NCT05071053

STATISTICAL ANALYSIS PLAN

Protocol title:	**Open-label study of tusamitamab ravtansine (SAR408701) in combination with ramucirumab in participants previously treated for advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma with CEACAM5-positive tumors**
Protocol number:	**ACT16444**
Compound number (INN/Trademark):	**SAR408701** **tusamitamab ravtansine/Not applicable**
Study phase:	**Phase 2**
Short Title:	**Tusamitamab ravtansine (SAR408701) in combination with ramucirumab in pretreated participants with gastric cancer CARMEN-GC01**
Statistician:	[redacted]
Statistical project leader:	[redacted]
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VERSION HISTORY

This statistical analysis plan (SAP) for Study ACT16444 is based on the protocol dated 19-Apr-2021. The first participant was enrolled in the dose escalation part on 21-Nov-2021. This SAP is approved before the primary analysis of Objective Response Rate (ORR).

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	17-Jul-2023	Estimands attributes have been updated for efficacy endpoints.	Corrections to align with ICH E9 (R1) definitions.
		Definition of DLT-evaluable population (for Part 1) has been updated.	Clarification on the definition.

1 INTRODUCTION

1.1 STUDY DESIGN

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

The study will comprise 2 parts: Part 1 (Safety run-in) to assess the tolerability and to confirm the recommended dose (RD) of tusamitamab ravtansine in combination with ramucirumab; and Part 2, to assess the antitumor activity of tusamitamab ravtansine in combination with ramucirumab.

The screening phase will be performed only in prescreened participants determined to be CEACAM5-positive by immunohistochemistry (IHC) assessment.

Approximately 32 to 38 participants will be treated from approximately 21 sites to achieve a total of 32 participants treated at the RD and evaluable for activity.

The cycle duration is 14 days. The median expected duration of study per participant is estimated at 34 weeks (up to 4 weeks for screening, a median of 18 weeks for study intervention administration, a median of 12 weeks for end-of-treatment (EOT) assessments, and the safety follow-up visit).

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

This will be a 2-part study.

- Part 1 (safety run-in): participants will receive ramucirumab 8 mg/kg followed by tusamitamab ravtansine at 170 mg/m² at Day 1 Cycle 1, and ramucirumab 8 mg/kg followed by tusamitamab ravtansine 100 mg/m² at Cycle 2 Q2W in all subsequent cycles. In the case that it is decided to reduce the initial loading dose of tusamitamab ravtansine to Dose Level (DL)-1 (Table 1), a tusamitamab ravtansine loading dose of 150 mg/m² will be administered to participants at Day 1 of Cycle 1.

Table 1 - Dose levels in safety run-in part

Dose Level (DL)	Tusamitamab revtansine	Ramucirumab
Starting dose	170 mg/m² Q2W Cycle 1; 100 mg/m² Q2W Cycle 2 and thereafter	8 mg/kg Q2W
Minus -1 (DL-1)	150 mg/m² Q2W Cycle 1; 100 mg/m² Q2W Cycle 2 and thereafter	8 mg/kg Q2W

DL-1 = dose level -1; Q2W = every 2 weeks

- Part 2: Participants enrolled in the dose expansion part will receive SAR408701 at the RD determined at the end of the safety run-in (Part 1).

1.2 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

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

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

1.2.1 Estimands

The primary estimand defined for the primary efficacy endpoint is summarized in Table 3. More details are provided in Section 3.

Table 3 - Summary of primary estimand for primary efficacy endpoint

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary efficacy objective: To assess the antitumor activity of tusamitamab ravtansine loading dose Q2W in combination with ramucirumab in advanced gastric or GEJ adenocarcinoma				
Primary endpoint (primary estimand for Part 2)	Confirmed objective response (confirmed CR or PR as BOR) as per RECIST 1.1	All-treated population at the recommended tusamitamab ravtansine loading dose	Regardless of IMP discontinuation (treatment policy strategy) "While not initiating further systemic anticancer therapy" strategy)	ORR, defined as the rate of participants with confirmed objective response, and 2-sided 95% confidence interval (CI) using the Clopper-Pearson method. In the absence of confirmed objective response, participants will be considered as nonresponders, whatever the reason (including participants with nonevaluable BOR).

2 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 4 - Populations for analyses

Population	Description
Prescreened	All participants who signed the prescreening informed consent for CEACAM5 assessment of their biopsy.
Screened	All participants who signed the screening informed consent for study participation.
Enrolled	Participants from screened population who have been allocated to intervention regardless of whether the intervention was received or not.
All-treated	All enrolled participants exposed to the study treatment, regardless of the amount of treatment administered. All safety analyses will be performed on this population, which is also the primary population for analysis of all efficacy parameters.
DLT-evaluable (Part 1)	All enrolled participants who received 2 cycles with at least 80% of the intended dose for both tusamitamab ravtansine and ramucirumab at each of the first 2 infusions. Any participant who experienced a DLT during that period will also be DLT-evaluable.
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.
Pharmacokinetic (PK)	All participants from the all-treated population with at least 1 postbaseline PK concentration (whatever the cycle and even if dosing is incomplete) with adequate documentation of dosing and sampling dates and times.
ATA	All participants from the all-treated population with at least 1 postbaseline ATA result (negative, positive, or inconclusive).
Population without trial impact (disruption) due to COVID-19	All treated participants: • without any critical or major deviation related to COVID-19 • and who did not permanently discontinue treatment due to COVID-19 • and who did not permanently discontinue study due to COVID-19.

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 “Yes” in the “Completion of screening phase” e-CRF page.

In practice, a participant will be included in the DLT-evaluable population (applicable to Part 1 only) if a “Dose Limiting Toxicities” e-CRF page has been filled in at the end of Cycle 1 and at the end of Cycle 2 (or Cycle 1 only if participant did not receive Cycle 2 because of a DLT). This includes any participant followed up to the end of the DLT observation period, or having experienced a DLT before the end of the DLT observation period and validated by the Study Committee. A participant with an overdose (defined as a dose received at least 30% above the intended dose) of tusamitamab ravtansine or ramucirumab at any of the 2 first infusions will be excluded from the DLT-evaluable population.

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.

In practice, participants whose BOR is nonevaluable due to minimum criteria for SD duration not met (ie, overall response of SD and the minimum duration, defined as 0.75 x duration between the first IMP intake and the first planned tumor assessment is not met) and there is no subsequent evaluable tumor assessment, or documented PD after two or more non-evaluable tumor assessments (ie, overall response of PD and the time between the date of first IMP intake and the documentation of PD is greater than the theoretical planned date of the second tumor assessment) will be considered as not evaluable for the activity population.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

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

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

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

The baseline value is defined as the last available value before the first dose IMP.

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

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

Observation period

The observation period will be divided into 4 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration.
- The **on-treatment period** (ie, treatment-emergent (TE) period) is defined as the period from the first IMP administration to the last IMP administration +30 days.
- The **post-treatment period** is defined as the period from the end of the on-treatment period.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

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

3.2.1 Definition of endpoint(s)

3.2.1.1 Study-drug related DLT at Cycle 1 and Cycle 2

The primary safety endpoint is study-drug related DLTs during the DLT observation period (ie, from Cycle 1 Day 1 to Cycle 2 Day 14). The list of DLTs to be considered for the study is defined in Table 6 of the protocol. For analysis purposes, DLTs will be identified based on the Adverse Events (AEs) reported on the e-CRF DLT page during observation period in Part 1. Statistical analysis for DLTs is described in Section 3.6.2.

