STATISTICAL ANALYSIS PLAN

Protocol title:	**Open-label, multi-cohort, Phase 2 trial, evaluating the efficacy and safety of tusamitamab ravtansine (SAR408701) monotherapy and in combination in patients with CEACAM5-positive advanced solid tumors**
Protocol number:	**ACT16432**
Compound number (INN/Trademark):	**SAR408701 tusamitamab ravtansine/Not applicable**
Study phase:	**Phase 2**
Short Title:	**Tusamitamab ravtansine monotherapy and in combination in patients with CEACAM5-positive advanced solid tumors (CARMEN-BT01)**
Statistician:	[redacted]
Statistical project leader:	[redacted]
Date of issue:	**11-Dec-2023**

Regulatory agency identifier number(s):

IND:	144484
EudraCT:	2020-003096-18
NCT:	NCT04659603
WHO:	U1111-1244-1644
EUDAMED:	Not applicable
Other:	Not applicable

Date: 11-Dec-2023 Total number of pages: 49

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VERSION HISTORY

This statistical analysis plan (SAP) for study ACT16432 is based on the amended protocol 02 dated 25-Jul-2022. The first participant was enrolled on 12-Apr-2021. This SAP is approved before the interim analysis for the pancreatic cancer cohort in combination is conducted.

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	17-Dec-2021	Not applicable	Original version
2	Current version	Addition of analyses applicable to Cohort C (pancreatic cancer with SAR408701 in combination with gemcitabine)	Protocol amendment 02
		Subgroup analyses updated	To provide more details on the ORR according to tumor location
		Criteria on overdose added in the definition of the DLT-evaluable population (change versus protocol)	To better evaluate the intended dose
		Modification of AE groupings for AESIs and other AEs of interest	To be aligned with other Tusamitamab ravtansine studies
		Addition of safety analyses (Ocular/visual symptoms TEAE in overview TEAE table, ECOG, QTcF)	To be aligned with other Tusamitamab ravtansine studies
		Analyses on visual acuity test and slit lamp examination further detailed	To provide more details and be aligned with other Tusamitamab ravtansine studies
		Update of Immunogenicity section	To be aligned with other Tusamitamab ravtansine studies
		Removed mention of interim analysis for mBC Cohort A	The mBC cohort A stopped enrollment

1 INTRODUCTION

1.1 STUDY DESIGN

This is a Phase 2, open-label, multi-cohort, multi-center study assessing the efficacy (antitumor activity), safety, and immunogenicity of tusamitamab ravtansine in the treatment of participants with metastatic Breast Cancer (mBC, Cohort A [monotherapy]) and metastatic Pancreatic Adenocarcinoma [(mPAC, Cohort B [monotherapy] and Cohort C (in combination with gemcitabine])] with CEACAM5-positive tumors (defined as CEACAM5 IHC intensity ≥2+ in ≥50% of tumor cells).

During the pre-screening phase, participants' tumor samples will be collected to evaluate CEACAM5 status (central assessment by IHC). During the screening phase (up to 28 days), only participants with mBC and mPAC determined to be CEACAM5-positive will go through protocol screening procedures.

Treatment allocation will be performed using an Interactive Response Technology (IRT). After being screened, the eligible participants will receive tusamitamab ravtansine as single agent treatment or receive tusamitamab ravtansine and gemcitabine combined treatment until documented disease progression, unacceptable toxicity, new anti-cancer therapy initiation, or the participant's or Investigator's decision to stop the treatment.

In Cohorts A and B, participants will receive a tusamitamab ravtansine loading dose at 170 mg/m² on Day 1 of Cycle 1, followed by 100 mg/m² every 2 weeks (Q2W) from Cycle 2 and in all other cycles.

