a pre-screening informed consent will be signed in order to collect available CEACAM5 expression results on archival tumor tissue from EFC15858 study and the circulating CEA value.

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 AE, initiation of a new anticancer therapy, or the participant's or Investigator's decision to stop the treatment, whichever comes first. 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 anticancer therapy, whichever is earlier, for end-of-treatment (EOT) assessments.
- Follow-up period: a safety follow-up visit will be performed approximately 90 days after the last dose of IMP
  - Participants who discontinue the study treatment due to documented progressive disease (PD), do not need further follow-up visit, if any ongoing related AE/ adverse events of special interest (AESI)/serious adverse event (SAE) is resolved or stabilized. Otherwise follow-up visits will be performed every 12 weeks,
  - Participants who stop treatment before documented PD should undergo a tumor assessment and a follow-up visit every 12 weeks (±7 days) after the last tumor assessment until radiological disease progression, start of a new anticancer therapy, study cut-off date for secondary endpoints, or withdrawal of participant's consent, whichever comes first. After documented PD or a start of new anticancer therapy, the participant will be followed until any ongoing IMP related AE/AESI/SAE is resolved or stabilized.

The study cut-off date for the interim analysis corresponds to the date when the first 20 evaluable treated participants have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study treatment for any reason. For participants with 2 postbaseline tumor assessments and occurrence of response at the second postbaseline tumor assessment, the confirmatory assessment will also be included.

The study cut-off for analysis of the primary endpoint, objective response rate (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 treatment for any reason. For participants with 2 postbaseline tumor assessments and occurrence of response at the second postbaseline tumor assessment, the confirmatory assessment will also be included. This study cut-off can be up to approximately 20 weeks (16 weeks for 2 tumor assessments and 4 weeks for confirmation of response, if needed) after the last participant's first IMP administration. Of note, disease control rate (DCR) will be also assessed at this cut-off.

The final study cut-off for analysis of the secondary efficacy endpoints, which include duration of response (DOR) and progression-free survival (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.

Study intervention(s)

Investigational medicinal product(s)

- 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 vials.
- Route(s) of administration: Intravenous infusion (IV).
- Dose regimen: tusamitamab ravtansine will be administered on Day 1 as 100 mg/m^2 given via IV infusion and repeated Q2W. The duration of 1 cycle will be 14 days (1 administration of tusamitamab ravtansine per cycle). For participants with a body surface area (BSA) >2.20 m², the dose will be calculated based on a BSA of 2.20 m².

Noninvestigational medicinal products (NIMP)

Premedication with histamine H1 antagonist (diphenhydramine 50 mg or equivalent [eg, dexchlorpheniramine] given approximately 15 minutes [IV] to 1 hour [oral] before tusamitamab ravtansine administration) is required for all participants before administration of tusamitamab ravtansine. After first study intervention of SAR408701, patients should be observed for acute reactions at site up to 4 hours depending on any sign of drug-induced allergic reaction. Detailed instructions for dilution and administration of the IMP are provided in Pharmacy Manual. If a participant has experienced an infusion reaction in a previous tusamitamab ravtansine administration, premedication will also include dexamethasone 10 mg IV for future infusions. If the case participant does not experience any hypersensitivity reactions after 4 cycles, the premedication can be discontinued at the discretion of the Investigator.

Posttrial access to study medication: Not applicable.

Duration of study intervention

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 40 weeks (up to 4 weeks for screening, a median of 24 weeks for treatment, and a median of 12 weeks for end of treatment assessments and the safety follow-up visit.

Statistical considerations:

- **Sample size calculations:**
  - Assuming a pre-screening failure rate of 84% and a study screening failure rate of 15%, approximately 285 participants will be pre-screened to achieve approximately 38 treated participants in the study. The initial plan is to treat a total of 38 participants evaluable for anti-tumor activity (at least 1 postbaseline tumor assessment, early clinical progression, or death due to disease progression).
- **Main analysis population:**
  - **All-treated population:** All enrolled participants exposed to the study treatment, regardless of the amount of treatment administered. All safety analyses will be

performed on this population, which is also the primary population for analysis of all efficacy parameters.

- **Activity population:** 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 analysis of efficacy parameters.
- **Pharmacokinetic population:** All participants from the all-treated population with at least 1 postbaseline PK concentration with adequate documentation of dosing and sampling dates and times.
- **Anti-therapeutic antibodies (ATA) population:** All participants from the all-treated population with at least 1 postbaseline ATA result (negative, positive, or inconclusive).

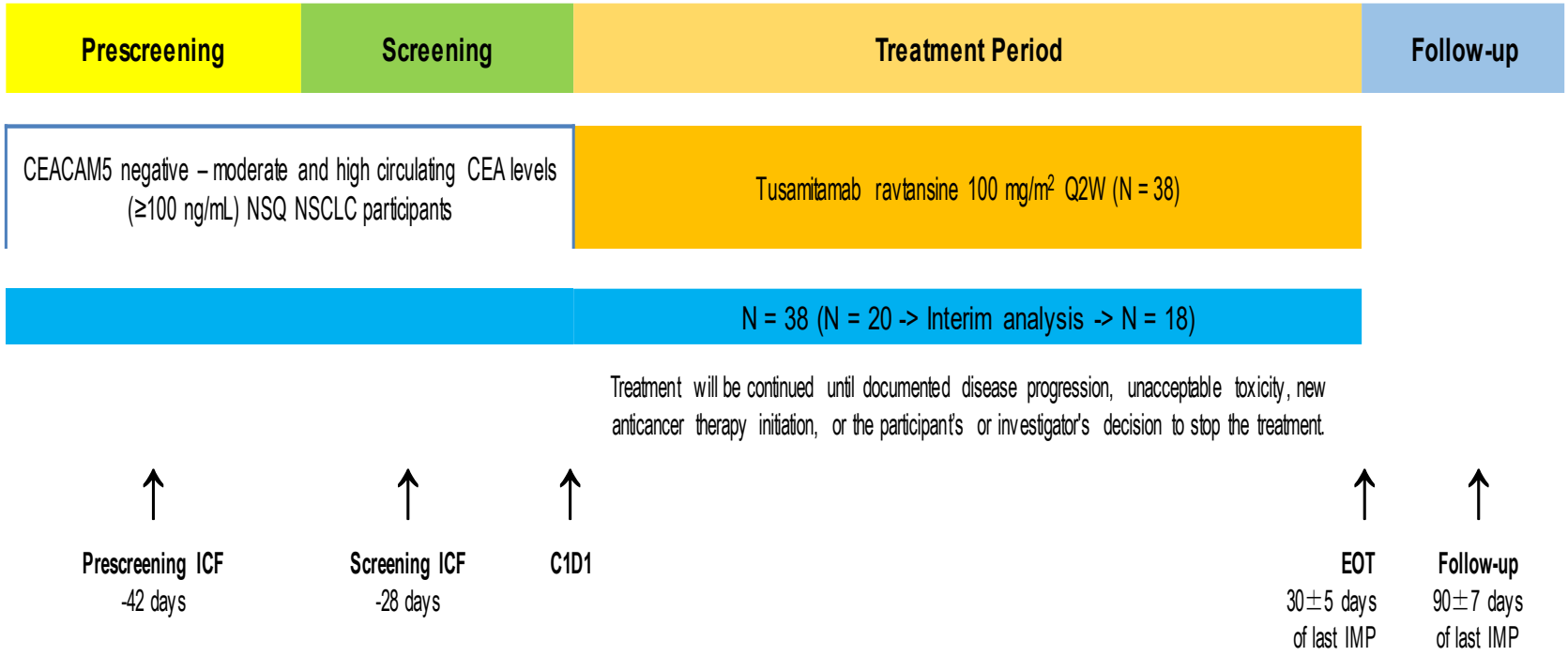
- **Analysis of primary endpoint:**
  - Objective response rate (ORR) will be summarized for the all-treated population using descriptive statistics and 95% exact CI will be provided using the Clopper-Pearson method. As a supplementary analysis, ORR will also be summarized on the activity population.
- **Analysis of secondary efficacy endpoints:**
  - Duration of response (DOR) will be summarized for the subgroup of participants who achieved confirmed objective response for the all-treated population with descriptive statistics using Kaplan-Meier methods. The median DOR and associated 95% CI will be provided,
  - Progression-free survival (PFS) will be summarized for the all-treated population using Kaplan-Meier methods. The median PFS and associated 95% CI will be provided, along with probabilities of being progression-free at different time points,
  - Disease control rate (DCR) will be summarized for the all-treated population using descriptive statistics and 95% CI 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 treatment-emergent adverse events (TEAEs) by primary system organ class (SOC) and preferred term (PT) will be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) V5.0 Grade (all grades, and Grade ≥3) for the all-treated population. Similar summaries will be prepared for TEAEs related to IMP, TEAEs leading to permanent study intervention discontinuation, TEAEs leading to dose modification or dose interruption, serious TEAEs, TEAEs with fatal outcome, AESIs, and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with any Grade 5 AE (TEAE and post-treatment) 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: No

1.2 SCHEMA

Figure 1 - Graphical study design



Moderate CEACAM5 expression is defined as intensity ≥2+ in ≥1% and <50% of tumor cells. Negative CEACAM5 expression is defined as intensity 1+ whatever the percentage of stained tumor cells or <1% of tumor cells

Abbreviations: C =cycle; CEA = carcinoembryonic antigen; CEACAM5 = carcinoembryonic antigen-related cell adhesion 5, D = Day, EOT = end-of-the-treatment, ICF = informed consent form, IMP = investigational medicinal product, N = number of participants, NSQ NSCLC = non-squamous non-small-cell lung cancer, Q2W = every 2 weeks.

1.3 SCHEDULE OF ACTIVITIES (SOA)

1.3.1 Study flow chart

Procedure	Pre-screening[a]	Screening[b]	Treatment Cycle 1		Subsequent Cycles (14 ±2 days from previous infusion)		End of treatment	Follow-up[d]	Notes
Day(D)	**Days prior to initial infusion**	**Days prior to initial infusion**	**D1 Pre-infusion**	**D8**	**D1 Pre-infusion[c] (±2 days)**	**Every 8 weeks (±7 days)**	**D30 after last infusion (±5 days)**	**D90 after last infusion (±7 days)**	
Available CEACAM5 expression status (archival tumor tissue) after pre-screening informed consent[a]	≤42								Available CEACAM5 expression results from EFC15858 Study assessed by central IHC will be used after pre-screening informed consent will be signed.
Informed consent		X							
Circulating CEA[e]	≤42	≤7				X	X	X	At pre-screening, after pre-screening informed consent signed. Then after informed consent signed. On infusion days, to be performed before infusion or the day before

Procedure	Pre-screening[a]	Screening[b]	Treatment Cycle 1		Subsequent Cycles (14 ±2 days from previous infusion)		End of treatment	Follow-up[d]	Notes
Day(D)	**Days prior to initial infusion**	**Days prior to initial infusion**	**D1 Pre-infusion**	**D8**	**D1 Pre-infusion[c] (±2 days)**	**Every 8 weeks (±7 days)**	**D30 after last infusion (±5 days)**	**D90 after last infusion (±7 days)**	
CEACAM5 expression status and RNA/DNA analysis on fresh tumor tissue[f]		≤28							After informed consent signed. Fresh biopsy at screening is optional.
IgG			X						Will be collected at C1D1 pre-infusion only.
Plasma for Circulating CEACAM5[g]		≤7				X			
Plasma for tumor cfDNA and whole blood for germline DNA			X						
IRT contact	X	X	X		X		X	X	
Inclusion and exclusion criteria		≤28	X						
Demography		≤28							
Medical/surgical/disease history[h]	X[i]	≤28							

Procedure	Pre-screening[a]	Screening[b]	Treatment Cycle 1		Subsequent Cycles (14 ±2 days from previous infusion)		End of treatment	Follow-up[d]	Notes
Day(D)	**Days prior to initial infusion**	**Days prior to initial infusion**	**D1 Pre-infusion**	**D8**	**D1 Pre-infusion[c] (±2 days)**	**Every 8 weeks (±7 days)**	**D30 after last infusion (±5 days)**	**D90 after last infusion (±7 days)**	
Physical examination, ECOG performance status		≤7	X		X		X	X	Examination of major body systems including cardiovascular, central nervous system, respiratory system, gastrointestinal system, hepatomegaly, splenomegaly, lymphadenopathy.
Height		≤7							
Weight		≤7	X		X		X		On Day 1 of each treatment cycle
Vital signs		≤7	X		X		X		Temperature, blood pressure, and pulse rate
Serum or urine pregnancy test (WOCBP only)[j]		≤7			Every 4 weeks		X		Mandatory serum test at screening and EOT. Serum or urine test every 4 weeks during study treatment period.
HBV & HCV serology; HIV test (only required at country level)		X							