3.2.1.2 Confirmed objective response

The primary efficacy endpoint is confirmed objective response determined according to RECIST 1.1. A confirmed objective response is defined as a confirmed CR or PR as BOR.

The BOR will be derived according to RECIST 1.1 definitions (1, 2) 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.

3.2.2 Main analytical approach

3.2.2.1 Confirmed objective response

The primary efficacy analysis is based on the primary estimand for part 2 introduced in Section 1.2.1. This primary estimand is defined according to the following attributes:

- The primary efficacy endpoint is confirmed objective response (confirmed CR or PR as BOR) as per RECIST 1.1. based on the investigator's assessment as defined in Section 3.2.1.2.
- The treatment condition of interest is tusamitamab ravtansine loading dose Q2W in combination with ramucirumab.
- The analysis population is the participants from all-treated population (defined in Section 2) treated at the RD of tusamitamab ravtansine loading dose Q2W regimen (ie, excluding participants treated at the starting dose, if this differs from the RD).
- 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 (including further systemic anticancer therapies) 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 2-sided 95% CIs 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 missing or non-evaluable BOR).

3.2.3 Sensitivity analysis

No sensitivity analysis is planned in this study.

3.2.4 Supplementary analyses

Number (%) of participants within each BOR category, including not evaluable as per RECIST 1.1 and reason for being not evaluable will be provided on the subgroup of participants from the all-treated population treated at the RD (ie, excluding participants treated at the starting dose if this differs from the RD).

As a supplementary analysis, confirmed objective response as per RECIST 1.1 will also be summarized on the subgroup of participants from activity population (defined in Section 2) treated at the RD for tusamitamab ravtansine in a loading-dose Q2W regimen (ie, excluding participants treated at the starting dose if this differs from the RD). The same analytical approach as described above will be used.

In addition, the best relative tumor change from baseline, defined as the smallest relative tumor change from baseline (where tumor change at time t is the difference between sum of the longest diameters of the target lesions at time t and baseline, resulting in a negative value in case of decrease), will be summarized using a waterfall plot on the participants on the all-treated population treated at the RD (ie, excluding participants treated at the starting dose if this differs from the RD). A swimmer plot will also be provided reporting the duration of treatment for all participants with their overall response and some baseline characteristics. This plot will differentiate responders from non-responders. In addition, a spider plot will also be provided reporting the tumor change from baseline over the time.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are the duration of response, the progression-free survival and the disease control rate. Other secondary endpoints analyses are defined in Section 3.6.2 (AE, SAE), Section 3.6.3.1 (laboratory abnormalities), Section 3.7.1.1 (PK) and Section 3.7.1.2 (immunogenicity).

3.3.1 Key/Confirmatory secondary endpoint(s)

No key/confirmatory endpoint is defined.

3.3.2 Supportive secondary endpoint(s)

3.3.2.1 Definition of endpoints

3.3.2.1.1 Duration of response

DOR is 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 progressive disease according to RECIST 1.1 (1, 2) or death due to any cause, whichever occurs first.

3.3.2.1.2 Progression-free survival

PFS is defined as the time from the date of the first administration of IMP to the date of the first documentation of objective progressive disease according to RECIST 1.1 (1, 2) or death due to any cause, whichever occurs first.

3.3.2.1.3 Disease control rate

The DCR is estimated by dividing the number of participants with confirmed objective response or SD (CR or PR or SD as BOR), determined according to RECIST 1.1, by the number of participants from the analysis population.

3.3.2.2 Main analytical approach

3.3.2.2.1 Duration of response

DOR analysis is based on an estimand defined according to the following attributes:

- The endpoint is duration of response as defined in Section 3.3.2.1.
- The treatment condition of interest is tusamitamab ravtansine loading dose Q2W in combination with ramucirumab.
- The analysis population is the participants from the all-treated population (defined in Section 2) treated at the RD of tusamitamab ravtansine in a loading-dose Q2W regimen (ie, excluding participants treated at the starting dose if this differs from the RD) limited to participants who achieved a confirmed objective response.
- Intercurrent events:
  - The study intervention discontinuation 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 (including further systemic anticancer therapies) intercurrent event will be handled with the hypothetical strategy. DOR will be assessed based on tumor assessments had a further anticancer therapy not been 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 from 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.

3.3.2.2.2 Progression-free survival

PFS analysis is based on an estimand defined according to the following attributes:

- The endpoint is progression-free survival.
- The treatment condition of interest is tusamitamab ravtansine loading dose Q2W in combination with ramucirumab.
- The analysis population is the participants from the all-treated population (defined in Section 2) treated at the RD of tusamitamab ravtansine in a loading-dose Q2W regimen (ie, excluding participants treated at the starting dose if this differs from the RD).
- Intercurrent events:
  - The study intervention discontinuation 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 (including further systemic anticancer therapies) intercurrent event will be handled with the hypothetical strategy. PFS will be assessed based on tumor assessments had a further anticancer therapy not been 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 25^{th}, 50^{th}, and 75^{th} percentiles and their associated 95% CIs using a log-log transformation of the survival function and the method of Brookmeyer and Crowley.

- Number (%) of participants at risk as well as the probabilities of being event-free at least at 3, 6, 9, and 12 months with 95% CIs using the Kaplan-Meier method and a log-log approach based on a normal approximation following the Greenwood's formula.
- Kaplan-Meier curve 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 post-baseline tumor assessments, alive without documented disease progression, event occurred after two 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 PFS event (documented disease progression or death) and no baseline tumor assessment or no evaluable postbaseline tumor assessment has been done.

3.3.2.2.3 Disease control rate

DCR analysis is 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 1.1.
- The treatment condition of interest is tusamitamab ravtansine loading dose Q2W in combination with ramucirumab.
- The analysis population is the participants from all-treated population (defined in Section 2) treated at the RD of tusamitamab ravtansine loading-dose Q2W regimen (ie, excluding participants treated at the starting dose if this differs from the RD).
- Intercurrent events:
  - The study intervention discontinuation 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 (defined as all further systemic anti-cancer therapies) 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 include the disease control rate, defined as the rate of participants with disease control response and 2-sided 95% CIs using the Clopper-Pearson method.

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

Disease control rate will also be summarized on the activity population as a supplementary analysis.

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

Analyses of tertiary/exploratory endpoints (eg, biomarkers) are defined in Section 3.7.1.3.

3.5 MULTIPLICITY ISSUES

No multiplicity issues are handled in this study.

3.6 OTHER SAFETY ANALYSES

All safety analyses will be performed on the all-treated population as defined in Section 2, by dose level (if applicable) and overall, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the all-treated population (eg, treated but not enrolled) will be provided.

3.6.1 Extent of exposure

3.6.1.1 Overall exposure

The dose information will be assessed by the following variables:

- Overall number of cycles started, defined by the number of cycles in which at least one dose of any study interventions is administered.
- Duration of overall exposure (in weeks) is defined as (Last day of exposure – first day of exposure +1)/7.
  - The first day of exposure is defined as the first administration date with non-zero dose for at least one of the IMP (tusamitamab ravtansine or ramucirumab).
  - The last day of exposure is the day before the theoretical date of the next administration (after the last administration), defined as the last administration date of at least one IMP + 14 days – 1 (tusamitamab ravtansine and ramucirumab).