In Cohort C, each treatment cycle will be 28 days (4 weeks). Cohort C will comprise 2 parts:

- Part 1 (Safety Run-In): In Part 1, participants will receive a tusamitamab ravantasine loading dose at 170 mg/m^2 on Day 1, followed by 100 mg/m^2 Q2W, participants will also receive gemcitabine 1000 mg/m^2 on Day 1, Day 8, and Day 15 every 4 weeks (Q4W). 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 135 mg/m^2 will be administered to participants on Day 1 of Cycle 1.

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

Dose level (DL)	Tusamitamab ravtansine	Gemcitabine
Starting dose	170 mg/m² on D1; 100 mg/m² Q2W thereafter	1000 mg/m² on D1, D8, and D15 Q4W
Minus -1 (DL -1)	135 mg/m² on D1; 100 mg/m² Q2W thereafter	1000 mg/m² on D1, D8, and D15 Q4W

BSA = body surface area; DL -1=dose level -1; Q2W = every 2 weeks; Q4W = every 4 weeks.
For participants with a BSA >2.2 m², the tusamitamab ravtansine dose will be calculated based on a BSA of 2.2 m².

- Part 2: the recommended dose (RD) confirmed in Part 1 will be evaluated for activity in 24 to 27 additional participants. A total of 30 participants, including participants treated at the RD in Part 1, will be evaluated for activity.

The expected duration of study treatment for participants may vary, based on the progression date and cohort; the median expected duration of the study per participant is estimated to be 8 months for Cohorts A and C and 6 months for the Cohort B (up to 1 month for screening, a median of 4 or 2 months for treatment in Cohorts A (breast cancer) and Cohort B/C (pancreatic cancer), respectively, a median of 1 month for EOT, and follow-up visit 90 days after the last IMP administration).

1.2 OBJECTIVE AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• For Cohort A, Cohort B and Cohort C Part 2: To assess the antitumor activity of tusamitamab ravtansine in mBC and tusamitamab ravtansine monotherapy and in combination with gemcitabine in mPAC • For Cohort C Part 1: To confirm the recommended tusamitamab ravtansine dose when administered in combination with gemcitabine	• 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 per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 • Incidence of dose-limiting toxicities (DLTs) in the 28 Day DLT observation period (Cycle 1)
Secondary	
To assess the safety and tolerability of tusamitamab ravtansine administered as monotherapy and in combination with gemcitabine	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 administered as monotherapy and in combination with gemcitabine	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 CR, PR or stable disease as per RECIST v1.1 Duration of response (DOR), defined as the time from first documented evidence of CR or PR until progressive disease determined per RECIST v1.1 or death from any cause, whichever occurs first
To assess the immunogenicity of tusamitamab ravtansine	Incidence of participants with anti-therapeutic antibodies (ATAs) against tusamitamab ravtansine
To assess the pharmacokinetics (PK) of tusamitamab ravtansine and gemcitabine when given in combination	Pharmacokinetic parameters of tusamitamab ravtansine and gemcitabine

Objectives	Endpoints
Tertiary/exploratory	
To explore CEACAM5 expression on circulating tumoral cells (CTCs)	CEACAM5 expression assessment on CTCs from participants with positive CEACAM5 expression on tumor tissue
To explore modulations of circulating CEA as a potential pharmacodynamics biomarker of response to tusamitamab ravtansine treatment	Circulating CEA at baseline and during the treatment period
To assess 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 from tumor DNA and RNA analyses, beside target expression, as potential biomarkers of response to tusamitamab ravtansine treatment	Biomarker annotation for tumor DNA and RNA at baseline

1.2.1 Estimands

Primary estimand defined for main endpoints are summarized below in Table 3. More details are provided in Section 4.

Table 3 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: For Cohort A, Cohort B and Cohort C Part 2: To assess the antitumor activity of tusamitamab ravtansine in mBC and tusamitamab ravtansine monotherapy and in combination with gemcitabine in mPAC				
Primary endpoint (primary estimand)	Confirmed objective response (confirmed CR or PR as BOR), determined according to RECIST 1.1	All-treated population	Regardless of 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 missing or non-evaluable BOR).