Procedure	Pre-screening[a]	Screening[b]	Treatment Cycle 1		Subsequent Cycles (14 ±2 days from previous infusion)		End of treatment	Follow-up[d]	Notes
Day(D)	**Days prior to initial infusion**	**Days prior to initial infusion**	**D1 Pre-infusion**	**D8**	**D1 Pre-infusion[c] (±2 days)**	**Every 8 weeks (±7 days)**	**D30 after last infusion (±5 days)**	**D90 after last infusion (±7 days)**	
Laboratory assessments[k]		≤7	X[l]	X	X		X		During first 2 cycles, hematology and liver function tests will be assessed weekly.
12-lead ECG		≤7	X		X		X		
Specific ocular test		≤28					X		Performed by the ophthalmologist include visual acuity, slit-lamp under dilatation, and Schirmer's test at screening, EOT and whenever clinically indicated
Assessment of ocular/visual symptoms[m]		≤28	X		X		X		

Procedure	Pre-screening[a]	Screening[b]	Treatment Cycle 1		Subsequent Cycles (14 ±2 days from previous infusion)		End of treatment	Follow-up[d]	Notes
Day(D)	**Days prior to initial infusion**	**Days prior to initial infusion**	**D1 Pre-infusion**	**D8**	**D1 Pre-infusion[c] (±2 days)**	**Every 8 weeks (±7 days)**	**D30 after last infusion (±5 days)**	**D90 after last infusion (±7 days)**	
Study intervention			X		X				Participants should receive study intervention until documented disease progression, unacceptable toxicity, new anti-cancer therapy initiation, or the participant's or Investigator's decision to stop the treatment, whichever comes first.
AE assessment		X[n]	←==========						
Concomitant medication review		X	←==========						

Procedure	Pre-screening[a]	Screening[b]	Treatment Cycle 1		Subsequent Cycles (14 ±2 days from previous infusion)		End of treatment	Follow-up[d]	Notes
Day(D)	**Days prior to initial infusion**	**Days prior to initial infusion**	**D1 Pre-infusion**	**D8**	**D1 Pre-infusion[c] (±2 days)**	**Every 8 weeks (±7 days)**	**D30 after last infusion (±5 days)**	**D90 after last infusion (±7 days)**	
Tumor assessment - RECIST v1.1 - CT/MRI[o]		≤28				X	X	X	Imaging assessments are to be scheduled using the C1D1 date as the reference for all time points and are not to be scheduled based on the date of the previous imaging time point. Please refer to Section 8.1 for further information.
Tusamitamab ravtansine PK			Refer to PK/ATA flowchart Section 1.3.2						Section 8.4
Tusamitamab ravtansine Immunogenicity (ATA)			Refer to PK/ATA flowchart Section 1.3.2				X		Section 8.7
NSCLC-SAQ, PGIS- LCS, FACT-GP5[p]			X	X	X		X	X	**Baseline**: Data collected on device at site pre-infusion on C1D1. **Post-baseline**: Data collected on device at site on C1D8 and on D1 pre-infusion of subsequent cycles during treatment; at EOT; and at the first follow-up visit.

Procedure	Pre-screening[a]	Screening[b]	Treatment Cycle 1		Subsequent Cycles (14 ±2 days from previous infusion)		End of treatment	Follow-up[d]	Notes
Day(D)	**Days prior to initial infusion**	**Days prior to initial infusion**	**D1 Pre-infusion**	**D8**	**D1 Pre-infusion[c] (±2 days)**	**Every 8 weeks (±7 days)**	**D30 after last infusion (±5 days)**	**D90 after last infusion (±7 days)**	
PGIC-LCS[p]				X	X		X	X	**Post-baseline**: Data collected on device at site pre-infusion (if applicable) on C1D8 and on D1 of subsequent cycles during treatment; at EOT; and at the first follow-up visit.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; ANC = absolute neutrophil count; ALP = alkaline phosphatase; AST = aspartate aminotransferase; ATA = anti-therapeutic antibody; BUN = blood urea nitrogen; C = cycle; CEA = carcinoembryonic antigen; CEACAM5 = carcinoembryonic antigen-related cell adhesion molecule 5; cfDNA = circulating free DNA; CT = computed tomography; D = Day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate ; EOT = end-of-treatment; FACT-GP5 = Functional Assessment of Cancer Therapy Item GP-5; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IgG = immunoglobulin G; IHC = immunohistochemistry; IMP = investigational medicinal product; IRT = interactive response technology; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NSCLC-SAQ = Non-Small-Cell Lung Cancer Symptom Assessment Questionnaire; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetics; PRO = patient reported outcomes; RBC = red blood cells; RECIST = response evaluation criteria in solid tumors; RNA = ribonucleic acid; SAE = serious adverse event; WBC = white blood cell; WES = whole exome sequencing; WOCBP = woman of childbearing potential.

a Pre-screening Informed Consent will be signed by the participant for the use of CEACAM5 assay results on archival tumor tissue (central assessment by IHC) obtained in study EFC15858 and who had negative or moderate expression status. Participants who were pre-screened in study EFC15858 using a fresh biopsy cannot be pre-screened in Study ACT17241 unless the fresh specimen is older than 6 months at the time of pre-screening. Circulating CEA will be assessed at the pre-screening visit no more than 42 days prior to initiation of therapy.

b Informed consent should be signed before any study specific procedures. Only participants with high circulating CEA (≥100 ng/mL) at pre-screening will be screened and will go through protocol screening procedures. Informed consent can be signed more than 28 days prior to initiation of therapy. Screening time indicates in which timeframe exams used to support eligibility have to be done prior to initiation of therapy. Routine baseline tests performed prior to ICF signature do not need to be repeated as long as they are within the screening-defined timeframe. Assessments must be performed prior to first IMP administration. Baseline evaluation should be completed within 1 week prior to initiation of therapy, except for tumor assessment, assessment of ocular/visual symptoms, and specific ocular tests that may be performed within 4 weeks prior to the first IMP administration. Results of these tests should be reviewed by the Investigator prior to initiation of therapy.

c D1 of each subsequent cycle corresponds to D15 of the previous cycle (±2 days). Procedures can be done on the day of infusion (before infusion) or the day before.

d All participants should attend an on-site follow-up visit 90 days (±7 days) after the last IMP administration. SAEs/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 (stabilization is defined as an event ongoing without any change for at least 3 months). If ongoing IMP-related AEs/SAEs/AESIs are resolved or stabilized, no further safety follow-up visit is needed. If IMP related AEs/SAEs/AESIs ongoing, an on-site follow up visit will be performed every 12 weeks (±7 days). Participants who stopped treatment before documented progressive disease should undergo a tumor assessment and an on-site follow-up visit every 12 weeks (±7 days) until radiological disease progression, the start of new anti-cancer therapy, withdrawal of participant's consent, or cut-off date for secondary efficacy endpoints, whichever comes first. After documented progressive disease or the start of a new anti-cancer therapy, participants will be followed until any ongoing IMP related AEs/SAEs/AESIs are resolved or stabilized. Further anticancer treatment will be collected, including date of progression if any.

e Circulating CEA: As per local laboratory, at pre-screening (no more than 42 days prior to initiation of therapy); at screening (within 7 days prior to initiation of therapy), then during treatment every 8 weeks, at EOT and at the follow-up visit. At screening and first tumor assessment, an additional sample for circulating CEA is requested for central assessment.

f A fresh tumor biopsy at screening (optional) could be proposed for CEACAM5 expression assessment by IHC (retrospective, results not needed for screening and IMP treatment), WES and RNA sequencing.: Block (preferred option) or 5 slides at 5 µm thickness for IHC and 3 slides at 10 µm thickness (or equivalent quantity) for DNA/RNA evaluation are requested.

g Plasma for Circulating CEACAM5 (central assessment) at screening within 7 days prior to initiation of therapy (the same day and time as sample for local circulating CEA assessment) and at first tumor assessment (the same day and time as sample for local circulating CEA assessment).

h Includes histologic types, stage at diagnosis, disease extent at study entry.

i Smoking history, tumor mutation status and PD-L1 expression.

j Women of childbearing potential (WOCBP) must have a negative serum pregnancy test result within 7 days prior to the initial dose of IMP.

k See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed. If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC ≥0.5 x 10^9/L). In case of Grade ≥3 liver function abnormal tests, additional tests will be repeated every 2-3 days until recovery to baseline value. During first 2 cycles, hematology, and liver function tests will be assessed weekly. Additional tests will be performed when clinically appropriate. Tests can be performed on the same day or within the 2 days before initiating study intervention

l Cycle 1 Day 1 hematology and blood chemistry tests may be omitted if screening tests performed within 7 days are normal. If screening tests are abnormal, they should be repeated within 2 days of first study intervention.

m Ocular/visual symptoms must be assessed by the Investigator at screening, before each IMP infusion and at EOT, and whenever clinically indicated. If any visual symptom is reported, an ophthalmologist visit must be scheduled.

n Only AEs related to the fresh biopsy procedure (if applicable) and occurring within 1 month after the fresh biopsy will be recorded in the eCRF.

o Chest, abdomen, pelvic CT-scan or MRI and any other examinations as clinically indicated will be performed to assess disease status at screening and then every 8 weeks until EOT, and also every12 weeks during follow-up period until progressive disease or new anti-cancer therapy if the discontinuation is due to other reason than progressive disease. Bone CT-scan or MRI and other examinations should be performed if clinically indicated. Brain CT-scan or MRI should be performed at screening only for known stable lesions or if clinically indicated and followed during treatment only for participants with brain lesions at screening.

p PRO assessments: NSCLC-SAQ, PGIS-LCS, PGIC-LCS, and FACT-GP5 are completed by each study participant after informed consent and prior to any treatment- or study-related activities, including administration of IMP, laboratory work, radiological assessments, discussion with the participant regarding their treatment or health status, and similar activities.

1.3.2 PK/ATA flow chart

PK/ATA flowchart of Tusamitamb ravtansine					
Cycle	**Day within cycle**	**Relative Nominal time**	**PK Sample ID[b]**	**ATA Sample ID**	**Time window allowance**
Cycle 1	1	SOI	P00[a]	AB00[a]	Within 24h before SOI
		EOI	P01	-	±10 min around the EOI
	3	48h	P02	-	Whenever between 24 and 72h
Cycle 2	1	SOI	P00[a]	AB00[a]	Within 24h before SOI
Cycle 3	1	SOI	P00[a]	AB00[a]	Within 24h before SOI
		EOI+1h	P01	-	±10 min
Cycle 4	1	SOI	P00[a]	-	Within 24h before SOI
Cycle 5	1	SOI	P00[a]	-	Within 24h before SOI
Cycle 6	1	SOI	P00[a]	-	Within 24h before SOI
Cycle 7	1	SOI	P00[a]	AB00[a]	Within 24h before SOI
Cycle 13	1	SOI	P00[a]	AB00[a]	Within 24h before SOI
Cycle 19 then every 6 Cycles	1	SOI	-	AB00[a]	Within 24h before SOI
EOT	30	EOT	-	ABF00	30 ±5 days after last IMP

ATA = anti-therapeutic anti bodies; EOI = end of infusion (ie, when the pump beeps before flush); EOT = End of Treatment; IMP = investigational medicinal product; PK= pharmacokinetics; SOI = start of infusion.

a Samples collected strictly before start of infusion (SOI).

b No more PK samples will be collected after the cut-off for analysis of the primary endpoint.

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

Despite recent progress in the treatment of advanced NSCLC, there remains a need for effective new treatment at the time of disease progression after the first-line therapy. Current therapeutic approaches for subsequent systemic options consist of a combination of an inhibitor of angiogenesis with a systemic cytotoxic agent such as docetaxel that entails serious hematological and other toxicities or docetaxel, pemetrexed or gemcitabine as single cytotoxic agent with very limited other options (1) therefore, targeted cytotoxic therapies may offer an improvement in safety and tolerability as well as efficacy.