The total number of cycles started, and the number of cycles started by participants will be summarized as a quantitative variable and by category (number (%) of participants receiving at least 1 cycle, at least 2 cycles, etc). The duration of overall exposure will be summarized quantitatively.

The following variable will be computed to describe overall dose modification (cycle delay):

- Cycle delay: A cycle is deemed as delayed if the start date of the current cycle – 14 days – start date of the previous cycle is >2 days. Cycle delay is not defined for the first cycle.

Cycle delay will be analyzed at the participant (with number of participants used as denominator) and cycle (with number of cycles used as denominator) levels, as follows:

- Number (%) of participants with a least 1 cycle delayed
  - Number (%) of participants with a cycle delayed between 3 and 7 days (using maximum delay across all cycles)
  - Number (%) of participants with a cycle delayed between 8 and 14 days (using maximum delay across all cycles)
  - Number (%) of participants with a cycle delayed >14 days (using maximum delay across all cycles)
- Number (%) of cycles delayed
  - Number (%) of cycles delayed between 3 and 7 days
  - Number (%) of cycles delayed between 8 and 14 days
  - Number (%) of cycles delayed >14 days

3.6.1.2 Tusamitamab ravtansine exposure

The dose information will be assessed by the following:

- Total number of cycles started
- Number of cycles started per participant.
- Duration of tusamitamab ravtansine exposure (in weeks) is defined by date of last administration of tusamitamab ravtansine + number of theoretical days until the next administration – date of first administration of tusamitamab ravtansine/7.
- Actual dose (in mg/m²). In case of dose interruption, actual dose will be the sum of the actual doses administered before and after the dose interruption.
- Cumulative dose (mg/m²): the cumulative dose is the sum of all actual doses of tusamitamab ravtansine, given from first to last administration.
- Actual dose intensity (ADI in mg/m²/week): defined as the cumulative dose divided by the duration of tusamitamab ravtansine exposure (in weeks).

- Planned dose intensity (PDI in mg/m²/week): corresponds to the planned dose at C1D1 + planned dose at subsequent cycles multiplied by the theoretical total number of doses started and divided by the theoretical cycle duration expressed in weeks (ie, 2 weeks per cycle started). Note: Theoretical total number of doses started is derived based on cycles where at least one IMP is administered (even in case of dose omission), up to the end of treatment of tusamitamab ravtansine.
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/m}^2\text{/week)}}{\text{PDI (mg/m}^2\text{/week)}}$.

The total number of cycles started and the number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc). Duration of tusamitamab ravtansine exposure, cumulative dose, ADI and RDI will be summarized quantitatively.

The following variables will be derived to describe dose modifications and dose interruptions:

- Dose reduction: The first administration (loading dose) and second administration (first 100 mg/m² infusion) will not be counted as a dose reduction. For the third and subsequent tusamitamab ravtansine administrations, dose reduction will be determined using the dose level intervals provided in Table 5, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

Table 5 - Tusamitamab ravtansine dose reduction criteria

Actual dose level	Dose level interval
Starting dose (100 mg/m²)	>90 mg/m²
Dose level -1 (80 mg/m²)	>72.5 mg/m² and ≤90 mg/m²
Low dose	>0 mg/m² and ≤72.5 mg/m²

- Dose delay: A dose will be considered as delayed if the tusamitamab ravtansine administration date of the current cycle – 14 days – tusamitamab ravtansine administration date of the previous cycle is >2 days. Dose delay is not defined for the first cycle.
- Dose omission is defined as a dose not administered at the scheduled visit but administered afterwards.
- Dose interruption: A dose will be considered as interrupted if the tusamitamab ravtansine administration is stopped during an infusion regardless of whether it is restarted or not.

Dose modifications and dose interruptions will be analyzed by participant and cycle as follows:

- **Participant** (number of participants treated will be used as denominator)
  - Number (%) of participants with at least 1 dose modification
    - Number (%) of participants with at least 1 dose delayed
    - Number (%) of participants with at least 1 dose reduction
    - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with a least 1 dose interruption

- **Cycle** (number of cycles started will be used as denominator)
  - Number (%) of cycles with at least 1 dose modification
    - Number (%) of cycles with at least 1 cycle delayed
    - Number (%) of cycles with at least 1 dose reduction
    - Number (%) of cycles with at least 1 dose omission
  - Number (%) of cycles with at least 1 dose interruption

3.6.1.3 Ramucirumab exposure

The dose information will be assessed by the following:

- Total number of cycles started.
- Number of cycles started per participant.
- Duration of ramucirumab exposure (in weeks) is defined by date of last administration of ramucirumab + number of theoretical days until the next administration – date of first administration of ramucirumab/7.
- Actual dose (in mg/kg). In case of dose interruption, actual dose will be the sum of the actual doses administered before and after the dose interruption.
- Cumulative dose (mg/kg): the cumulative dose is the sum of all actual doses of ramucirumab, given from first to last administration.
- Actual dose intensity (ADI in mg/kg/week): defined as the cumulative dose divided by the duration of ramucirumab exposure (in weeks).
- Planned dose intensity (PDI in mg/kg/week): corresponds to the planned dose multiplied by the theoretical total number of doses started and divided by the theoretical cycle duration expressed in weeks (ie, 2 weeks per cycle started). Note: Theoretical total number of doses started is derived based on cycles where at least one IMP is administered (even in case of dose omission), up to the end of treatment of ramucirumab.
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/kg/week)}}{\text{PDI (mg/kg/week)}}$.

The total number of cycles started, number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc). Duration of ramucirumab exposure, cumulative dose, ADI and RDI will be summarized quantitatively.

The following variables will be derived to describe dose modifications and dose interruptions:

- Dose reduction: The first administration will not be counted as a dose reduction. For the second and subsequent ramucirumab administrations, dose reduction will be determined using the dose level intervals provided in Table 6, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

Table 6 - Ramucirumab dose reduction criteria

Actual dose level	Dose level interval
Starting dose (8 mg/kg)	>7 mg/kg
Dose level -1 (6 mg/kg)	>5.5 mg/kg and ≤7 mg/kg
Dose level -2 (5 mg/kg)	> 4 mg/kg and ≤5.5 mg/kg
Low dose	>0 mg/kg and ≤4 mg/kg

- Dose delay: A dose will be considered as delayed if the ramucirumab administration date of the current cycle – 14 days – ramucirumab administration date of the previous cycle is >2 days. Dose delay is not defined for the first cycle.
- Dose omission is defined as a dose not administered at the scheduled visit but administered afterwards.
- Dose interruption: A dose will be considered as interrupted if the ramucirumab administration is stopped during an infusion regardless of whether it is restarted or not.

Dose modifications and dose interruptions will be analyzed by participant and cycle as follows:

- **Participant** (number of participants treated will be used as denominator)
  - Number (%) of participants with at least 1 dose modification
    - Number (%) of participants with at least 1 dose delayed
    - Number (%) of participants with at least 1 dose reduction
    - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with a least 1 dose interruption
- **Cycle** (number of cycles started will be used as denominator)
  - Number (%) of cycles with at least 1 dose modification
    - Number (%) of cycles with at least 1 cycle delayed
    - Number (%) of cycles with at least 1 dose reduction
    - Number (%) of cycles with at least 1 dose omission
  - Number (%) of cycles with at least 1 dose interruption

3.6.2 Adverse events

General common rules for adverse events

All AEs will be graded according to NCI-CTCAE Version 5.0 and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

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, the deaths will be analyzed in the pre-treatment, treatment-emergent, and post-treatment periods.