2 SAMPLE SIZE DETERMINATION

Assuming a prescreening failure rate of 90% for Cohort A, 85% for Cohort B, and 58% for Cohort C, and a screening failure rate of 20% for the 3 cohorts, approximately 440 participants for the Cohort A, 242 participants for Cohort B, and 90 participants for Cohort C will be prescreened to achieve up to approximately 35 treated participants evaluable for activity (at least one postbaseline tumor assessment, early progression, or death due to progressive disease) for the mBC Cohort A, 29 treated participants evaluable for activity for mPAC Cohort B, and 30 treated participants evaluable for activity in mPAC Cohort C.

For Cohort C safety run-in (Part 1), the actual sample size is expected to vary depending on DLTs observed. It is anticipated that around 3 to 12 DLT-evaluable participants will be enrolled. Table 4 and Table 5 list the estimated ORRs and 95% exact CIs by the numbers of responders from a sample size of 35 treated participants evaluable for activity for the mBC cohort and 29 treated participants evaluable for activity for mPAC cohort, and Table 6 lists the estimated ORRs and CIs 30 treated participants evaluable for activity for combination cohort.

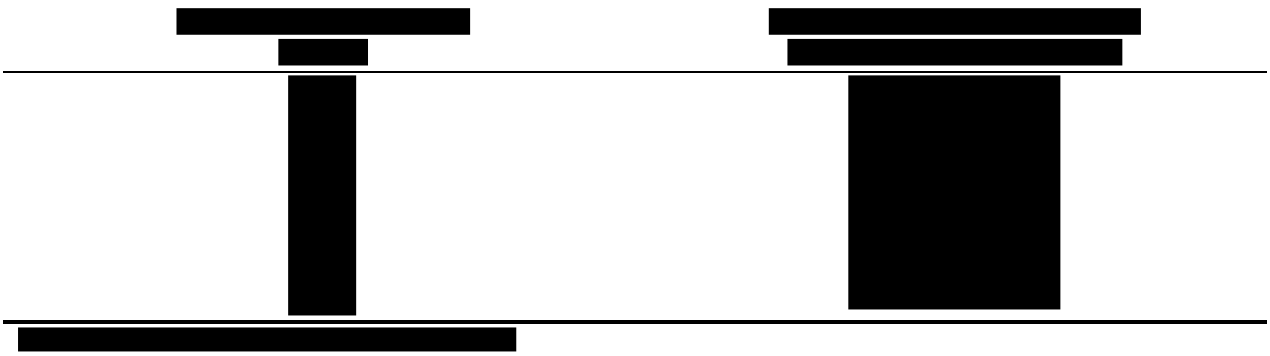
Table 4 - [redacted]

[redacted]

Table 5 - [redacted]

[redacted]

Table 6 - [redacted]



3 ANALYSIS POPULATIONS

The following populations are defined (Table 7):

Table 7 - Populations for analyses

Population	Description
Pre-screened	All participants who signed the pre-screening informed consent for CEACAM5 assay assessment of their biopsy.
Screened	All participants who signed screening informed consent for study participation.
Enrolled	Participants from screened population who have been allocated to intervention regardless of whether the intervention was received or not.
All-treated	All enrolled participants exposed to the study treatment, regardless of the amount of treatment administered. All safety analyses will be performed on this population, which is also the primary population for analysis of all efficacy parameters.
DLT-Evaluable (Cohort C Part 1)	All participants who have completed DLT observation period and who received 1 cycle with at least 80% of the intended dose for both tusamitamab ravtansine at each of the first 2 infusions and gemcitabine at each of the 3 first infusions. Any participant who experienced a DLT during that period will also be DLT-evaluable, except in case of overdose (defined as a dose received of at least 30% above the intended dose) of tusamitamab ravtansine or gemcitabine at any of the infusions of Cycle 1.
Activity	All treated participants who have measurable disease at study entry and at least one post-baseline evaluable tumor assessment. Participants with no post-baseline evaluable tumor assessment but with an early progression or who died due to disease progression will also be included in this set. This population is the secondary population for analysis of efficacy parameters
Pharmacokinetic (PK)	All treated participants with at least 1 postbaseline PK result with adequate documentation of dosing and sampling dates and times
ATA	All treated participants with at least one post-baseline 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 study intervention due to COVID-19, • and who did not permanently discontinue study due to COVID-19.