One feature that can be used to target some tumor cells is surface expression of carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5), first described in 1965 as a tumor-associated antigen in human colon cancer tissue extracts (2). High levels of CEACAM5 expression have since been observed in several epithelial tumors, whereas in normal adult tissue, its expression is limited to few tissues (3, 4). Immunostaining of CEACAM5 in a large panel of human tumor tissue microarray samples has shown the highest prevalence of cell surface CEACAM5 expression in adenocarcinomas of the colon and of the stomach and its signet ring cell subtype as well as NSQ NSCLC.

Maytansinoids are antimitotic agents that inhibit microtubule formation to act as very potent cytotoxic agents against tumor cell lines in vitro, with IC_{50} values 100- to 1000-fold more potent than conventional tubulin binding compounds, including docetaxel. Tusamitamab ravtansine (SAR408701) is an antibody to CEACAM5 conjugated to the cytotoxic maytansinoid agent, (DM4). Encouraging preliminary anti-tumor activity of tusamitamab ravtansine in participants heavily pre-treated for NSQ NSCLC has been demonstrated in an ongoing study (TED13751).

2.1 STUDY RATIONALE

In the FIH, TED13751 study, a cohort of 64 participants with heavily pre-treated NSQ NSCLC with high CEACAM5 expression using the IHC method applied at pre-screening on archived tumor sample (defined as ≥2+ in intensity in at least 50% of the tumor cells) were treated with tusamitamab ravtansine at 100 mg/m² Q2W. Tusamitamab ravtansine has shown an encouraging anti-tumor activity which was associated with an overall response rate of 20.3% (13 participants who had PR) per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (95% CI: 12.27%-31.71%) (5). These data warranting further development of tusamitamab ravtansine and being the basis for the start of a pivotal phase 3 study (EFC15858) to treat this patient population.

In the TED13751 study the cohort of NSQ NSCLC participants with high CEACAM5 expression on tumor (≥2+ in intensity in ≥50% of tumor cells), 10 out of 13 responding participants had high baseline circulating CEA (≥100 ng/mL). Potential responses to tusamitamab ravtansine have also been evaluated in a cohort of NSQ NSCLC participants with moderate CEACAM5 expression on tumor (≥2+ in intensity in ≥1% and <50% of tumor cells) but only a limited number of participants (7 out of 28 participants) presented high circulating CEA levels at baseline.

No anti-tumor activity response data are available from the negative CEACAM5 expression on tumor by IHC (intensity 1+ whatever the percentage of stained tumor cells or <1% of tumor cells) with high circulating CEA level (≥100 ng/mL) cohort.

The CEACAM5 expression status may have differed between the initial tumor at diagnosis and the tumor at the time of the enrollment in the clinical trial. Even though a correlation is expected between circulating CEA and CEACAM5 expression status on tumor, there are no available data on concomitant CEACAM5 expression on fresh tumor biopsy and circulating CEA. Biomarkers in oncology are most accurate and best correlated with clinical outcomes when they are assessed immediately prior to therapy.

Participants are pre-screened in the EFC15858 Phase 3 study in second or third-line therapy based on the expression of CEACAM5 that is assessed on archival biopsy at the time of diagnosis, prior to first-line therapy, which can be months or years before enrollment. This is potentially important for participants who are pre-screened in the EFC15858 and whose diagnostic biopsies are negative, but who could have high CEACAM5 expression at the time of a fresh biopsy, either due to heterogeneous expression of CEACAM5 or upregulation of CEACAM5 expression after first-line therapy. In this study ACT17241, a fresh biopsy will be proposed (optional) at screening to explore the relationship between CEACAM5 expression at diagnosis and at the time of enrollment as well as the relationship between high circulating CEA and high CEACAM5 expression at the time of enrollment. The fresh biopsy will be assessed retrospectively as due to the heterogenicity of tumors, participants with negative CEACAM5 expression may have high expression on other tumor locations.

The aim of this study is to evaluate if participants with high circulating CEA level at baseline could benefit from tusamitamab ravtansine treatment despite negative or moderate CEACAM5 expression on archival biopsy, assuming that a high circulating CEA level reflects a high CEACAM5 expression on tumor at the time of the enrollment. To this end, the anti-tumor activity will be assessed in participants with NSQ NSCLC with high circulating CEA levels despite negative or moderate CEACAM5 expression on tumor by IHC testing in third- or fourth-line treatment.

2.2 BACKGROUND

Lung cancer is one of the most commonly diagnosed cancers and is the leading cause of cancer-related mortality worldwide (6). Non-small-cell lung cancer (NSCLC) accounts for 85% of all lung cancers (7) and comprises several histopathological subtypes, of which adenocarcinoma (60%) and squamous-cell carcinoma (15%) are the most common (8).

The majority of patients with NSCLC present an advanced stage at the time of diagnosis. These patients have a median overall survival of up to 8 to 12 months (9), and in 2015, a 5 year survival rate of approximately 25% (10). About 15% to 20% of patients with NSCLC have tumors with key genomic alterations that are amenable to targeted therapy, which include epidermal growth factor receptor (*EGFR*) mutations and ROS receptor tyrosine kinase 1 (*ROS1*) and anaplastic lymphoma kinase (*ALK*) rearrangements (11).

Until recently the only available treatment option for advanced or metastatic NSQ NSCLC lacking targetable mutations was chemotherapy. Systemic therapy with platinum-based doublet regimens, with or without maintenance therapy, was the current first-line treatment for patients with advanced NSCLC (12).

More recently, immunotherapy has initiated a new paradigm for the treatment of NSCLC. In particular, monoclonal antibodies targeting the programmed death-1 receptor (PD-1)/PD ligand-1 (PD-L1) pathway have emerged as powerful new therapeutic tools in several clinical trials. Four drugs targeting the PD-1 pathway (nivolumab, pembrolizumab, atezolizumab, and cemiplimab) have been approved for the treatment of both chemotherapy-naïve and/or previously treated advanced stage NSCLC (13, 14, 15, 16), however only a small subset (20% to 30%) of patients responds to these treatments. Despite an improvement in outcomes with newer lines therapy, including anti-PD-1/PD-L1 antibodies, the disease often progresses.

The standard second-line treatment for NSCLC has been docetaxel (17); docetaxel's activity was found to be enhanced by the addition of ramucirumab (18). There are other available options as single agent treatment such as docetaxel, pemetrexed or gemcitabine, however, there is an unmet medical need for subsequent systemic therapy (1).

Additional therapeutic options are needed to improve the clinical efficacy in patients with advanced/metastatic NSCLC.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected AEs of tusamitamab ravtansine may be found in the Investigator's brochure (IB).

2.3.1 Risk assessment

To date, efficacy and safety data from ongoing studies of tusamitamb ravtansine (TED13751, TCD15054, and EFC15858) support the continued clinical development of tusamitamb ravtansine. Based on available safety data, the main anticipated risk to patients is corneal toxicity presenting as microcystic keratopathy, which is reversible and manageable with dose delay and dose reduction in some patients. Peripheral neuropathy is an identified risk in patients previously exposed to neurotoxic drugs.

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; Table 1).

Table 1 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention: tusamitamab ravtansine		
Microcystic keratopathy/Keratitis	**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**: Reversible non-inflammatory, microcystic keratopathy/keratitis. Main dose-limiting toxicity (DLT) in the dose escalation part of study TED13751. Observations in the different phases of the clinical trial showed nonserious, mild to moderate AEs, no Grade 4-5 AEs were reported. The corneal TEAEs were manageable and reversible. Corneal TEAEs appeared: - In TED13751 study in 30.1% of patients (56/186) in the pool of patients at 100 mg/m^2 Q2W, 32.1% of patients (9/28) in the Loading dose cohort, and 40.0% of patients (6/15) in the Dose Escalation Q3W phase. - In TCD15054, in 50% of patients in the main dose escalation (3/6 patients) and in 50% of patients in the loading dose (8/16 patients). Regarding the ongoing studies ACT16525, ACT16146, ACT16432, EFC15858 among the patients treated there was no serious TEAE of keratopathy/keratitis.	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**: Symptoms may be sensory (paresthesia, dysesthesias, pain, change in proprioception), motor (weakness), and neural dysfunctions. TEAEs In TED13751 study peripheral neuropathy was observed in 26.3% (49/186) of patients in the pool of patients at 100 mg/m² Q2W, 21.4% of patients (6/28 patients) in the loading dose cohort and 33.3% of patients (5/15 patients) in the Dose Escalation Q3W phase. In the loading dose escalation cohort and the Q3W cohort, there was no SAE and only grade 1 AEs of Keratopathy/keratitis were reported. TCD15054 study, TEAEs appeared in 1 patient (16.7%) in the main dose escalation part at DL 100 mg/m^2, Q2W, and 1 patient (6.3%) in the loading dose part. No serious TEAE were reported in ACT16525, ACT16146, ACT16432, and EFC15858 studies.	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 gastrointestinal tract (tongue, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon and/or rectum) in mice and monkeys. 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**: Based on clinical observations, patients with known underlying colitis or gastrointestinal tract conditions are noted to be at highest risk for such events. In the TED13751 study relevant symptoms of colitis were observed in 1 patient (0.5%) in the pooled data of patients treated at 100 mg/m^2 Q2W and developed by 2 additional patients in the main dose escalation phase. No relevant observation were made in TCD15054 study, ACT16525, ACT16146, ACT16432, EFC15858.	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 red blood cells 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**: Hematologic cytopenias (including clinically relevant alteration and/or laboratory data abnormalities) are frequently observed with ADC in general, and in tusamitamab ravtansine clinical development program. The observations were in favor of a higher risk in patients with a known history of cytopenias (leucopenia, neutropenia, thrombocytopenia, or anemia) due to previous cytotoxic drugs treatment. The incidence of TEAEs grade ≥3 was low as follows: TED13751: Pooled data at DL 100 mg/m^2 Q2W: Grade≥ 3 in 5 patients (2.7%) under blood and lymphatic system disorders SOC, 2 patients (1.1%) under Investigations SOC with platelet count decreased. Regarding laboratory data, the following abnormalities were observed: anemia Grade 3 in 10 patients (5.4%), platelet count decreased Grade 3 in 1 patient (0.5%) and Grade 4 in 4 patients (2.2%), lymphocyte count decreased Grade 3 in 20 patients (10.9%) and Grade 4 in 2 patients (1.1%). - Loading dose: 1 patient (3.6%) had Anemia ≥Grade 3 and 1 patient (3.6%) was reported with Platelet count decreased (Grade≥ 3). - Dose Escalation Q3W: no Grade 3 or 4 Hematologic cytopenias.	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 be performed on weekly basis. If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC ≥0.5 x 10^9/L.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	TCD15054 study: 2 patients with Grade 3 Lymphocyte count decreased. ACT16525, ACT16146, ACT16432 studies: no serious TEAEs of Hematologic cytopenias reported. EFC15858 study: 4 patients (3.3%) reported with serious AE of febrile neutropenia Grade 3- 4, 1 patient with serious AE of Neutropenia, 1 patient was reported with serious AE of Grade 4 neutrophil count decreased, 1 patient with serious AE of Grade 3 anaemia.	
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. Compound-related effects on ECG parameters observed in some monkeys at the top dose (7 mg/kg/adm) using an external telemetric methodology were 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**: TED13751 study: - Pooled data at 100 mg/m² Q2W: 2 patients with BBB right (1.1%), 1 patient (0.5%) with each of the following AEs: angina pectoris, atrioventricular block first degree. ECG QT prolonged in 2 patients [1.1%]), none of them was Grade 3 or 4. EFC15858 study: 1 patient (0.8%) experienced 2 Myocardial infarctions considered as not related to the study treatment, another patient (0.8%) with underlying cardiovascular risk factors (Hypercholesterolemia, hypertension, coronary bypass and angioplasty) developed serious Grade 3 Angina pectoris + serious Grade 1 Troponin T increased.	Cardiovascular examination. Monitoring of potential cardiac conduction defects by regular ECG.
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**: No “Hy's law” cases have been observed. Grade ≥3 TEAEs were observed as follows: In TED13751 study: - Pooled data at 100 mg/m² Q2W: Hepatic cytolysis in 2 patients (1.1%), AST increased in 4 patients (2.2%),	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.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	Transaminases increased in 2 patients (1.1%), ALT increased in 2 patients (1.1%), Gammaglutamyltransferase increased in 2 patients (1.1%), Blood ALP increased in 1 patient (0.5%), Blood bilirubin increased in 1 patient (0.5%). The analysis of clinical laboratory data showed ALT increased Grade 3 in 3 patients (1.6%) and Grade 4 in 2 patients as well (1.1%); AST increased Grade 3 in 9 patients (4.9%) and Grade 4 in 3 patients (1.6%); ALP increased Grade 3 in 15 patients (8.2%) and blood bilirubin increased Grade 3 in 7 patients (3.8%). - Loading dose: no Grade ≥3 TEAEs. - Dose Escalation Q3W: ALT increased Grade 3 in 1 patient (6.7%), AST increased Grade 3 in 3 patients (20.0%), and ALP increased Grade 3 in 2 patients (13.3%). In TCD15054 study: 2 patients (12.5%) reported with AST increased, 1 patient (6.3%) reported with ALT increased, 1 patient (6.3%) reported with Blood ALP increased and 1 patient (6.3%) reported with Gamma-glutamyltransferase increased. The analysis of clinical laboratory data showed 1 patient (7.7%) reported with ALT increased Grade 4 (none with Grade 3), 1 patient (9.1%) reported with AST increased Grade 4. and 1 patient (14.3%) reported with ALP increased Grade 3. ACT16146: 1 patient (12.5%) with serious Grade 3 TEAE of Hepatic enzyme increased. EFC15858 study: 1 patient reported with serious AE of Grade 3 Transaminases increased. ACT16525, ACT16432: no serious TEAEs of Hepatotoxicity reported.	
Systemic acute hypersensitivity reactions (including anaphylaxis)	**Nonclinical:** Not observed. **Clinical:** ADCs are known to have the potential for hypersensitivity. In tusamitamab ravtansine development program very limited number of patients developed this profile of reactions.	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 infusion reaction, the flow rate can be decreased; minimum authorized flow 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