The primary AE analyses will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. A missing grade will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase, using the maximum (worst) grade by treatment phase. 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.

The AE tables will be sorted as indicated in Table 7.

Table 7 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT, and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs, and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the SAR408701 overall incidence
b The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any Grade ≥3 TEAE
- Grade 5 TEAE (any TEAE with a fatal outcome during the treatment-emergent period)

- Any treatment-emergent SAE
- Any treatment-emergent adverse event of special interest (AESI)
- Any TEAE leading to permanent full study intervention discontinuation
- Any TEAE leading to permanent partial discontinuation of tusamitamab ravtansine
- Any TEAE leading to permanent partial discontinuation of ramucirumab
- Any TEAE related to IMP
- Any Grade ≥3 TEAE related to IMP
- Any serious TEAE related to IMP
- Any treatment-emergent corneal event (CMQ "Corneal events compound level")
- Any treatment-emergent peripheral neuropathy event TEAE (SMQ "Peripheral neuropathy" [Narrow and Broad])
- Any ocular/visual symptoms TEAE (CMQ "Eye disorders exclude corneal disorders")

The AE summaries of Table 8 will be generated with number (%) of participants experiencing at least 1 event. The analyses will be performed for all grades combined and for Grade ≥3.

Table 8 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HLGT, HLT and PT
	Primary SOC and PT
	PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE related to tusamitamab ravtansine as per Investigator's judgment	Primary SOC and PT
TEAE related to ramucirumab as per Investigator's judgment	Primary SOC and PT
Treatment-emergent SAE	Primary SOC, HLGT, HLT and PT
	Primary SOC and PT
Treatment-emergent SAE related to IMP as per Investigator's judgment	Primary SOC and PT
Treatment-emergent SAE related to tusamitamab ravtansine as per Investigator's judgment	Primary SOC and PT
Treatment-emergent SAE related to ramucirumab as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent full study intervention discontinuation	Primary SOC and PT
TEAE leading to permanent partial discontinuation of tusamitamab ravtansine	Primary SOC and PT
TEAE leading to permanent partial discontinuation of ramucirumab	Primary SOC and PT

Type of AE	MedDRA levels
TEAE leading to death[b]	Primary SOC and PT
TEAE related to tusamitamab ravtansine and leading to death[b]	Primary SOC and PT
TEAE related to ramucirumab and leading to death[b]	
AE leading to death[b]	
- In context of disease progression[c]	
- In context other than disease progression[d]	
Pretreatment AE	Overview[a]
	Primary SOC and PT
Pre-treatment SAE	Primary SOC and PT
Post-treatment AE	Overview[a]
	Primary SOC and PT
Post-treatment SAE	Primary SOC and PT
TEAE leading to dose modification of tusamitamab ravtansine (including dose delay, dose reduction and dose omission)	Primary SOC and PT
TEAE leading to dose modification of ramucirumab (including dose delay, dose reduction and dose omission)	Primary SOC and PT
TEAE leading to dose interruption of tusamitamab ravtansine	Primary SOC and PT
TEAE leading to dose interruption of ramucirumab	Primary SOC and PT

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent full study intervention discontinuation (except for pretreatment)
b Death as an outcome of the AE as reported by the Investigator in the AE page
c Death within 30 days from last IMP administration and the cause of death is disease progression
d Death within 30 days from last IMP administration and for whom cause of death is not disease progression or the death occurred more than 30 days from last IMP administration and the cause of death is AE

Analysis of deaths

In addition to the analyses of deaths included in Table 8 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods by study period and reason for death
- An overview of Grade 5 AEs will be provided with the following categories:
  - Grade 5 AE (TEAE and post-treatment).
  - Fatal TEAE (regardless of date of death/period).
    - Grade 5 TEAE with a fatal outcome during the treatment period,
    - Any Grade TEAE with a fatal outcome during the posttreatment period.
  - Post-treatment Grade 5 AE (excluding a TEAE that worsened to Grade 5 during the post-treatment period).
- Deaths in non-enrolled participants or enrolled but not treated participants.

Analysis of adverse events of special interest (AESIs) and other AEs of interest

AESIs and other AEs of interest will be selected for analyses as indicated in Table 9. Number (%) of participants experiencing at least 1 TEAE will be provided overall for AESIs, and for each other event of interest, by SOC and PT (if applicable). DLT observed during the DLT observation period will be listed in the DLT-evaluable population. Tables will be sorted as indicated in Table 7.

Table 9 - Selections for AESIs and other AEs of interest

AESIs and other AEs of interest	Selection
AESIs	
Grade ≥3 keratopathy	e-CRF AESI specific tick box on the AE page. It could include Grade ≥3 events with PTs from CMQ of corneal events
Bundle branch blocks or any conduction defect	e-CRF AESI specific tick box on the AE page. It could include events with PTs from SMQ "Conduction defects" (Narrow)
Grade ≥3 liver enzyme increased (symptomatic or asymptomatic)	e-CRF AESI specific tick box on the AE page. It could include Grade ≥3 PTs from the SMQ "Hepatic disorders" (Narrow and Broad)
Symptomatic overdose (serious or nonserious) with IMP/NIMP	e-CRF symptomatic overdose specific tick box on the Overdose page.
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/NIMP	e-CRF specific tick box for AE linked to pregnancy on the Pregnancy page.
DLT during DLT observation period	e-CRF specific DLT page
Other AEs of interest	
Any AE meeting DLT criteria beyond DLT observation period	AEs reported on the e-CRF specific DLT page outside the DLT observation period
Corneal events (reported as AEs)	CMQ "Corneal events compound level" containing the PTs included in both SOC "Eye disorders" and SMQ "Corneal disorders" (Narrow)
Ocular/visual adverse events (excluding corneal disorders)	CMQ "Eye disorders exclude corneal disorders" containing the PTs included in SOC "Eyes disorders" and excluding PTs in SMQ "Corneal disorders" (Narrow)
Cardiac conduction defects	SMQ "Conduction defects" (Narrow)
Peripheral neuropathy events	SMQ "Peripheral neuropathy" (Narrow and Broad)
Colitis events (excluding infective)	CMQ "Colitis (excluding infective)" containing PTs included in HLT "Colitis (excl infective)")
Hypersensitivity events	SMQ "Hypersensitivity" (Narrow) and adverse event occurring on the day or the day after the infusion
Hepatic disorders adverse events	SMQ "Hepatic disorders" (Narrow and Broad)
Hematological adverse events	SMQ "Haematopoietic cytopenias" (Narrow and Broad)
AE related to COVID-19 illness	SMQ "COVID-19" (Narrow)

An overview of corneal TEAEs will be provided with the following AE categories: any corneal TEAEs, Grade ≥3 corneal TEAEs, treatment-emergent corneal SAEs, corneal TEAEs related to IMP, Grade ≥3 corneal TEAEs related to IMP, corneal TEAEs leading to permanent full intervention discontinuation, corneal TEAEs leading to permanent partial discontinuation of tusamitamab ravtansine, and corneal TEAEs leading to dose modification (cycle delay, dose reduction, or dose omission) of tusamitamab ravtansine.