CEACAM5 = carcinoembryonic antigen-related cell adhesion molecule 5; ATA = anti-therapeutic antibodies.

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” e-CRF page.

In practice, a participant will be included in the DLT-evaluable population (applicable to mPAC Cohort C Part 1 if a “Dose Limiting Toxicities” e-CRF page has been filled in at the end of Cycle 1. 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 gemcitabine at any of the infusions of Cycle 1 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.

4 STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

This study is designed to obtain preliminary efficacy and safety data on the use of tusamitamab ravtansine administered to participants with CEACAM5-positive tumors known to be sensitive to antitubulin agents at a loading dose of 170 mg/m² on Day 1 of Cycle 1, followed by 100 mg/m² Q2W for Cohorts A and B, and at a loading dose of 170 mg/m^2 (or 135 mg/m^2) on Day 1 of Cycle 1, followed by 100 mg/m2 Q2W, combined with gemcitabine 1000 mg/m^2 on Day 1, Day 8, and Day 15 Q4W, for Cohort C.

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; 95% CIs will be provided for the primary and secondary efficacy endpoints.

Objective response rate, as well as PFS, DCR and DOR, will be derived using the local radiologist's/Investigator's assessment.

Unless otherwise specified, analyses will be performed by cohort.

The study cut-off for the primary analysis (ORR) for each cohort corresponds to the date on which all treated evaluable participants of the cohort had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or discontinued the study 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.

An interim analysis will be performed when the first 15 treated evaluable participants in Cohort C have had at least 2 postbaseline tumor assessments, experienced confirmed objective response, or discontinued the study for any reason. Once 15 participants have been treated, enrollment may be paused until a decision regarding the interim analysis can be made.

The analysis cut-off date for secondary efficacy endpoints including DOR and PFS (final cut-off date) will be 6 months after the study cut-off for the primary analysis. The primary analysis of ORR and DCR will also be updated at that time.

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

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

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to the first IMP administration.
  - The **pre-screening period** is defined as the time from when the participants give pre-screening informed consent to the day before the screening informed consent.

  - The **screening period** is defined as the time from when the participants give screening informed consent to the first administration of the IMP.
- 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.

4.2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 7 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 one of the study drugs (tusamitamab ravtansine or gemcitabine) but the other is continued (mPAC cohort C)
- Permanent **full** intervention discontinuation is defined as the discontinuation of SAR408701 (cohorts other than mPAC Cohort C) or both tusamitamab ravtansine and gemcitabine (mPAC cohort C)

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

- Enrolled participants.
- Enrolled but not exposed participants.
- Enrolled and exposed participants.
- Participants who fully discontinued the study intervention and main reason for permanent full intervention discontinuation.
- Participants who partially discontinued the study intervention, and main reason for permanent discontinuation of tusamitamab ravtansine (mPAC Cohort C)
- Participants who partially discontinued the study intervention, and main reason for permanent discontinuation of gemcitabine (mPAC Cohort C)
- Participants still on study intervention.
- Participants who discontinued the study and main reason for study discontinuation.

Reasons for permanent study intervention and study discontinuation “adverse event” and “other reasons” will be split as related versus not related to COVID-19, if applicable.

The number (%) of exposed and not enrolled participants will also be summarized.