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
		the previous infusion rate after the recovery.

Abbreviations: ADC = anti-body drug conjugate; AE = adverse events; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BBB= Bundle branch block; DLT = dose-limiting toxicity; ECG = electrocardiogram; EOT = end-of-the-treatment; GI = gastrointestinal; GLDH = glutamate dehydrogenase; HR = heart rate; IMP = Investigational medicinal product; IV = Intravenous; Q2W = every 2 weeks; Q3W = every 3 weeks; SAE = serious adverse event; SOC = system organ classes; TEAE = treatment-emergent adverse events; WBC = white blood cells.

2.3.2 Benefit assessment

Based on the current data obtained in the ongoing monotherapy studies of tusamitamab ravtansine (TED13751 and TCD15054) in NSQ NSCLC participants, anticipated benefits in the treatment support continued clinical development in this indication.

Participants with high circulating CEA level at baseline could benefit from tusamitamab ravtansine treatment despite negative or moderate CEACAM5 expression on archival biopsy, assuming that a high circulating CEA level reflects a high CEACAM5 expression on tumor at the time of the enrollment.

2.3.3 Overall benefit/risk conclusion

Considering the measures taken to minimize risk to participants of this study, the potential risks identified in association with tusamitamab ravtansine are justified by the anticipated benefits that may be afforded to participants with NSQ NSCLC in third- or fourth-line treatment with high unmet medical need.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the anti-tumor activity of tusamitamab ravtansine when given every 2 weeks (Q2W) in non-squamous non-small-cell-lung-cancer (NSQ NSCLC) participants with negative or moderate CEACAM5 expression tumors and high circulating carcinoembryonic antigen (CEA) levels	• Objective Response Rate (ORR) of tusamitamab ravtansine, defined as the proportion of participants who have a confirmed complete response (CR) or partial response (PR) as best overall response (BOR) per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1
Secondary	
• To assess the safety and tolerability of tusamitamab ravtansine	• Incidence of participants with 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 other efficacy parameters of tusamitamab ravtansine	• Progression-free survival (PFS), defined as the time from the date of first tusamitamab ravtansine administration to the date of the first documented disease progression or death due to any cause, whichever comes first. • Disease control rate (DCR), defined as the percentage of participants who have achieved confirmed CR or PR, or stable disease as BOR per RECIST v1.1 • Duration of response (DOR), defined as the time from first documented evidence of CR or PR until progressive disease (PD) determined per RECIST v1.1 or death from any cause, whichever occurs first
• To evaluate the immunogenicity of tusamitamab ravtansine	• Incidence of participants with anti-therapeutic antibodies (ATAs) against tusamitamab ravtansine
• To document the pharmacokinetics (PK) of tusamitamab ravtansine	• Tusamitamab ravtansine concentrations
Tertiary	
• To evaluate patient-reported outcomes (PROs)	• Time to deterioration in the overall severity of disease-related symptoms (cough, pain, dyspnea, fatigue, appetite) as measured by the NSCLC-Symptom Assessment Questionnaire (SAQ) • Patient global impression of severity (PGIS) and patient global impression of change (PGIC) in disease-related symptoms will be measured by generic PGIS lung cancer symptom (PGIS-LCS) and PGIC lung cancer symptom (PGIC-LCS) scales

	• Change from baseline in overall side effect impact as measured by the Functional Assessments of Cancer Therapy Item GP-5 (FACT-GP5)
• To explore modulations of circulating CEA as a potential pharmacodynamic biomarker of response to tusamitamab ravtansine treatment and to evaluate circulating CEA levels at pre-screening and its correlation with CEACAM5 tumor expression on fresh biopsy (if available)	• Circulating CEA at pre-screening, screening, during the treatment period and during the follow-up period; tumor CEACAM5 expression (on fresh biopsy tumor sample, if available)
• To explore the relationship between CEACAM5 expression in archived and fresh biopsy at screening (if available)	• CEACAM5 expression on archived and fresh biopsy at screening
• To explore the relationship between the tumor mutation profiles detected in the circulating free DNA (cfDNA) at baseline with efficacy outcome	• Mutation analysis for tumor cfDNA at baseline
• To explore potential sets of biomarkers including tumor mutation profiles from tumor DNA and RNA analyses on fresh biopsy (if available), beside target expression, as potential biomarkers of response to tusamitamab ravtansine treatment.	• Mutation analysis and biomarker annotation for tumor DNA and RNA on fresh biopsy at screening (if available).

Primary estimand defined for primary efficacy endpoint is summarized in Table 3 below. More details are provided in Section 9.2.

For this estimand, the study intervention of interest will be tusamitamab ravtansine.

Table 3 - Summary of primary estimands for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To assess the anti-tumor activity of tusamitamab ravtansine Q2W in NSCLC participants with negative or moderate CEACAM5 expression tumors and high circulating CEA levels				
Primary endpoint (primary estimand)	Confirmed objective response (confirmed CR or PR as BOR), determined according to RECIST v1.1	All-treated population	Regardless of investigational medicinal product IMP discontinuation (treatment policy strategy) Based on tumor assessments done before initiation of further anticancer therapy ("while not initiating anticancer therapy" strategy)	Objective response rate defined as rate of participants with confirmed objective response and two-sided 95% confidence interval (CI) using the Clopper-Pearson method. In the absence of confirmed objective response, participants will be considered as non-responders, whatever the reason (including participants with non-evaluable BOR).

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy or anti-tumor activity and safety assessments chosen for use in this study are 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 single group, Phase 2, open-label, multi-center study assessing efficacy (anti-tumor activity), safety, and PK of tusamitamab ravtansine single agent in NSQ NSCLC participants with negative or moderate CEACAM5 expression tumors and high circulating CEA (≥100 ng/mL) at baseline.

Moderate CEACAM5 expression is defined as intensity ≥2+ in ≥1% and <50% of tumor cells.

Negative CEACAM5 expression is defined as intensity 1+ whatever the percentage of stained tumor cells or <1% of tumor cells.

During the pre-screening phase, participants who were pre-screen failed in the EFC15858 Phase 3 trial with available CEACAM5 status (central assessment by IHC) as negative or moderate expression on archival tumor tissue can be pre-screened. Participants with high circulating CEA (≥100 ng/mL) will be screened and will go through protocol screening procedures.

After being screened, the eligible participants will receive tusamitamab ravtansine as a single agent treatment at the dose of 100 mg/m² Q2W until disease progression, unacceptable AE, initiation of a new anticancer therapy, or the participant's or Investigator's decision to stop the treatment, whichever comes first. A total of approximately 38 participants are planned to be treated. An interim analysis is planned after 20 participants treated are evaluable for anti-tumor activity or efficacy. If at least 2 confirmed objective responses are reported, the recruitment will continue to achieve a total of 38 evaluable treated participants.

The duration of the study for a participant will include:

- Pre-screening period: a pre-screening informed consent will be signed in order to collect available CEACAM5 expression results on archival tumor tissue from EFC15858 study and the circulating CEA value.
- Screening period: up to 28 days.
- Treatment period: once successfully screened, enrolled participants may receive study intervention until disease progression, unacceptable AE, initiation of a new anticancer therapy, or the participant's or Investigator's decision to stop the treatment, whichever comes first. 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 IMP administration or before the participant receives another anticancer therapy, whichever is earlier, for end-of-treatment (EOT) assessments.
- Follow-up period: a safety follow-up visit will be performed approximately 90 days after the last dose of IMP.

- Participants who discontinue the study treatment due to documented PD, do not need further follow-up visit, if any ongoing related AE/AESI/SAE is resolved or stabilized. Otherwise, follow-up visits will be performed every 12 weeks,
- Participants who stop treatment before documented PD should undergo a tumor assessment and a follow-up visit every 12 weeks (±7 days) after the last tumor assessment until radiological disease progression, start of a new anticancer therapy, study cut-off date for secondary endpoints, or withdrawal of participant's consent, whichever comes first. After documented PD or a start of new anticancer therapy, the participant will be followed until any ongoing IMP related AE/AESI/SAE is resolved or stabilized.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Lung cancer is one of the most commonly diagnosed cancers and is the leading cause of cancer-related mortality worldwide (6). Despite recent progress in the treatment of advanced NSCLC, there remains a need for effective new treatment at the time of disease progression after the first and second-line therapies.

The primary endpoint for this efficacy single arm signal seeking study is ORR. This will allow an earlier efficacy assessment with small sample size.

4.3 JUSTIFICATION FOR DOSE

In the main dose-escalation phase of the first-in-human study TED13751 exploring 5 to 150 mg/m^2 SAR408701 doses administered once every 2 weeks, the recommended dose was determined to be 100 mg/m^2 administered every 2 weeks. A cohort of heavily pretreated NSQ NSCLC patients with CEACAM5-positive tumor at the membrane (≥2+ in intensity involving at least 50% of the tumor cell population) have been treated with SAR408701 at the recommended dose of 100 mg/m² every 2 weeks. The 64 treated patients showed encouraging anti-tumor activity and was associated with a response rate of 20.3% (95% CI: 12.27%-31.71%); 28 (43.8%) had stable disease. The recommended dose of 100 mg/m^2 will be used 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 (SoA) (Section 1.3) for the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA.

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 of the following criteria apply:

Age

I 01. Participant must be ≥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 proven diagnosis of NSQ NSCLC metastatic disease at study entry.

I 03. Documented disease progression after at least 1 prior first chemotherapy line that must contain platinum-based chemotherapy (at least 2 cycles) and an immune checkpoint inhibitor (ICI, can be given as combined with chemotherapy or sequential, whatever the order) but no more than 2 prior chemotherapies lines are allowed. Maintenance therapy following platinum-based chemotherapy is not considered as a separate regimen. Adjuvant/neoadjuvant treatment for a participant who had a relapse with metastatic disease during or within 6 months of completion of treatment will be considered as first chemotherapy line treatment.

I 04. For a tumor genotype with a sensitizing EGFR mutation or BRAF mutation or ALK/ROS alteration, demonstrated disease progression while receiving approved treatment for that genotype in addition to platinum-based chemotherapy and ICI.

I 05. Moderate or negative CEACAM5 expression assessed by a central IHC assay in an archival tumor sample. Moderate CEACAM5 expression is defined as intensity ≥2+ in ≥1% and <50% of tumor cells. Negative CEACAM5 expression is defined as intensity 1+ whatever the percentage of stained tumor cells or <1% of tumor cells.