A summary of treatment-emergent corneal events will be provided.

- Cycle of first occurrence regardless of the grade
- Cycle of first occurrence of the worst grade
- Number (%) of participants by worst grade
- Relationship to study intervention: in case of multiple occurrences in a single participant with different relationships, if any event is related, then the relationship will be considered as related for that participant
- Action taken with the study intervention: in case of multiple occurrences with different actions in a single participant, the most severe action taken will be tabulated and selected according to the following order of severity: drug withdrawn, dose reduced, drug interrupted, dose not changed
- Outcome: in case of multiple occurrences with different outcomes in a single participant, the most severe outcome will be tabulated and selected according to the following order of severity: fatal, not recovered or resolved, recovering and resolving, recovered and resolved with sequelae, recovered and resolved, unknown.

In addition, analyses on occurrence and recurrence of corneal events will be provided.
An occurrence of a corneal event will be defined as 1 or a group of concomitant corneal events.
A recurrence will be defined as any occurrence of corneal event starting after a previously resolved occurrence.

- The number of occurrences by participant
- The time to first onset of corneal event will be described using Kaplan-Meier curves. Time to first onset is defined as the time from the date of first IMP administration to the date of the first occurrence of the event. In the absence of an event before the analysis cut-off date, it will be censored at the end date of the treatment-emergent period, analysis cut-off date, or date of death, whichever occurs first.
- The time to recovery will be summarized using descriptive statistics in participants who have had at least 1 recovered or resolved occurrence of a corneal event (with or without sequelae), considering the longest duration among all occurrence by participant.
- The time to recurrence will be summarized using descriptive statistics in participants who have had at least one recurrence, considering the shortest time among all recurrences by participant.

Beside the AE categorized as ocular/visual adverse events, all ocular symptoms (coded term) recorded in e-CRF will be reported as descriptive analysis. Same descriptive analysis will be done separately for ocular/visual symptoms associated to treatment-emergent corneal events (CMQ).

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units.

- Hematology and coagulation:
  - Red blood cells, platelets and coagulation: hemoglobin, hematocrit, red blood cell count, platelet count, prothrombin time (expressed as international normalized ratio [INR]) and activated partial thromboplastin time (aPTT).
  - White blood cells: white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, basophils, eosinophils.
- Clinical chemistry:
  - Metabolism: glucose, total protein and albumin.
  - Electrolytes: sodium, potassium, phosphate and corrected calcium. Corrected calcium (mmol/L) will be derived using the following formula: measured total calcium (mmol/L) + 0.8 x 0.25 × (4.0 – [serum albumin (g/L) × 0.1]), where 4.0 represents the average albumin level.
  - Renal function: creatinine, blood urea nitrogen (BUN), urea, estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease (MDRD method.
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total and direct bilirubin.
- Urinalysis:
  - Urinalysis dipstick: proteins, red blood cell count, white blood cell count, glucose, pH.
  - Urinalysis: protein assessed on 24 hour urine collection.
- Vital signs: temperature, pulse rate, systolic and diastolic blood pressure, weight and Eastern Cooperative Oncology Group (ECOG) Performance status (PS).
- ECG variables: heart rate, PR, QRS, QT, and corrected QTc (according to Fridericia).

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification will be replaced by ULOQ value.

For hematological parameters and biochemistry parameters, local normal ranges (LLN, ULN) will be used for grading.

Quantitative analyses

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

For QRS and QTc variables, blood pressure and heart rate, mean changes from baseline with the corresponding standard error will be plotted over time.

Analyses according to potentially clinically significant abnormalities (PCSA) and NCI grading

For laboratory variables, analyses according to NCI grading will be made based on NCI-CTCAE Version 5.0. In addition, for laboratory variables for which an 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 on-treatment period, using all measurements (either local or central, either scheduled, nonscheduled, or repeated).

QTcF prolongation will be graded according to NCI-CTCAE Version 5.0. The frequency of participants in each grade of QTcF prolongation during the on-treatment period will be summarized. For participants with multiple occurrences of QTcF prolongation during the treatment, the maximum grade per participant will be used.

For laboratory variables, vital signs and ECG variables above, the incidence of participants with at least 1 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

The number (%) of participants with QTcF abnormality worsening during the on-treatment period (worst value per participant) according to baseline value will be displayed.

For laboratory variables graded by NCI-CTCAE,

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

For laboratory variables not graded by NCI-CTCAE nor by PCSA, the number (%) of participants with laboratory tests outside normal ranges will be provided.

For ECOG PS, the number (%) of participants in each grade (considering the worst grade during the TE period) will be provided according to baseline.

Additional analyses for drug-induced liver injury

The following additional analyses will be performed for drug-induced liver injury:

- For each liver function test (eg, ALT), participants having experienced a PCSA will be summarized considering worst on-treatment value.
- An e-DISH-like plot of peak bilirubin/ULN versus peak alanine aminotransferase or aspartate aminotransferase (worst value)/ULN will be provided. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 ULN for ALT/AST and a horizontal line corresponding to 2 ULN for total bilirubin.
- For each liver function test (eg, ALT), participants having experienced a PCSA (eg, ALT >5 x ULN) will be summarized using the following categories: Returned to baseline PCSA status (or returned to value ≤ULN in case of missing baseline) before last IMP dose, Returned to baseline PCSA status after last IMP dose, Never returned to baseline PCSA status, No assessment after elevation. This summary will be performed by categories of elevation (ALT >3, >5, >10, >20 x ULN).

3.6.3.2 Ophthalmological examinations

Schirmer test

Participants reported Schirmer's test will be classified into 3 classes at baseline: normal (≥10 mm), moderate (<10 and >5 mm), severe (≤5 mm) (3). The worst classification between the laterality will be considered. A frequency table of the baseline status with and without anaesthetics will be provided for the participants with corneal events (CMQ) during the treatment-emergent period and for the participants without an event.

Visual acuity test

Analyses are done on the best corrected visual acuity (BCVA) assessed using Snellen Chart method.

Frequency tables on BCVA measured during the on-treatment period will be performed separately on all participants and on participants who experienced at least one treatment-emergent corneal event:

- On the worst change from baseline: No worsening versus baseline (no line decrease), Worsening versus baseline (1 to 3 lines decrease versus baseline, or >3 lines decrease versus baseline).
- On the worst absolute value: No change versus baseline, Worsening versus baseline (BCVA equals to 20/40 or better, BCVA worse than 20/40 up to 20/200, BCVA 20/200 or worse).
- On the CTCAE worst vision decrease: BCVA equals to 20/40 or better or 1 to 3 lines decrease versus baseline, BCVA worse than 20/40 up to 20/200 or >3 lines decrease versus baseline, BCVA 20/200 or worse.

- For participants who had worsening versus baseline (at least one line decrease) on BCVA, the worst outcome on the last BCVA will be displayed: Recovered to baseline, Not recovered to baseline, Lost to follow-up or dead with ongoing corneal events.

A participant will be considered as lost to follow-up if the participant discontinued the study and did not perform any follow-up visit.

A shift table of the category of the last BCVA value (Normal (20/20 or better), worse than 20/20 up to 20/40, worse than 20/40 up to 20/200 or 20/200 or worse) versus the category of the worst BCVA value (20/40 or better, worse than 20/40 up to 20/200, 20/200 or worse) will be performed for participants who experienced at least one treatment-emergent corneal event.