In addition, the number (%) of participants prescreened, prescreen-failed, screened, screened-failed, enrolled, enrolled and exposed, with permanent intervention discontinuation, and with study discontinuation will be provided by country and site.

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 versus not related to COVID-19 if applicable.

4.3 PRIMARY ENDPOINT(S) ANALYSIS

4.3.1 Definition of endpoint

4.3.1.1 Study-drug related DLT at Cycle 1 (Cohort C – Part 1)

For mPAC Cohort C Part 1, the primary safety endpoint is study-drug related DLTs during the DLT observation period (ie, approximately 28 days). For analysis purpose, DLTs will be identified based on the Adverse Events (AEs) reported on the e-CRF DLT page during DLT observation period in Part 1.

4.3.1.2 Confirmed objective response (Cohort A, Cohort B and Cohort C – Part 2)

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 best overall response.

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

4.3.2 Main analytical approach

Statistical analysis for DLTs for Cohort C – Part 1 is described in Section 4.7.2.

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

- The endpoint is confirmed objective response (confirmed CR or PR as BOR) as per RECIST 1.1.
- The treatment condition of interest is tusamitamab ravtansine Q2W with a loading dose for Cohorts A and B and in combination with gemcitabine for Cohort C.
- The analysis population is the participants from the all-treated population (defined in Section 3).

- 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 and radiotherapies with curative intent) intercurrent event will be handled with the "while not initiating further anticancer therapy" strategy. Confirmed objective response will be assessed based on tumor assessments up to the time of initiation of further anticancer therapy.
- The population-level summary will include the objective response rate, defined as the rate of participants with confirmed objective response and two-sided 95% confidence intervals 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 best overall response).

4.3.3 Sensitivity analysis

No sensitivity analysis is planned in this study.

4.3.4 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 participants from all-treated population.

As a supplementary analysis, confirmed objective response as per RECIST 1.1 will also be summarized on the participants from activity population (defined in Section 3). The same analytical approach as primary efficacy analysis defined in Section 4.3.1.2 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 from the activity population (defined in Section 3). A swimmer plot will also be provided reporting the duration of treatment for all patients with their overall response, the baseline characteristics. This plot will differentiate responders from non-responders.

4.3.5 Subgroup analyses

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

- Race (White, Other)
- Age group (<65, ≥65 years)

- Sex (Male, Female)
- ECOG PS at baseline (0, 1)
- Region (South America, Asia, Europe, North America)
- mBC subtype (non-triple-negative Breast Carcinoma, triple-negative Breast Carcinoma) (mBC cohort)
- Circulating CEA at baseline (<100, ≥100 µg/L) and (<80, ≥80 µg/L)
- Time from initial diagnosis (<12 months, ≥12 months for both mPAC cohorts and <5 years, ≥5 years for mBC cohort)
- Brain metastases (Yes, No)
- Liver and Lung metastases (Yes, No)
- Number of organs involved (including primary tumor location) (≤2, >2)
- Primary tumor location (for both mPAC cohorts) (Head, Body, Tail, Other)
- Tumor burden at baseline, ie, sum of the longest diameters of the target lesions (<100, ≥100 mm)
- Prior chemotherapy treatment as advanced intent (≤1, >1 for both mPAC cohorts, and <2, ≥2 for mBC cohort)
- Prior Taxane (Yes, No) (cohorts mBC and mPAC B)
- Prior T-DM1 (mBC cohort) (Yes, No)
- Refractory to taxane/anthracyclines/T-DM1 (defined as progression within 60 days after last administration) (Yes, No)
- Sensitivity to first-line chemotherapy line (duration of treatment 4-6 months Yes/No; ≥6 months Yes/NO)
- Sensitivity to second-line chemotherapy line (duration of treatment 4-6 months Yes/No; ≥6 months Yes/NO)

If a sufficient number of responses is observed tables will be provided, otherwise subgroup information will be displayed in listings only. For tables, objective response rate estimate and the corresponding 95% confidence interval will be provided for each subgroup using the same method as applied to the primary analysis. Forest plots will be provided. In addition, analysis of DOR and DCR will be conducted by mBC subtype (TNBC vs non-TNBC).