I 06. Circulating CEA levels ≥100 ng/mL at pre-screening.

I 07. Measurable disease by RECIST v1.1 (Section 10.12), 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 08. Eastern Cooperative Oncology Group (ECOG) performance status 0-1.

Weight

Not Applicable.

Sex, contraceptive/barrier method and pregnancy testing requirements

I 09. 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 (Section 10.4) 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 (serum) 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 10. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) 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 that may be considered active or history of leptomeningeal disease. Patients with previously treated brain metastases may participate provided they are stable (ie, without evidence of progression by imaging for at least 4 weeks prior to the first administration of study intervention, and any neurologic symptoms have returned to baseline), and there is no evidence of new or enlarging brain metastases, and the patient does not require any systemic corticosteroids for management of brain metastases within 4 weeks prior to the first dose of study intervention.

E 02. Life expectancy less than 3 months.

E 03. 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 04. History within the last 3 years of an invasive malignancy other than the one 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 05. Any major surgery within 3 weeks prior to Day 1 of first study intervention administration.

E 06. Known uncontrolled infection with human immunodeficiency virus (HIV). Participants with well controlled HIV infection/disease (Section 10.10) must be on antiretroviral therapy (ART) to be eligible.

E 07. 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 08. 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 09. Unresolved corneal disorder or any previous corneal disorder considered by an ophthalmologist to predict higher risk of drug-induced keratopathy.

E 10. 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.

Prior/concomitant therapy

E 11. Medical condition requiring concomitant administration of a medication with a narrow therapeutic window, that is metabolized by cytochrome P450 (CYP450) (see Appendix 11 [Section 10.11]), and for which a dose reduction cannot be considered.

E 12. Medical conditions requiring concomitant administration of strong CYP3A inhibitor (see Appendix 11 [Section 10.11]), unless it can be discontinued at least 2 weeks before the first administration of study intervention.

E 13. Concurrent treatment with any other anticancer therapy.

E 14. 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 anti-tumor therapy (chemotherapy, targeted agents, immunotherapy and radiotherapy, or any investigational treatment), if palliative radiotherapy washout period of less than 2 weeks.

E 15. Any prior therapy targeting CEACAM5.

E 16. Prior maytansinoid treatment (DM1 or DM4 anti-body drug conjugate [ADC]).

Prior/concurrent clinical study experience

E 17. 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 18. Poor organ function as defined by any 1 of the following prior to IMP administration:

a) Serum creatinine >1.5 × upper limit of normal (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).

Other exclusions

E 19. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized

E 20. 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 21. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures

E 22. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the International Conference on Harmonisation –Good Clinical Practice (ICH-GCP) Ordinance E6)

E 23. Any specific situation during study implementation/course that may raise ethics considerations

E 24. 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

A screen failure occurs when a participant who consents to participate in the clinical study is 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.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number by IRT for every screening event.

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

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 9 (Section 10.9) Contingency measures for a regional or national emergency that is declared by a governmental agency should be considered for pre-screening/screening/enrollment administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Using an infusion-controlled pump, tusamitamab ravtansine will be administered by IV infusion over 1 hour 30 minutes.

Prior to dosing, each participant's dose will be individually prepared by the study pharmacist or delegate and labeled with protocol number, participant number and treatment description.

One Day 1 of each treatment cycle, the patient's BSA will be determined using the current weight and baseline height. For patients with a BSA >2.20 m², the dose will be calculated on the basis of 2.20 m² BSA. After first administration of tusamitamab ravtansine, patients should be observed for acute reactions at site up to 4 days depending on any sign of drug allergic reaction.

Detailed instructions for dilution and administration of the IMP are provided in the Pharmacy Manual.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 4 - Study intervention(s) administered

Intervention label	Tusamitamab ravtansine
Intervention name	Tusamitamab ravtansine
Intervention description	Tusamitamab ravtansine, Intravenous infusion 100 mg/m² Day 1 every 2 weeks
Type	Drug
Dose formulation	Concentrate for solution for Intravenous (IV) infusion
Unit dose strength(s)	5 mg/mL 125 mg/25 mL
Dosage level(s)	Tusamitamab ravtansine Intravenous (IV) infusion 100 mg/m² Day 1 every 2 weeks
Route of administration	Intravenous infusion
Use	experimental
IMP and NIMP	IMP

Packaging and labeling	Tusamitamab ravtansine is supplied in a 30 mL type I glass vial. Each IMP kit contains 1 vial of 125 mg/25 mL of tusamitamab ravtansine labeled with a multilingual booklet. The content of the labeling at vial and box level is in accordance with the local regulatory specifications and requirements
Current/former name(s) or alias(es)	Tusamitamab ravtansine

Abbreviations: IMP = investigational medicinal product; NIMP = noninvestigational medicinal product

Table 5 - Study arm(s)

Arm title	Tusamitamab ravtansine
Arm type	Experimental
Arm description	Participants will receive intravenous (IV) administration 100 mg/m^2 every 2 weeks (Q2W)
Associated intervention labels	Not applicable

The tusamitamab ravtansine may be supplied at the site or from the PI/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

After the study cut-off date for the secondary efficacy endpoints, participants with observed clinical benefit who are still receiving study treatment can continue on study treatment.

Study intervention will be administered until documented disease progression, unacceptable toxicity, new anti-cancer therapy initiation, or the participant's or Investigator's decision to stop the treatment, whichever comes first.

Noninvestigational medicinal product (NIMP): Premedication for tusamitamab ravtansine

Tusamitamab ravtansine has a potential risk of infusion-related reaction (IRR) and premedication should be used. All the drugs used as premedication will be entered to the concomitant premedication page.

Premedication with histamine H1 antagonist (diphenhydramine 50 mg or equivalent [eg, dexchlorpheniramine] given approximately 15 minutes [IV] to 1 hour [oral] before tusamitamab ravtansine administration) is required for all participants before administration of tusamitamab ravtansine. After first study intervention of SAR408701, patients should be observed for acute reactions at site up to 4 hours depending on any sign of drug-induced allergic reaction. Detailed instructions for dilution and administration of the IMP are provided in Pharmacy Manual. If a participant has experienced an IRR in a previous tusamitamab ravtansine administration, premedication will also include dexamethasone 10 mg IV for future infusions. If the participant does not experience any hypersensitivity reactions after 4 cycles, the premedication can be discontinued at the discretion of the Investigator.

Target infusion time is 1.5 hour. In case of an IRR ≥ Grade 2, tusamitamab ravtansine administration will be interrupted. The infusion may be resumed at half of the previous infusion rate after the recovery. The flow rate can be decreased; minimum authorized flow rate is 33 mL/h.

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 (Section 10.9): Contingency measures for a regional or national emergency that is declared by a governmental agency.

6.2 PREPARATION, HANDLING, STORAGE, AND 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).
4. Partially-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 treatments will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.
5. The Investigator must not destroy the unused IMP unless sanofi provides written authorization.
6. Further guidance and information for the final disposition of 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 notified 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, in order 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 as this is a single-arm, nonrandomized, open-label study; however, the specific study intervention to be taken by a participant will be assigned using an interactive response technology (IRT). The site will contact the IRT prior to the start of the study intervention

administration of each participant. The site will record the study intervention assignment on the applicable case report form.

6.4 STUDY INTERVENTION COMPLIANCE

- Methods used by the Investigator or his/her delegate to ensure that the IMP was administered.
  - The person responsible for drug dispensing is required to maintain adequate records of the IMPs. 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. The person responsible for drug administration to the participant will precisely record the date and the time of the drug administration to the participant.
- IMP compliance:
  - The Investigator records the dosing information on the appropriate page(s) of the case report form (CRF)
  - The monitor in charge of the study then checks the CRF data by comparing them with the IMP which he/she has retrieved and intervention log forms

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each 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.

6.5 DOSE MODIFICATION

Dose adjustment and/or cycle delay are permitted in case of adverse reaction. In case of toxicity, cycle delays and dose modifications should be implemented according to the 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 adverse reaction observed within a cycle. If a participant experiences several adverse reactions 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.

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

All changes to study treatment administration must be recorded in the electronic CRF (eCRF).

The acceptable treatment window for tusamitamab ravtansine administrations is 2 days.

One dose reduction is allowed for safety reason. Dose delay is allowed for safety management. Retreatment of patients that require more than one-month dose delay need to be justified with case by case risk benefit assessment. See Table 10 in Appendix 6 (Section 10.6) for guidance in dose modification or discontinuation. During the conduct of the study, second dose reduction may be needed, and need to be decided on a case by case basis following discussion with the sponsor.

If a dose reduction is necessary, the study intervention will be administered as follows:

Table 6 - Individual tusamitamab ravtansine dose reduction

Drug name	Dose	Reduced dose
Tusamitamab ravtansine	100 mg/m^2 Q2W	80 mg/m^2 Q2W

6.5.1 Retreatment criteria

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. Throughout the study, study intervention will be unblinded.

On Day 1 of each subsequent cycle, the participant must meet all of the following criteria to be eligible for retreatment:

- Neutrophils count $\geq 1.5 \times 10^9$/L.
- Platelets $\geq 100 \times 10^9$/L.
- Total bilirubin $\leq 3.0 \times$ ULN, with direct bilirubin $\leq 1.5 \times$ ULN.
- AST, ALT $\leq 2.5 \times$ ULN or $\leq 5 \times$ ULN in case of documented liver metastasis.
- No IMP-related toxicity Grade >1 (except for alopecia) or baseline severity.

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 greater than at least 30% above the intended administered dose expressed in units per BSA or any dose administered in less than half the recommended duration of administration, will be considered an overdose.

In the event of an overdose, the Investigator should:

- Contact the Sponsor immediately.
- Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Obtain a plasma sample for PK analysis as soon as possible, if requested by the Sponsor (determined on a case-by-case basis).
- 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 (Appendix 10 [Section 10.10]) 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 first cycle. Secondary prophylaxis or therapeutic administrations are allowed.
- Use of prophylactic erythropoietin during the first 2 cycles.
- Participants treated or intended to be treated with drugs identified as CYP450 substrates with narrow therapeutic range (NTR) (Appendix 11 [Section 10.11]) should be carefully monitored.
- Concomitant use of strong CYP3A inhibitors (Appendix 11 [Section 10.11]) should be avoided from 2 weeks before tusamitamab ravtansine administration up to the last tusamitamab ravtansine administration.

6.8.1 Rescue medicine

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1.9).

7.1 DISCONTINUATION OF STUDY INTERVENTION

- Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in the dose modification and toxicity management guidelines or if the Investigator believes that it is in best interest of the participant.
- If a clinically significant finding on electrocardiogram (ECG) is identified after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.
- Any potentially clinically significant abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation and repeated after 24 hours to document evolution before making a decision of permanent intervention discontinuation for the concerned participant.

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. 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 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.

Study intervention should be discontinued in any of the following cases:

- Unacceptable AE.
- Disease progression.
- Poor compliance to the study protocol.
- Other such as concurrent illness, that prevent further administration of study intervention.

Handling of participants after permanent intervention discontinuation

Participants will be followed-up 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 a pharmacokinetics sample and immunogenicity assessments, if appropriate.

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 [Section 10.9]): Contingency measures for a regional or national emergency that is declared by a governmental agency). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF or eCRF.

7.1.3 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned AE was unlikely and if the selection criteria for the study are still met (refer to Section 6.5.1).

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

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, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether 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.

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 timeframe defined in the SoA.

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

8.1 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in the SoA.

The assessment of antitumor activity of tusamitamab ravtansine with regard to ORR per RECIST v1.1 is the primary efficacy objective.

All participants treated must have at least 1 measurable lesion as per RECIST v1.1 for inclusion based on tumor assessment defined in the SoA (Section 1.3)

Tumor assessment will be made every 8 weeks (±7 days 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 screening; then every 8 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. 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 participants without imaging performed within past 4 weeks.

A participant who stops treatment before documented progressive disease should undergo a tumor assessment and a follow-up visit every 12 weeks (±7 days) after the last tumor assessment until radiological disease progression, start of a new anticancer therapy, study cut-off for secondary endpoints, or withdrawal of participant's consent, whichever comes first.