For the summary table on participants who experienced at least one treatment-emergent corneal event, the worst value and the worst change from baseline are measured during any of the treatment-emergent corneal events experienced by the participant (between start date and end date of the corneal events). For summary table on all participants, all on-treatment BCVA values are considered.

The worst classification between the laterality will be considered for the worst absolute value, the worst change from baseline and the last value separately even if not measured on the same eye. If the worst absolute value is the same for both eyes, then the eye with the worst change from baseline is considered, and if identical, then the eye with the worst last value is considered.

Participants whose baseline visual acuity had been reported in naked eye instead of BCVA (ie, whenever the baseline value was worse than the values reported during the treatment period/treatment-emergent corneal event) will be excluded from this analysis.

Slit lamp examination

Descriptive statistics of slit lamp examination will be provided separately at baseline and at the time of first abnormal slit lamp after occurrence of a treatment-emergent corneal event, and at the time of the worst BCVA value during a treatment-emergent corneal event for participants experiencing treatment-emergent corneal events (CMQ). The outcome (normal, abnormal), and for abnormal findings, the type of lesions and the distribution will be described by laterality (unilateral, bilateral, all).

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

All concentration values below the LLOQ will be treated as zero in individual listing and respective descriptive statistics. Geometric mean will not be computed in case at least one concentration is below LLOQ.

Individual observed predose concentrations (C_{trough}) and concentrations observed at end of infusion (C_{eoi}, C_{eoi+1h} if any) of tusamitamab ravtansine and ramucirumab will be listed and summarized with standard descriptive statistics (such as the number of observations, arithmetic and geometric means, median, standard deviation, coefficient of variation, minimum, and maximum) by visit and by dose level (if applicable).

For the descriptive statistics, C_{trough} following any dose modification (delay or reduction as defined in Section 3.6.1.2) will be excluded. C_{eoi} and C_{eoi+1h} will be excluded following dose reduction.

A graphical representation of mean C_{trough} (±SD) profile over time, by drug in separate figure and by dose level superimposed in the same figure (if applicable), will be provided throughout the course of treatment.

3.7.1.1.1 Population PK analyses

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

3.7.1.1.2 IgG

In the all-treated population, the level of IgG in blood at pre-infusion of Cycle 1 Day 1 will be summarized with standard descriptive statistics (such as the number of observations, arithmetic and geometric means, median, standard deviation, coefficient of variation, minimum and maximum) for tusamitamab ravtansine. A listing will also be provided.

3.7.1.2 Immunogenicity analyses

Participant's ATA status, response variable, and kinetics of ATA responses (see definitions below) will be summarized on the ATA population.

Kinetics of ATA responses will be described for participants with treatment-induced ATA and for participants with treatment-boosted ATA, separately. Time to ATA onset and duration of ATA will be described with minimum, Q1, median, Q3, and maximum statistics.

Peak titer will be described with minimum, Q1, median, Q3, and maximum statistics for participants with treatment-induced ATA and for participants with treatment-boosted ATA, separately.

Sample status (negative, positive, inconclusive) and titers will also be described overtime using descriptive statistics.

The impact of positive immune response on efficacy, PK, and safety variables may be further explored, depending on ATA incidence.

Participant's ATA status

- Participants with **pre-existing ATA**s correspond to participants with ATAs present in samples drawn before first administration of intervention. Participants with missing ATA sample at baseline will be considered as without pre-existing ATA.
- Participants with **treatment-emergent ATA** correspond to participants with at least 1 treatment-induced/boosted ATA.
  - Participants with **treatment-induced ATA**s correspond to participants with ATAs that developed at any time after first IMP administration and without pre-existing ATA (including participants without pre-treatment samples).
  - Participants with **treatment-boosted ATA**s correspond to participants with pre-existing ATAs that are boosted at any time after first IMP administration to a significant higher titer than the baseline. A 2-fold serial dilution schema is used during titration, so at least a 4-fold increase will be considered as significant.
- Participants with **unclassified ATA** correspond to participants with pre-existing ATAs that cannot be classified as treatment-boosted ATA because of missing titer(s) (ie, a positive ATA sample at any time after first IMP administration in a participant with pre-existing ATA but with missing titer at this sample or at baseline).
- Participants **without treatment-emergent ATA** correspond to participants without treatment-induced/boosted ATA and without any inconclusive sample nor unclassified ATA at any time after first IMP administration.
- Participants **with inconclusive ATA** are defined as participants which cannot irrefutably be classified as with or without treatment-emergent ATA.

Kinetics of ATA response

Kinetics of ATA response will be derived for participants with treatment-induced/boosted ATA.

- **Time to onset of ATA response** is defined as the time period between the first IMP administration and the first treatment-induced/boosted ATA.
- **Duration of ATA response** is defined as the time between the first treatment-induced/ boosted ATA and the last treatment-induced/boosted ATA, irrespective of negative samples or positive samples not reaching the boosted threshold in-between. ATA duration will be summarized only for participants with persistent ATA response.
- **Persistent ATA response** is defined by treatment-induced/boosted ATA with a duration of ATA response of at least 16 weeks.
- **Transient ATA response** is defined by treatment-induced/boosted ATA with a duration of ATA response of less than 16 weeks and the last sample is not treatment-induced/boosted.
- **Indeterminate ATA response** is defined by treatment-induced/boosted ATA that are neither persistent nor transient.

ATA response variable:

- **ATA incidence** is defined as the proportion of participants found to have seroconverted (treatment-induced ATAs) or boosted their pre-existing ATA response (treatment-boosted ATAs) at any time after first IMP administration.

3.7.1.3 Biomarker analyses

Several exploratory objectives related to pharmacodynamic endpoints will be considered in this study.

The circulating CEA will be considered as a quantitative variable or as a binary variable when considering different binary thresholds: <3, <5, <50, <80 or <100 µg/L.

Circulating CEA values below the LLOQ will be replaced by half of the LLOQ.

3.7.1.3.1 Circulating CEA levels before IMP and CEACAM5 IHC

In the pre-screened population, the CEACAM5 IHC expression status (negative (0%), moderate (1-49%) and high expressers (≥50%) based on the % of cells expressing CEACAM5 at the membrane with intensity >= 2+) and the H-score will be described using descriptive statistics.

Circulating CEA levels before IMP will be correlated with IHC CEACAM5 expression status (for prescreened participants). To this end, the closest circulating CEA assessment to biopsy (or the oldest value before IMP if the date of the biopsy is missing) will be considered. The circulating CEA levels (quantitative and by thresholds) will be presented using descriptive statistics by IHC CEACAM5 expression status (negative, moderate and high CEACAM5 expressers) and overall.

The correlation between the circulating CEA levels (quantitative) and the IHC CEACAM5 expression will be also assessed, and graphically visualized. To this end, Pearson correlation, Spearman's rank, or Kendall's tau coefficient will be considered depending on the nature of the data. The time between the tumor biopsy specimen collection date and the date of the considered circulating CEA assessment will also be described and investigated in the correlation.

To evaluate the variability of circulating CEA values before IMP, an intraclass correlation coefficient will be calculated between circulating CEA values (when two values are available). A graphical visualization may be provided to observe the degree of concordance.