4.4 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are the progression-free survival, the duration of response and the disease control rate. Other secondary endpoints analyses are defined in Section 4.7.2 (AE, SAE, laboratory abnormalities) and Section 4.8 (PK and immunogenicity).

4.4.1 Key/Confirmatory secondary endpoint(s)

No key/confirmatory secondary endpoint is defined.

4.4.2 Supportive secondary endpoint(s)

4.4.2.1 Definition of endpoints

4.4.2.1.1 Progression-free survival

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

4.4.2.1.2 Disease control rate

The DCR will be estimated by dividing the number of participants with confirmed objective response or stable disease (CR or PR or stable disease (SD) as BOR), determined according to RECIST v1.1, by the number of participants from the analysis population.

4.4.2.1.3 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 definitions (1, 2) or death due to any cause, whichever occurs first.

4.4.2.2 Main analytical approach

4.4.2.2.1 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 Q2W with a loading dose for Cohorts A and B and in combination with gemcitabine for Cohort C.
- The analysis population is the participants from the all-treated population (defined in Section 3).
- 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 anti-cancer therapy (including further systemic anticancer therapies and radiotherapies with curative intent) 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 two 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% confidence intervals 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 2, 4, 6, 8, 10 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 (document 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 assessment, 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 baseline tumor assessment or no evaluable postbaseline tumor assessment has been done.

4.4.2.2.2 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 stable disease (SD) as BOR) as per RECIST 1.1.
- The treatment condition of interest is tusamitamab ravtansine Q2W with a loading dose for Cohorts A and B and in combination with gemcitabine for Cohort C.
- The analysis population is the participants from all-treated population (defined in Section 3).
- Intercurrent events:
  - The study intervention discontinuation will be handled with the treatment policy strategy. Confirmed objective response or stable disease will be assessed based on tumor assessments regardless of study intervention discontinuation.
  - The further anticancer therapy (defined as all further anti-cancer treatments and radiotherapies with curative intent) 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 objective response rate, defined as the rate of participants with disease control response and two-sided 95% confidence intervals 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 best overall response).

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

4.4.2.2.3 Duration of response

Duration of response (DOR) analysis is based on an estimand defined according to the following attributes:

- The endpoint is duration of response.
- The treatment condition of interest is tusamitamab ravtansine Q2W with a loading dose for Cohorts A and B and in combination with gemcitabine for Cohort C.
- The analysis population is the participants from the all-treated population (defined in Section 3), limited to participants 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 (including further systemic anticancer therapies and radiotherapies with curative intent) 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 two 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% confidence interval using Kaplan-Meier methods.

In the absence of documented disease progression or death before the study 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.

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

Analyses of tertiary/exploratory endpoints (ie, biomarkers) are defined in Section 4.8.3.

4.6 MULTIPLICITY ISSUES

No multiplicity issues are handled in this study.

4.7 SAFETY ANALYSES

All safety analyses will be performed on the all-treated population as defined in Section 3, 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 separately.

4.7.1 Extent of exposure

4.7.1.1 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 intervention 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 IMPs (tusamitamab ravtansine or gemcitabine for Cohort C)
  - The last day of exposure is the day before the theoretical date of the next administration (after the last administration), defined as the maximum between:
    - The last administration date + number of theoretical days until the next administration - 1 for tusamitamab ravtansine,
    - The last administration date + the number of theoretical days until the next administration -1 for gemcitabine for Cohort C.

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 – theoretical cycle duration – start date of the previous cycle is >3 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 4 and 7 days (using maximum delay across all cycles),
  - Number (%) of participants with a cycle delayed >7 days (using maximum delay across all cycles).
- Number (%) of cycles delayed
  - Number (%) of cycles delayed between 4 and 7 days,
  - Number (%) of cycles delayed between 8 and 28 days,
  - Number (%) of cycles delayed >28 days.