Brain CT-scan or MRI should be performed at screening only for known stable lesions or if clinically indicated and followed during treatment only for participants with brain lesions at screening.

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 v1.1 criteria will be followed for assessment of tumor response, see Appendix 11 (Section 10.12).

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than AE which are presented in Section 8.3.

Planned timepoints 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 cardiovascular, respiratory, gastrointestinal and neurological systems. Height (only at screening) and weight will also be measured and recorded.
- Performance status will be evaluated using ECOG scale (19).
- 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 will include: assessment of ocular/visual symptoms and ocular exams.

Ocular/visual symptoms must be assessed by the Investigator at screening, at each visit before study treatment administration (including C1D1), at EOT, and whenever clinically indicated. If any visual symptom is reported, an ophthalmologist visit must be scheduled.

Specific ocular tests performed by the ophthalmologist at screening, at EOT, and whenever indicated will include:

- Visual acuity.
- Slit lamp under dilatation.
- Schirmer's test.

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. Schirmer's test is mandatory for baseline assessment; it can be omitted from further ocular assessments if not considered a required examination per reported events category (ie, no symptom/findings of dry eye).

8.2.3 Vital signs

- Temperature, pulse rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device, unless 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 ECG(s) 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 can be performed on the same day before the study intervention administration or on the day before when requested on Day 1 pre-infusion. 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 Clinical safety laboratory tests

- 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 (ie, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total and direct bilirubin) will be assessed weekly.

- If Grade 4 neutropenia occurs, assess absolute neutrophil count (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.

8.2.6 Guidelines for management of adverse events

Management of AEs related to tusamitamab ravtansine is summarized in Appendix 6 (Section 10.6).

8.2.6.1 Hypersensitivity reactions

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

In case of event of hypersensitivity reactions, please refer to the recommended dose modification or discontinuation Table 10 (Section 10.6).

8.2.6.2 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 out on according to SoA (Section 1.3). Ocular evaluation will be performed at screening, 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 the discretion of an ophthalmologist when applicable.

8.2.6.3 Keratopathy/keratitis management

- Reversible non-inflammatory, microcystic keratopathy was identified as the dose limiting toxicity (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 the preferred term unless otherwise specified by an ophthalmologist due to inflammatory findings on eye exams leading to a 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.

8.2.6.4 Management of anemia

- Close surveillance of any signs and symptoms is required: a routine blood hematology workup, including red blood cells (RBC) counts, hemoglobin, hematocrit, white blood cells (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).

8.2.6.5 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 Granulocyte colony-stimulating factor (G-CSF) should be implemented per American Society of Clinical Oncology (ASCO) guidelines (20) 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).

8.2.6.6 Liver function tests

- Hepatic enzyme increase has been reported with tusamitamab ravtansine administration. 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.
- Grade ≥3 (ie, >5 × ULN) increased liver enzyme events should be reported as AESIs.

8.2.6.7 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).

8.2.6.8 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 gastrointestinal 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.

8.2.7 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) as described in Section 1.3.
- Pregnancy testing (urine or serum as required by local regulations) must be conducted corresponding with the time frame for female participant contraception.
- 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 AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.7.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) 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 the study intervention (see Section 7).

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).

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 timepoints specified in the SoA (Section 1.3).

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading 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 will be specified in the reference safety information in the IB.
- 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 IB 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 (See Section 5.1).
- 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 after obtained informed consent 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 participant/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 events of special interest

An 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 Appendix 4 [Section 10.4])
- Symptomatic overdose (serious or nonserious) with IMP
  - An 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/keratitis.
- Bundle branch blocks or any conduction defects.
- Grade ≥3 liver enzyme increased (symptomatic or asymptomatic).

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

- Whole blood samples will be collected for measurement of plasma concentrations of tusamitamab ravtansine as specified in the PK/ATA flowchart (Section 1.3.2).
- Instructions for the collection and handling of biological samples will be provided by the Sponsor's designee in a separate document. The actual date and time of each sample will be recorded. Pharmacokinetic samples will be tested by the Sponsor or Sponsor's designee.
- Data from plasma concentrations of tusamitamab ravtansine will be used for population PK analysis by non-linear mixed effects modeling. Data from previously conducted studies might be added for model development. This analysis will involve an estimation of

inter-patient PK variability, the determination of the population PK parameters estimates and the quantitative evaluation of potential effect of patient characteristics on the main PK parameters. Empirical Bayesian estimation of individual exposure parameters such as maximum concentration (C_{max}), trough concentration (C_{trough}) and area under the curve (AUC) will also be performed. Those individual exposure parameters will then be investigated as predictive factors for clinical outcomes including safety and efficacy endpoints, if possible.

- Pharmacokinetic samples could be used for testing analytical method performance such as comparability and incurred sample reproducibility and for possible exploratory analysis of drug metabolites. The exploratory data will not be included in the study report but will be kept on file.

8.5 GENETICS

8.5.1 Circulating tumor DNA analysis

A 20 mL blood sample corresponding to about 10 mL of plasma for tumor cfDNA isolation and an additional 2 mL blood sample for germline DNA will be collected at preinfusion of Cycle 1 Day 1.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

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

Fragmented 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. Mutation profiling analysis will be performed and the potential correlation of specific mutation(s) with clinical outcomes will be assessed.

List (not exhaustive) of the genes that could be mutated is: AKT1, ALK, BRAF, CDKN1B, CDKN2A, CDKN2D, EGFR, ESR1, FGFR4, HER2, HRAS, KRAS, MDM2, MED1, MET, NRAS, PIK3CA, PTEN, RB1, RET, ROS1, TP53.

8.5.2 Tumor DNA and RNA analyses

Although high circulating CEA levels at baseline reflecting concomitant CEACAM5 tumor expression may be an important parameter driving the activity of an anti-CEACAM5 ADC such as tusamitamab ravtansine, other factors may significantly contribute. Tumor tissue from a fresh tumor biopsy at screening will therefore also be proposed to explore the potential relationship between clinical endpoints following tusamitamab ravtansine therapy and potential sets of

biomarkers besides target expression that could be predictive of response. For that purpose, a tissue block (preferred option) or 3 × 10 µm slides (or equivalent such as 6 × 5 µm or other) is requested at screening. The samples may serve to investigate other potential biomarkers of response. In tumor tissue, biomarker annotation could include, but may not be restricted to, genomic annotation by sequencing, gene copy number variation, gene expression (messenger RNA [mRNA] and microRNA [miRNA]), and proteomic profiling. See Appendix 5 (Section 10.5) [Genetics] for information regarding genetic research]. Details on processes for collection and shipment and destruction of these samples can be found in the study laboratory manual.

8.6 BIOMARKERS

Collection of samples for other biomarker research is also part of this study. 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 at screening (optional) and assayed for CEACAM5 expression centrally.
- Blood samples for circulating CEA will be collected for local assessment. At screening and first tumor assessment, an additional sample (2 mL of blood, corresponding to 1 mL of serum) for circulating CEA is requested for central assessment.
- Plasma for Circulating CEACAM5 (central assessment) will be collected. For this test 1 mL of blood will be collected, corresponding to 500 µL of plasma.
- Blood sample will be collected for IgG dosage to explore impact of immunoglobulin G (IgG) level on PK of tusamitamab ravtansine. For this test 2 mL of blood will be collected, corresponding to 1 mL of serum.

Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate laboratory manual.

8.7 IMMUNOGENICITY ASSESSMENTS

- Antibodies to tusamitamab ravtansine will be evaluated in plasma samples collected from all participants as specified in the PK/ATA flowchart (Section 1.3.2).
- Instructions for the collection and handling of biological samples will be provided by the Sponsor's designee in a separate document. These samples will be tested by the Sponsor or Sponsor's designee.
- A 3-tiered approach will be employed to assess the immunogenicity of tusamitamab ravtansine when applicable: Samples will be screened and then confirmed for antibodies binding to tusamitamab ravtansine and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of tusamitamab ravtansine.

8.8 HEALTH ECONOMICS

No health economics data will be collected.

8.9 PATIENT-REPORTED OUTCOMES

All patients enrolled in the trial are expected to fill out the patient-reported outcome (PRO) assessments at clinic sites according to the pre-defined schedule in the SoA (Section 1.3). There are no PRO-specific eligibility criteria for the trial. As stated in the SoA (Section 1.3), PRO assessments are to be administered to each study participant after informed consent and prior to any treatment- or study- related activities, including administration of IMP, laboratory work, radiological assessments, discussion with the participant regarding their treatment or health status, and other similar activities. The administration schedule for PRO assessments must be adhered to as much as possible, regardless of protocol deviations. Four PRO measures will be used in this trial: the Non-Small-Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ), patient global impression of severity- lung cancer symptom (PGIS-LCS), patient global impression of change- lung cancer symptom (PGIC-LCS), and Functional Assessments of Cancer Therapy Item GP-5 (FACT-GP5). Together, these assessments include a total of 10 items, which is estimated to take approximately 5 minutes to complete. The PRO assessments will always be administered in the following standardized order: NSCLC-SAQ, PGIS-LCS, PGIC-LCS, and FACT-GP5.

All PRO assessments are designed for self-completion. The primary mode of administration is via electronic clinical outcome assessment (eCOA) using an application on participants' own devices. If the eCOA application fails, a web-based eCOA platform will be used as a back-up option. Provisioned back-up devices will be available at each site for participants without their own devices. The clinical report forms will include a question whether the PRO assessments have been filled in, and if not, the reason why. It is recommended that a key person (eg, research nurse) not directly involved in the participant's clinical care at each institution should be responsible for questionnaire data collection in order to optimize the participant compliance and to ensure the completeness of the data.

In case patients are not be able to physically attend hospital visits due to unforeseen restrictions (eg, Coronavirus disease-2019 [COVID-19] pandemic restrictions), the PRO measures can be collected by electronic assessment at home. Patients should be instructed to complete the PRO assessments within the intended timepoint (according to protocol SoA). Where participants completed their PRO assessment (ie, home versus site) will be documented.

8.9.1 NSCLC-SAQ

The NSCLC-SAQ assesses patient-reported symptom severity associated with NSCLC (21). The NSCLC-SAQ is a qualified clinical outcome assessment (COA) through the FDA's Drug Development Tool program (DDT COA #000009) (21, 22, 23), and has shown adequate evidence of content validity and cross-sectional measurement properties in adult patients with NSCLC (24). The 7 items of the NSCLC-SAQ assess 5 different cardinal NSCLC-related symptom concepts over a 7 day recall period: cough (1 item), pain (2 items), dyspnea (1 item), fatigue (2 items), and

appetite (1 item). The measure uses a 5-point Likert-type, verbal rating scales ranging from "No <symptom> at All" to "Very severe <symptom>" for cough and pain items and from "Never to Always" for dyspnea, fatigue, and appetite items. Domain scores are calculated based on the scale developer's procedures to form a total score, where higher scores indicate higher NSCLC symptom severity (23, 24). The NSCLC-SAQ is estimated to take approximately 2-3 minutes to complete. The instrument has been translated in 50 languages according to a standardized translation procedure (25).

8.9.2 PGIS-LCS and PGIC-LCS

The Patient Global Impression scale (PGI) is the patient-reported counterpart to the Clinical Global Impressions scale (CGI) which was published in 1976 by the US National Institute of Mental Health (26). Over the years, PGI scales were used in a broad range of diseases and were modified for the purpose of clinical settings. In this study, the PGIS and PGIC (1 item each) based on the CGI are adapted to the current setting. The PGIS-LCS measures severity in lung cancer symptoms at the time of assessment; while the PGIC-LCS measures change in lung cancer symptoms over time.

8.9.3 FACT-GP5

The FACT-GP5 ("I am bothered by side effects of treatment") is a single-item from the Functional Assessment of Cancer Therapy-General (FACT-G) scale assesses the overall impact of treatment side effects (27). Responses are given on a 5-point Likert-type scale recalling the past 7 days. Higher scores indicate a higher degree of side effect bother (28). The FACT-GP5 has been translated in over 50 languages according to a standardized translation procedure (29).

8.10 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, mechanism of action, or possible 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 (leftover) and/or extra (additional) clinical samples, data and samples may be used 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.

Remaining leftover samples will be used only after the study ends, ie, end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol.

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 alignment with the information provided to participants in the ICF Part 2 (future research). For future research projects, all biological samples and relating data to be used will be coded such that no participant direct identifiers will be linked to them. These 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).