3.7.1.3.2 Circulating CEA levels at baseline and clinical response

Circulating CEA levels before IMP administration will be correlated with confirmed objective response (for all treated participants). To this end, the last circulating CEA assessment before (closest to) IMP administration will be considered and reported as the baseline value.

Baseline circulating CEA values will be presented using descriptive statistics by response status and overall. The confirmed objective response rate and two-sided 95% CIs using the Clopper-Pearson method will be presented for each circulating CEA subgroups (base on the predefined thresholds).

The correlation between the circulating CEA levels (quantitative) and the tumor burden at baseline will be also assessed and visualized graphically. To this end, Pearson correlation, Spearman's rank, or Kendall's tau coefficient will be considered depending on the nature of the data.

3.7.1.3.3 Modulations of circulating CEA as a potential PD biomarker of response to tusamitamab ravtansine treatment

A graphic visualization (spaghetti plot) will show the relative change from baseline of circulating CEA values for each participant, and will be annotated with the BOR.

3.7.1.3.4 Mutational profiling

Genomic alterations locally assessed and entered in the eCRF at prescreening as per protocol will be presented. For each gene, participants will be grouped into two groups: "altered" (ie, participants with at least one alteration for the gene) and "wild-type" (ie, participants without alteration for the gene) and described using descriptive statistics by IHC CEACAM5 expression and overall. The confirmed objective response rate and two-sided 95% CIs using the Clopper-Pearson method will be presented for each gene in the all-treated population.

Circulating-free DNA (cfDNA) centrally assessed may be also generated and will be analyzed in the same way as genomic alterations entered locally in the eCRF.

3.7.1.4 Analyses of pharmacokinetic/pharmacodynamic

Efficacy endpoints for PK/PD analysis include response status, tumor shrinkage (eg, best relative tumor shrinkage or best tumor shrinkage). The relationship between those endpoints and PK will be assessed through descriptive statistics and plots.

The relationship between response status and the prognostic PK parameters may be analyzed by fitting a logistic regression model if a sufficient number of responses is observed. Moreover, if relevant, the relationship between best relative tumor shrinkage and the prognostic PK parameters may be analyzed by fitting a linear regression model.

3.7.2 Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, analyses will be performed on the primary efficacy endpoint (defined in Section 3.2.1.2) across the following subgroups (categories with fewer than 5 participants may be combined with other categories):

- Race (White, Black or African American, Asian, Other)
- Age group (<65, ≥65 years)
- Sex (Male, Female)
- ECOG PS at baseline (0, 1)
- PD-L1 expression (<1%, ≥1%; <5%, ≥5%)

- Circulating CEA at baseline (<100, ≥100 µg/L; <80, ≥80 µg/L and <50, ≥50 µg/L)
- Prior ICI treatment administration (Sequential, Combination with chemotherapy, no ICI)
- Time from initial diagnosis (<12 months, ≥12 months)
- Number of organs involved (excluding primary tumor location) (<3, ≥3)
- Tumor burden at baseline, ie, sum of the longest diameters of the target lesions (<100 mm, ≥100 mm)
- Primary tumor (Gastric, GEJ)
- Previous treatment (doublet [FOLFOX or XELOX], triplet [other Chemotherapy+FOLFOX or other Chemotherapy+XELOX])
- Histology types (Intestinal, Diffuse, Mixed, Other)
- Peritoneal metastases (Yes, No)
- Previous gastrectomy (Partial, Total, No)
- Presence of ascites (Yes, No)
- Time to PD on first-line: <6 months; ≥6 months
- Region (Europe, East Asia, Other region)
- Prior treatment with a HER2 therapy (Yes, No)

If a sufficient number of responses is observed tables/plots will be provided, otherwise subgroup information will be displayed in listings only. For tables, objective response rate estimate and the corresponding 95% CI will be provided for each subgroup using the same method as applied to the primary analysis. Forest plots will be provided.

3.8 INTERIM ANALYSES

No formal interim analysis is planned in this study.

The study analysis will be conducted in 2 steps.

The first analysis step will be conducted when all evaluable treated participants have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. This study cut-off will occur approximatively 16 weeks after the date of the first IMP administration of the last participant: 12 weeks for 2 tumor assessment, and 4 weeks if a confirmation of response is needed.

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

The final analysis will be conducted at the end of the study. Only safety analyses will be updated at this time.

For each analysis step, the analysis cut-off date will be defined as the date of the database extraction that will be performed for the analysis after the cut-off (study cut-off for the first analysis step and second analysis step).

Analyses methods and conventions described in the other sections of this SAP will be applied for all analyses if applicable. The following additional rules will apply at the first analysis step and second analysis step:

- Participants without end of treatment status performed at the time of the analysis cut-off date will be considered as ongoing. Therefore:
  - Participants who did not discontinue the study intervention at the analysis cut-off date will be analyzed as “ongoing” in the disposition summary.
  - Their TE period and concomitant medication period will end at the analysis cut-off date.

4 SAMPLE SIZE DETERMINATION

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

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

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

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

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

Sample size for Part 2:

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

Estimated ORR and 95% exact CIs by number of responders from a sample size of 32 evaluable participants for activity are listed in Table 10:

Table 10 - Estimated objective response rate (ORR) depending on number of responders

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

Abbreviation: CI = confidence interval

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADI:	actual dose intensity
AEs:	adverse events
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATA:	antitherapeutic antibody
BCVA:	best corrected visual acuity
BOR:	best overall response
BUN:	blood urea nitrogen
CEA:	carcinoembryonic antigen
CEACAM5:	carcinoembryonic antigen related cell adhesion molecule 5
cfDNA:	circulating-free deoxyribonucleic acid
CI:	confidence interval
CMQ:	company MedDRA queries
COVID-19:	coronavirus disease 2019
CR:	complete response
CTCAE:	common terminology criteria for adverse events
DCR:	disease control rate
DL:	dose level
DLT:	dose-limiting toxicity
DOR:	duration of response
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
eGFR:	estimated glomerular filtration rate
EOT:	end of treatment
GEJ:	gastroesphageal junction
HLGT:	high level group term
HLT:	high-level term
IHC:	ImmunoHistoChemistry
IMP:	investigational medicinal product
INR:	international normalized ratio
IRT:	interactive response technology
ITT:	intent-to-treat
LDH:	lactate dehydrogenase
LLN:	lower limit of normal
LLOQ:	lower limit of quantification
LLT:	lower-level term
MDRD:	modification of diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities

NCI:	National Cancer Institute
ORR:	objective response rate
PCSA:	potentially clinically significant abnormalities
PD:	progressive disease
PDI:	planned dose intensity
PFS:	progression-free survival
PK:	pharmacokinetic
PR:	partial response
PS:	performance status
PT:	preferred term
RD:	recommended dose
RDI:	relative dose intensity
RECIST:	response evaluation criteria in solid tumors
SAEs:	serious adverse events
SAP:	statistical analysis plan
SD:	stable disease
SOC:	system organ class
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
ULOQ:	upper limit of quantification
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 4 will be summarized. Reasons for exclusion from the population without trial impact (disruption) due to COVID-19 will be summarized.

Prescreen failures are defined as participants who consent to participate in the prescreening phase of the study but are not subsequently screened. The number (%) of prescreen failures and reasons for prescreen failures will be provided in the prescreened population.