In addition, summaries will be provided by trial impact (disruption) due to COVID-19 (if applicable).

4.7.1.2 Tusamitamab ravtansine

The dose information will be assessed by the following:

- Total number of cycles started.
- Number of cycles started per participant.
- Duration of exposure (in weeks) is defined by (date of last administration of tusamitamab ravtansine + 14 days – date of first administration of the 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 (in 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 - 1 and divided by the theoretical cycle duration expressed in weeks (ie, 2 weeks per cycle started).
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI ([mg/m²/week])}}{\text{PDI ([mg/m²/week])}}$.

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 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/m^2 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 8, 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 8 - Tusamitamab ravtansine dose reduction criteria

Actual dose level	Dose level interval
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: within a cycle, dose delay for tusamitamab ravtansine is deemed as delayed if the actual start date of the dose - theoretical start date of a doseis >2 days.
- 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 cycle delayed
    - Number (%) of participants with at least 1 dose reduction
  - 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 interruption

If applicable, summaries will be provided by trial impact (disruption) due to COVID-19.

4.7.1.3 Gemcitabine

For Cohort C only, the dose information will be assessed by the following:

- Total number of cycles started.
- Number of cycles started per participant.
- Duration of gemcitabine exposure (in weeks) is defined by date of last administration of gemcitabine + number of theoretical days until the next administration – date of first administration of gemcitabine /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 gemcitabine, given from first to last administration.
- Actual dose intensity (ADI in mg/m²/week): defined as the cumulative dose divided by the duration of gemcitabine exposure (in weeks).
- Planned dose intensity (PDI in mg/m²/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 gemcitabine.
- 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, 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 gemcitabine 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 gemcitabine administrations, dose reduction will be determined using the dose level intervals provided in Table 9, by comparing the current dose level to the previous dose level.

Table 9 - Gemcitabine dose reduction criteria

Actual dose level	Dose level interval
Starting dose (1000 mg/m²)	>=900 and <1100
Dose level -1 (800 mg/m²)	>=700 and <900
Dose level -2 (600 mg/m²)	>=500 and <700
Low dose	<500

- Within a cycle, dose delay for gemcitabine: a dose is deemed as delayed if the actual start date of the dose – theoretical start date of a dose is >2 days.
- 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 gemcitabine 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

4.7.2 Adverse events

General common rules for adverse events

All AEs will be graded according to National cancer institute common terminology for adverse events (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.
- Treatment-emergent adverse events (TEAE)s: 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. 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 10.

Table 10 - 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]
PT	By decreasing frequency of PTs

a 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 AESI
- Any TEAE leading to permanent full study intervention discontinuation
- Any TEAE leading to permanent partial intervention discontinuation (discontinuation of tusamitamab ravtansine) (Cohort C only)
- Any TEAE leading to permanent partial intervention discontinuation (discontinuation of gemcitabine) (Cohort C only)
- Any TEAE related to IMP
- Any Grade ≥3 TEAE related to IMP
- Any serious TEAE related to IMP
- Any Treatment-emergent Corneal events (with CMQ as defined in Table 12)
- Any Treatment-emergent Peripheral neuropathy events (with SMQ "Peripheral neuropathy" (Narrow and Broad))
- Any ocular/visual symptoms TEAE (CMQ ("Eye disorders exclude corneal disorders")

The AE summaries of Table 11 will be generated with number (%) of participants experiencing at least one event. The analyses will be performed for all grades combined and for grades ≥3. The all TEAE summary by Primary SOC and PT (and other safety summaries (eg, SAEs, deaths), if deemed needed after TEAE evaluation) will be performed by trial impact (disruption) due to COVID-19.