Relating data and biological samples for future research will be stored for up to 25 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.

Participant's coded datasets 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

This study is designed to obtain preliminary efficacy, safety, and PK data on tusamitamab ravtansine administered as 100 mg/m² Q2W to participants with NSQ NSCLC tumors with CEACAM5 moderate-negative tumor expression and high circulating CEA levels.

As this study is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design.

9.1 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 7 - Population for analyses

Population	Description
Pre-screened	All participants who signed the pre-screening informed consent.
Screened	All participants who signed the screening informed consent for study participation.
Enrolled	All 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. All safety analyses will be performed on this population, which is also the primary population for analysis of all efficacy parameters.
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 analysis of efficacy parameters.
PK	All participants from the all-treated population with at least 1 postbaseline PK concentration 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 = anti-therapeutic antibody; PK = pharmacokinetic.
Note: In practice, a participant will be included in the enrolled population if the question "Will the subject continue in the treatment phase?" has been answered as "Yes" in the "Completion of screening phase" electronic case report form page.

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 "all-treated" 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.

9.2 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.

9.2.1 General considerations

This study is not intended to explicitly test a hypothesis. For the 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 IMP.

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 treatment for any reason. For participants with 2 postbaseline tumor assessments and occurrence of response at the second postbaseline tumor assessment, it will also include the confirmatory assessment. This study cut-off can be up to approximately 20 weeks (16 weeks for 2 tumor assessments and 4 weeks for confirmation of response, if needed) after the last participant's first IMP administration. Of note, DCR will be also assessed at this cut-off.

The final study cut-off 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 **pre-treatment period** is defined as the period up to first IMP administration.
    - The **pre-screening period** is defined as the period from the pre-screening 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 period) is defined as the period from the first IMP administration to 30 days after the last IMP administration.
- The **post-treatment period** is defined as the period from the end of the on-treatment period.

9.2.2 Primary endpoint analyses

The primary analysis will be based on a primary estimand introduced in Section 3. It is defined according to the following attributes:

- The primary endpoint is confirmed objective response (confirmed CR or PR as BOR) as per RECIST v1.1 (30). The best overall response (BOR) will be derived according to RECIST v1.1 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.
- The analysis population is the all-treated population (defined in Section 9.1).
- 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 further anticancer therapy intercurrent event will be handled with the "while not initiating further anticancer therapy" strategy. Confirmed objective response will be assessed based on tumor assessments done up to the time of initiation of further anticancer therapy.
- The population-level summary will be the ORR, defined as the rate of participants with confirmed objective response and two-sided 95% CI using the Clopper-Pearson method.

In the absence of confirmed objective response before the analysis cut-off date (taking into account the intercurrent event handling strategies), participants will be considered as non-responders, whatever the reason (including participants with non-evaluable BOR).

As a supplementary analysis, ORR as per RECIST v1.1 will also be summarized on the activity population (defined in Section 9.1). The same analytical approach as described above will be used.

9.2.3 Secondary endpoints analyses

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

9.2.3.1 Progression-free survival

Analysis of PFS will be based on an 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 date of the first documentation of objective PD according to RECIST v1.1 or death due to any cause, whichever comes first.
- The treatment condition of interest is tusamitamab ravtansine.
- The analysis population is the all-treated population (defined in Section 9.1).
- 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 further anticancer therapy intercurrent event will be handled with the hypothetical strategy. PFS will be assessed based on tumor assessments had a further anticancer therapy not being taken. PFS will be assessed based on tumor assessments up to the time of initiation of further anticancer therapy.
  - Two or more consecutive missing/unevaluable tumor assessments immediately before documented PD or death will be handled with the hypothetical strategy. PFS will be assessed based on tumor assessments had 2 consecutive tumor assessments not been missed immediately before documented PD or death. PFS will be assessed based on tumor assessments up to the last evaluable tumor assessment documenting no progression.
- 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.

  In addition, the number (%) of participants with an event and the type of event (documented disease progression or death without documented disease progression) and the number (%) of censored participants and reason for censoring (no baseline tumor assessment, no evaluable postbaseline tumor assessment, alive without documented disease progression, event occurred after 2 or more non-evaluable tumor assessments, or initiation of further anticancer therapy) will be analyzed.

  In the absence of documented disease progression or death before the analysis cut-off date (taking into account the intercurrent event handling strategies), PFS will be censored at the date of the last evaluable tumor assessment (not showing documented disease progression)

performed before the analysis cut-off date, or at the date of the first administration of IMP (Day 1) if no baseline tumor assessment or no evaluable postbaseline tumor assessment.

9.2.3.2 Disease control rate

Analysis of the DCR will be based on an estimand defined according to the following attributes:

- The endpoint is disease control response (confirmed CR or PR, or SD as BOR) as per RECIST v1.1.
- The treatment condition of interest is tusamitamab ravtansine.
- The analysis population is the all-treated population (defined in Section 9.1).
- 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 further anticancer therapy intercurrent event will be handled with the "while not initiating further anticancer therapy" strategy. Disease control response will be assessed based on tumor assessments done up to the initiation of further anticancer therapy.
- The population-level summary will be the 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 disease control response before the analysis cut-off date (taking into account the intercurrent event handling strategies), participants will be considered as non-responders, whatever the reason (including participants with non-evaluable BOR). As a supplementary analysis, DCR as per RECIST v1.1 will also be summarized on the activity population (defined in Section 9.1). The same analytical approach as described above will be used.

9.2.3.3 Duration of response

Analysis of the DOR will be based on an 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 documentation of objective PD according to RECIST v1.1 or death due to any cause, whichever occurs first.
- The treatment condition of interest is tusamitamab ravtansine.
- The analysis population is the subgroup of participants from the all-treated population (defined in Section 9.1) who achieved a confirmed objective response.
- 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 further anticancer therapy intercurrent event will be handled with the hypothetical strategy. DOR will be assessed based on tumor assessments had a further anticancer therapy not being taken. DOR will be assessed based on tumor assessments up to the time of initiation of further anticancer therapy,
- Two or more consecutive missing/unevaluable tumor assessments immediately before documented PD or death will be handled with the hypothetical strategy. DOR will be assessed based on tumor assessments had 2 consecutive tumor assessments not been missed immediately before documented PD or death. DOR will be assessed based on tumor assessments up to the last evaluable tumor assessment documenting no progression.

- The population-level summary will include the median DOR and associated 95% CI using Kaplan-Meier methods.

  In the absence of documented disease progression or death before the analysis cut-off date (taking into account the intercurrent event handling strategies), 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. In the absence of confirmed objective response before the analysis cut-off date (taking into account the intercurrent event handling strategies), DOR will not be derived.

9.2.4 Tertiary/exploratory endpoint(s) analyses

Analyses of PRO outcomes, circulating CEA and CEACAM5 expression will be described in the statistical analysis plan (SAP).

9.2.5 Safety analyses

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

9.2.5.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed worsened or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period.

Similarly, deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment 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 PT or a prespecified grouping), all treatment emergent SAEs and all TEAEs leading to permanent study intervention discontinuation.

The AE summaries will be generated with number (%) of participants experiencing at least 1 event.

Deaths will also be analyzed.

9.2.5.2 Laboratory variables, vital signs and electrocardiograms (ECGs)

Quantitative analyses

When relevant, for vital signs and ECG variables, descriptive statistics for results and changes from baseline will be provided for each planned visit and at 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 abnormality (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 version 5.0.

- 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.

9.2.6 Other analyses

Pharmacokinetic

The population PK analyses will be reported separately from the main clinical study report (CSR).

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.

Biomarkers

Other exploratory biomarkers analyses will be described in the SAP.

Other

For regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9.5): Contingency measures for a regional or national emergency that is declared by a governmental agency.

9.3 INTERIM ANALYSES

An interim analysis based on the number of confirmed objective responses observed in the activity population will be performed.

The study cut-off date for the interim analysis corresponds to the date on which the first 20 evaluable treated participants have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. For participants with 2 postbaseline tumor assessments and occurrence of response at the second postbaseline tumor assessment, the confirmatory assessment will also be included.

If 0 or 1 confirmed objective response is observed among the first 20 treated participants evaluable for anti-tumor activity, the enrollment will be stopped. Otherwise, the enrollment will continue with the 18 additional evaluable participants.

The statistical analysis plan will describe the planned interim analyses in greater detail.

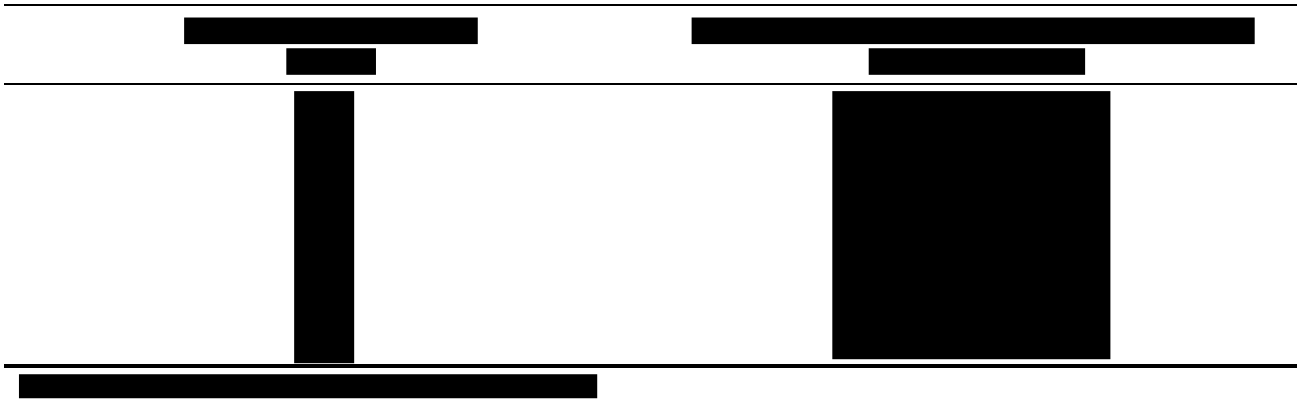
9.4 SAMPLE SIZE DETERMINATION

Assuming a pre-screening failure rate of 84% and a study screening failure rate of 15%, approximately 285 participants will be pre-screened to achieve approximately 38 treated participants in the study.

The initial plan is to treat a total of 38 participants evaluable for anti-tumor activity (at least 1 postbaseline tumor assessment, early clinical progression, or death due to disease progression).

Estimated ORR and 95% exact CIs by number of responders from a sample size of 38 evaluable participants for anti-tumor activity are listed in Table 8.

Table 8 - [redacted]



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, IB, [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 Code of Federal Regulations (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, including the risks and benefits, to the participants, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the GDPR and of the French law, 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).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, where applicable.

The participants who will be rescreened need to resign new screening ICF; there will be no re-pre-screening for CEACAM5 expression and the initial value will be applicable.

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): Contingency measures for a regional or national emergency that is declared by a governmental agency.

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. 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 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

Not applicable.

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 participants 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 "The European Federation of Pharmaceutical Industries and Associations (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 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 pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined 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, including definition of study critical data items and processes (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 reported on the CRF or 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.
- Every data point recorded in the CRF must have a source document. The Investigator/delegated site staff will report all the original data in the participant's medical chart or in a study specific source document created by him/her. If such document is used, the template should be reviewed by the clinical research associate (CRA). A list of source document and their location will be filed in the Investigator Study File.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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 is considered the first act of recruitment 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 9 will be performed by the local laboratory with the exception PK/Circulating CEACAM5, ATA, cfDNA/Germline DNA, and tumor DNA/RNA analysis and some additional circulating CEA, which will be performed in the central laboratory or another external 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 should be conducted in all WOCBP at Screening, then every 4 weeks from Cycle 2 before each IMP administration, and at the EOT, 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 and at the EOT evaluation (30 ±5 days after the last IMP administration).