Screen failures are defined as participants who consent to participate in the study but are not subsequently enrolled. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

Regarding intervention discontinuation, the following definitions will be used:

- Permanent **partial** intervention discontinuation is defined as the discontinuation of at least one of the study drugs but at least one is continued
- Permanent **full** intervention discontinuation is defined as the discontinuation of all the study drugs

The number (%) of participants in the following categories will be provided:

- Enrolled participants
- Enrolled but not treated participants
- Enrolled and treated participants
- Participants still on study intervention
- Participants who discontinued the study intervention, and main reason for permanent full study intervention discontinuation
- Participants who discontinued the study intervention, and main reason for permanent partial discontinuation of tusamitamab ravtansine
- Participants who discontinued the study intervention, and main reason for permanent partial discontinuation of ramucirumab
- Participants who discontinued the study, and main reason for study discontinuation

Reasons for permanent full/partial study intervention and study discontinuation such as "adverse event" and "other reasons" will be split as related versus not related to COVID-19 (if applicable).

Any treated and not enrolled participants will also be listed.

In addition, the number (%) of participants pre-screened, pre-screened failed, screened, screened-failed, enrolled, enrolled and treated, with permanent full intervention discontinuation and with early study discontinuation will be provided by country and site.

For all categories of participants (except for prescreened, screened, and nonenrolled categories), the percentage will be calculated using the number of participants in the all-treated population as the denominator.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the all-treated population, as well as displayed separately as related or not related to COVID-19 (if applicable).

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the all-treated population.

Demographic and baseline characteristics

- Age in years as quantitative variable and in categories (<65, 65 to <75, ≥75)
- Sex (Male, Female)

- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)
- Region (Europe [Belgium, Russian and Spain], East Asia [Japan, Korea], other region [Turkey])
- ECOG PS (0,1)
- Weight in kg as a quantitative variable
- BSA in m^2 as a quantitative variable

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Medical (or surgical) history includes relevant history of previous pathologies and surgeries. Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

Specific disease history includes primary tumor site (gastric, GEJ), histopathology type, staging, Siewert-Stein classification, histology type, time from initial diagnosis to first administration of IMP (in months).

Specific disease status at study entry includes extend of diseases, number (both excluding and including primary tumor location) and type of organs involved (including primary tumor location), ascites presence, PD-L1 expression (<1%, ≥1% and <5%, ≥5%), Peritoneal metastases (Yes, No).

CEACAM5 expression, circulating CEA (<100 µg/L, ≥100 µg/L, <80 µg/L, ≥80 µg/L, <50 µg/L, ≥50 µg/L, <5 µg/L, ≥5 µg/L and <3 µg/L, ≥3 µg/L) and type of tumor biopsy (archival /fresh) will also be described.

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant received prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to any IMP from the first administration of IMP to the last IMP intake +30 days.
- Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant medications will be summarized for the all-treated population, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

Premedications

As defined in the Section 6.1 of the study protocol, participants receive premedications prior to ramucirumab administration to prevent from infusion related allergic reactions to tusamitamab ravtansine and/or ramucirumab. Premedications are defined as non-investigational medicinal products and are reported on a specific e-CRF page.

Anticancer therapies

Prior anticancer therapies include anticancer treatment, surgery related to gastric cancer and radiotherapy.

- Number (%) of prior anticancer therapies including neoadjuvant, adjuvant and advanced regimen
- Number of participants with intent:
  - Neoadjuvant and adjuvant and advanced
  - Neoadjuvant or adjuvant and advanced
  - Neoadjuvant or adjuvant only
  - Advanced only
- Number (%) of prior anticancer therapies in the advanced setting
- Type of prior anticancer treatment including neoadjuvant, adjuvant and advanced regimens:
  - Biologics and small molecules
    - Tyrosine kinase inhibitor (TKI): EGFR inhibitors, antiangiogenics, BRAF kinase inhibitors, ALK inhibitors, RAS/RAF/MEK/ERK signaling pathway inhibitors, ROS1 inhibitors
    - Immune checkpoint inhibitor (ICI)
    - Anti-VEGF/VEGFR
    - Targeted therapies (HER2 therapy, Other)
    - Others
  - Chemotherapy: Doublet (FOLFOX or XELOX), Triplet (other Chemotherapy+FOLFOX or other Chemotherapy+XELOX), Other Chemotherapy (Chemotherapy+HER2, Chemotherapy + ICI, Chemotherapy+HER2+ICI)
  - Antibody drug conjugate (ADC)
  - Others

- Summary of last anticancer therapy:
  - Time from completion of last regimen to first administration of IMP (in months)
  - Time to disease progression on first-line <6 months; ≥6 months
  - Main treatments of last regimen
    - Doublet (FOLFOX or XELOX)
    - Triplet (other Chemotherapy+FOLFOX or other Chemotherapy+XELOX)
    - Other Chemotherapy (Chemotherapy+HER2, Chemotherapy + ICI, Chemotherap+HER2+ICI)
  - Best response to the last regimen
  - Reason for discontinuation of the last line of therapy
- Prior surgery: number (%) of participants with any prior surgery related to gastric cancer, type of surgery (total and partial gastrectomy), and time from the last surgery to the first administration of IMP (in years)
- Prior radiotherapy: number (%) of participants with any prior radiotherapy related to gastric cancer, intent, analgesic intent (if palliative), and time from last dose of radiotherapy to first administration of IMP (in years)

Further anticancer therapies (including systemic anticancer therapies, surgeries, and radiotherapies) after discontinuation of study intervention will be summarized based on WHO-DD coding.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Unscheduled visits

Unscheduled visit measurements will be used for computation of baseline and worst treatment-emergent values and/or grades.

Unscheduled tumor assessments will be used for computation of efficacy endpoints based on radiological assessments of tumor burden.

Corrected QT formula

The QTc parameter will be derived following the Fridericia method:

$$QTcF = QT/RR^{0.33}$$

Where RR interval (in seconds) is 60 divided by heart rate.

5.5 APPENDIX 5 SANOFI SPONSOR GENERIC RANGES FOR HEMATOLOGICAL AND BIOCHEMISTRY PARAMETERS

The current list of generic ranges (for adults) for hematological, coagulation and biochemistry parameters (4) are provided in tables below.

Table 11 - Generic ranges for hematological and coagulation parameters

Parameter	Gender	Unit	LLN	ULN
Basophils		10^9/L	0	0.15
Eosinophils		10^9/L	0	0.4
Hematocrit	M	Fraction of 1	0.41	0.53
Hematocrit	F	Fraction of 1	0.36	0.46
Hemoglobin	M	g/L	135	175
Hemoglobin	F	g/L	120	160
Leukocytes (WBC) count		10^9/L	4.5	11
Lymphocytes		10^9/L	1	2
Monocytes		10^9/L	0.18	0.5
Neutrophils		10^9/L	1.8	3.15
Platelets count		10^9/L	150	350
Prothrombin time		INR	0.8	1.2

Table 12 - Generic ranges for biochemistry parameters

Parameter	Unit	LLN	ULN
Albumin	g/L	35	55
Blood Urea Nitrogen	mmol/L	3.6	7.1
Corrected calcium	mmol/L	2.2	2.6
Glucose	mmol/L	3.9	7
Chloride	mmol/L	80	115
Potassium	mmol/L	3.5	5
Sodium	mmol/L	136	145
Phosphate	mmol/L	1	1.4
Protein	g/L	55	80
Urea	mmol/L	3.6	7.1

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