Table 9 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils[a]
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Coagulation	International normalized ration (INR)
Clinical chemistry[b]	
	Urea or Blood urea nitrogen (BUN)
	Creatinine-eGFR (estimated glomerular filtration rate)
	Glucose
	Potassium
	Sodium
	Phosphate
	Chloride
	Calcium
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Lactate dehydrogenase (LDH)
	Alkaline phosphatase (ALP)
	Total and direct bilirubin
	Total protein
	Albumin
	Circulating carcinoembryonic antigen (CEA) (local assessment)
Pregnancy testing	• Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c]
Other screening tests	• Serology (Human immunodeficiency virus [HIV] antibody, hepatitis B surface antigen [HBsAg] or hepatitis B viral DNA, and hepatitis C virus antibody or Hepatitis C virus [HCV], RNA), and immunoglobulin G [IgG] if applicable as per local regulatory requirement

Laboratory tests	Parameters
	• Additional circulating carcinoembryonic antigen (CEA) and circulating CEACAM5 (central assessment) • Fresh biopsy as optional, for CEACAM5 expression status and DNA/RNA analysis (central assessment). • cfDNA/Germline DNA analysis on blood (central) • PK samples and anti-therapeutic antibody (ATA) (Central) • Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only).

NOTES:

a If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC ≥0.5 x 10^9/L.

b Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.2.6.6. All events of ≥ Grade 3 ALT/AST increase must be reported as an adverse event of special interest (AESI).

c Local urine testing will be standard for the protocol unless serum testing is required by local regulation or Institutional review board/Independent Ethics Committee. In addition, serum pregnancy test is mandatory for screening and end-of the treatment (EOT) evaluation

Investigators must document their review of each laboratory safety report.

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 nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a health care provider). The participants 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 the participant will be collected during an interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined 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 condition 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 an 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 that 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 untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

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) that 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,

- Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm,
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
  - Development of drug dependence or drug abuse,
  - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN,
  - Suicide attempt or any event suggestive of suicidality,
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
  - Bullous cutaneous eruptions.

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 one of the following categories according to NCI-CTCAE v5.0.

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An event is defined as "serious" when it meets at least 1 of the pre-defined 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. The Investigator will use clinical judgment to determine the relationship.
- 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.
- 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 monitoring 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 postmortem 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 offline 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 offline, 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 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 data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in 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).

10.5 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/RNA samples will be used for research related to tusamitamab ravtansine or non-squamous NSCLC and related diseases. They may also be used to develop tests/assays including diagnostic tests related to CEACAM5 targeting drug and NSQ NSCLC. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA/RNA samples will be analyzed for determination of tumor mutation profile on plasma cfDNA and tumor DNA/RNA. Subtractive mutation analysis will be performed with germline DNA data to identify tumor-specific somatic genetic aberrations.

- 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 will be retained while research on study intervention 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

Table 10 - Recommended Dose Modification or Discontinuation for SAR40870

Event	Symptoms severity (NCI-CTCAE v5.0)	Dose modification	Supportive care guidelines
Infusion-related reaction	Grade 1-2 eg, Grade ≤2 nausea, headache, tachycardia, hypotension, rash, shortness of breath.	Interrupt SAR408701 infusion. SAR408701 may be resumed only after participant recovery, at half the previous infusion rate[a].	Give diphenhydramine 50 mg IV and/or dexamethasone 10 mg IV. Dexamethasone can be added as premedication for upcoming cycles for SAR408701
	Grade 3-4 eg, symptomatic bronchospasm, urticaria lesions covering >30% BSA, hypotension, angioedema.	Interrupt SAR408701 infusion and definitively discontinue SAR408701.	Give diphenhydramine 50 mg IV and/or dexamethasone 10 mg IV and/or epinephrine and any required treatment per Investigator judgment.
Ocular toxicity: Keratopathy/keratitis[b] associated with SAR408701	Grade 1 Asymptomatic, Corneal lesions only observed on routine ocular examination and not requiring topical treatment.	Next infusion of SAR408701 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.

Event	Symptoms severity (NCI-CTCAE v5.0)	Dose modification	Supportive care guidelines
	Grade 2 Symptomatic, moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	1st episode: SAR408701 cycle delay until resolution to Grade 1 (asymptomatic) and restart SAR408701 at the same dose. 2nd episode: delay cycle until resolution to Grade 1 (asymptomatic) and SAR408701 dose reduction.	Standard ocular examination weekly until resolution[c]. Start curative treatment per ophthalmologist recommendation. After resuming study treatment, participant should be followed with standard ocular examination by every 2 cycles, even asymptomatic during next four cycles. If no recurrence, standard process with follow-up with ocular symptom is resumed. Management of study drug and follow-up process upon recurrence to be discussed according to Grade of the event at recurrence, clinical benefit from study drug and recommendation from the ophthalmologist.
	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 self-care ADL.	1st episode: SAR408701 cycle delay until resolution (asymptomatic) and restart SAR408701 with dose reduction. 2nd episode: definitive discontinuation of SAR408701.	
	Grade 4 Perforation, best corrected visual acuity of 20/200 or worse in the affected eye	Definitive discontinuation of SAR408701.	Complete the corneal examination as recommended by ophthalmologist. Repeat the standard ocular examination weekly[c] until resolution. Start curative treatment per ophthalmologist recommendation.
Conduction disorder associated with SAR408701	Grade 1 Mild symptoms	SAR408701 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	Definitive discontinuation of SAR408701.	ECG to be repeated twice weekly until event resolution. Prompt cardiology consultation Additional evaluations such as LVEF and Holter monitoring should be performed when relevant.
Neutrophil count decreased	Grade 1 <LLN-1500/mm^3 ; <LLN-1.5 × 10^9/L	No change in IMPs administration.	No intervention.

Event	Symptoms severity (NCI-CTCAE v5.0)	Dose modification	Supportive care guidelines
	Grade 2 <1500-1000/mm^3; <1.5-1.0 × 10^9/L	Delay the cycle until recovery of ANC >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. Restart the treatment when ANC >1500/mm^3 at the same dose. Prophylactic G-CSF can be considered in all subsequent cycles	Follow ASCO guidelines on usage G-CSF and antibiotherapy (20). Repeat the test every 3 days.
	Grade 4 >7 days <500/mm^3; <0.5 × 10^9/L	Delay the cycle until ANC >1500/mm^3. 1st episode: administer next cycle at the same dose and administer growth factors 2nd episode: administer SAR408701 at reduced dose 3rd episode: definitive discontinuation	Follow ASCO guidelines on usage G-CSF and antibiotherapy (20). Repeat the test every 3 days.
Febrile neutropenia	Grade 3 Absolute neutrophil count <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour	Delay cycle until ANC >1500/mm^3. 1st episode: administer next cycle at the same dose and administer G-CSF 2nd episode: administer SAR408701 at reduced dose 3rd episode: definitive discontinuation	To ensure relative dose intensity, G-CSF is recommended as secondary prophylaxis in all participants with Grade ≥3 febrile neutropenia ASCO guideline is recommended for supportive treatment if there are no defined clinical standards (20).
	Grade 4 Life-threatening consequences	Administration changes to be decided at the Investigator's discretion. 1st episode: administer next cycle at reduced dose and administer G-CSF or definitively discontinue 2nd episode: definitive discontinuation	
Hepatic enzyme increase	Grade 1-2	Administer SAR408701 as planned.	No intervention.
	Grade 3	Delay the cycle. Restart the treatment until recovery to Grade 1.	Additional liver function tests will be done every 2-3 days until recovery to baseline value.
	Grade 4	SAR408701 should be permanently discontinued.	Additional liver function tests will be done every 2-3 days until recovery to baseline value.
Peripheral neuropathy	Grade 1 Asymptomatic	No action	Participant who has ongoing grade 1 neuropathy has high risk of

Event	Symptoms severity (NCI-CTCAE v5.0)	Dose modification	Supportive care guidelines
	Grade 2 Moderate symptoms; limiting instrumental Activities of Daily Living	Delay cycle, dose reduction if no improvement with dose delay	worsening of his/her symptoms and should be closely followed.
	Grade 3 Severe symptoms; limiting self-care Activities of Daily Living	Definitive discontinuation	
	Grade 4 Life-threatening consequences; urgent	Definitive discontinuation	

ASCO = American Society of Clinical Oncology; BSA = Body surface area; ECG = Electrocardiogram; G-CSF = Granulocyte colony-stimulating factor; 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; and RBC = Red blood cell.

a SAR408701 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.

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 and in Section 5.5, Section 7.1.2, Section 8, Section 9.2.6, and Section 10.1.3 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 pre-screening/screening/enrollment/administration of study intervention may be temporarily delayed/halted (see Section 5.5).

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 pre-screening process

If there is no other way to conduct pre-screening 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 pre-screening ICF process compliant with country/site requirements for only those participants who have enough 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 pre-screening 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 pre-screening 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 obtain Circulating CEA value.

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 judgment 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 judgment, 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 direct 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 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.

10.9.6 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 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: CYP SUBSTRATES WITH NARROW THERAPEUTIC RANGE AND STRONG CYP3A INHIBITORS

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 Cytochrome (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.

Table 12 - List of strong CYP3A inhibitors

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

STRONG CYP3A INHIBITORS			
CYP3A inhibitors	**Precipitant Therapeutic Class**	**Victim (oral, unless otherwise specified)**	**AUC Ratio**
Potent CYP3A Inhibitors (yielding substrate AUC ratio >5)			
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 (Home Page: www.druginteractioninfo.org; https://didb.druginteractionsolutions.org/resources/list-of-substrates-inhibitors-and-inducers/?Oid=1130), updated in January 2021 and from FDA website (https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm) updated in June 2020.

10.12 APPENDIX 12: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1

Details provided in bibliographic reference (30).

10.12.1 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.

10.12.2 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 et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

10.13 APPENDIX 13: ABBREVIATIONS

ADC:	anti-body drug conjugate
ADL:	activities of dialy living
AE:	adverse event
AESI:	adverse event of special interest
ALK:	anaplastic lymphoma kinase
ALT:	alanine aminotransferase
ART:	antiretroviral therapy
AST:	aspartate aminotransferase
ATA:	anti-therapeutic antibodies
BOR:	best overall response
BSA:	body surface area
CEA:	carcinoembryonic antigen
CEACAM5:	carcinoembryonic antigen-related cell adhesion molecule 5
CI:	confidence interval
COVID-19:	coronavirus disease-2019
CR:	complete response
CSICF:	Core Study Informed Consent Form
CT:	computed tomography
CYP450:	cytochrome P450
DCR:	disease control rate
DOR:	duration of response
ECG:	electrocardiogram
eCOA:	electronic clinical outcome assessment
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form

eGFR:	estimated glomerular filtration rate
EGFR:	epidermal growth factor receptor
EOT:	end-of-treatment
FDG-PET:	fluorodeoxyglucose-positron emission tomography
FIH:	first in human
G-CSF:	Granulocyte colony stimulating factor
GDPR:	General Data Protection Regulations
HIV:	human immunodeficiency virus
HRT:	hormone replacement therapy
IB:	Investigator's Brochure
ICF:	informed consent form
ICH-GCP:	International Conference on Harmonisation- Good Clinical Practice
ICI:	immune checkpoint inhibitor
IEC:	Independent Ethics Committees
IHC:	immunohistochemistry
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IRR:	infusion-related rate
IRT:	interactive response technology
IV:	intravenous infusion
MRI:	magnetic resonance imaging
NCI-CTCAE:	National Cancer Institute- Common Terminology Criteria for Adverse Events
NE:	not evaluable
NIMP:	noninvestigational medicinal product
NSCLC-SAQ:	Non-Small-Cell Lung Cancer Symptom Assessment Questionnaire
NSQ NSCLC:	non-squamous non-small-cell lung cancer
NTR:	narrow therapeutic range
ORR:	objective response rate
PCSA:	potentially clinically significant abnormality
PD:	progressive disease
PD-1:	programmed death-1
PD-L1:	programmed death ligand-1
PFS:	progression-free survival
PGIC-LCS:	patient global impression of change-lung cancer symptom
PGIS-LCS:	patient global impression of severity-lung cancer symptom
PK:	pharmacokinetics
PR:	partial response
PRO:	patient-reported outcome
Q2W:	every 2 weeks
QTL:	quality tolerance limit
RBC:	red blood cells
RECIST:	Response Evaluation Criteria in Solid Tumours
ROS1:	ROS receptor tyrosine kinase 1
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	stable disease

SoA:	schedule of activities
SUSAR:	suspected unexpected serious adverse reaction
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
WBC:	white blood cells
WOCBP:	woman of childbearing potential

10.14 APPENDIX 14: PROTOCOL AMENDMENT HISTORY

Not applicable.

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