Table 11 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
	PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE related to tusmitamab ravtansine as per Investigator's judgment (Cohort C only)	Primary SOC and PT
TEAE related to gemcitabine as per Investigator's judgment (Cohort C only)	Primary SOC and PT
Treatment emergent SAE	Primary SOC, HGLT, 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 judgement (Cohort C only)	Primary SOC and PT
Treatment emergent SAE related to gemcitabine as per Investigator's judgement (Cohort C only)	Primary SOC and PT
TEAE leading to permanent full study intervention discontinuation	Primary SOC and PT
TEAE leading to permanent partial intervention discontinuation (discontinuation of tusamitamab ravtansine) (Cohort C only)	Primary SOC and PT
TEAE leading to permanent partial intervention discontinuation (discontinuation of gemcitabine) (Cohort C only)	Primary SOC and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
TEAE related to tusamitamab ravtansine and leading to death[b]	Primary SOC and PT
TEAE related to gemcitabine and leading to death[b] (Cohort C only)	Primary SOC and PT
Pre-treatment 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 and dose reduction)	Primary SOC and PT
TEAE leading to dose modification of gemcitabine (including dose delay and dose reduction) (Cohort C only)	Primary SOC and PT
TEAE leading to dose interruption of tusamitamab ravtansine	Primary SOC and PT
TEAE leading to dose interruption of gemcitabine (Cohort C only)	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 intervention discontinuation

Analysis of deaths

In addition to the analyses of deaths included in Table 11 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
- Summary of fatal AEs, by primary SOC and PT
  - In context of disease progression (death within 30 days from last study intervention administration and the cause of death is disease progression),
  - In context other than disease progression (death within 30 days from last study intervention administration and for whom cause of death is not disease progression or the death occurred more than 30 days from last study intervention administration and the cause of death is AE).
- An overview of Grade 5 AEs will be provided with the following categories:
  - Grade 5 AE (TEAE and post-treatment).
  - Fatal TEAE (regardless date of death/period).
    - Grade 5 TEAE with a fatal outcome during the treatment period,
    - Any Grade TEAE with a fatal outcome during the post-treatment 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

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 12. Number (%) of participants experiencing at least one treatment-emergent event will be provided for each event of interest, by SOC and PT (if applicable). Tables will be sorted as indicated in Table 10. DLT observed during the DLT observation period will be listed in the DLT-evaluable population (for Cohort C Part 1 only).

Table 12 - 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 defects	e-CRF AESI specific tick box on the AE page. It could include events with PTs from SMQ “Conduction defects”
Grade ≥3 liver enzyme increased (symptomatic or asymptomatic)	e-CRF AESI specific tick box on the AE page. It could include Grade ≥3 events 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

AESIs and other AEs of interest	Selection
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 adverse events linked to pregnancy on the Pregnancy page
DLT during DLT observation period (Cohort C Part 1 only)	e-CRF specific DLT page
Other AEs of interest	
Any AE meeting DLT criteria beyond DLT observation period (Cohort C)	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 PTs included in SOC "Eye 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 infusion
Hepatic disorders events	SMQ "Hepatic Disorders" (Narrow and Broad)
Hematological 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 SAE, corneal TEAE leading to permanent full intervention discontinuation, corneal TEAE leading to permanent partial intervention discontinuation (discontinuation of tusamitamab ravtansine), corneal TEAEs related to IMP, Grade ≥3 corneal TEAEs related to IMP, and corneal TEAEs leading to dose modification of tusamitamab ravtansine.

In addition, descriptive analyses will be provided on ocular/visual symptoms reported as associated with the corneal adverse events. These analyses will be performed based on the Investigator's reporting of ocular toxicities (using Investigator's terms collected in the category "Ocular/visual symptoms" in the AE page and using associated symptoms reported in the ocular/visual symptoms page during each corneal event).

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

- Number (%) of participants by worst grade
- Cycle of first occurrence regardless of the grade
- Cycle of first occurrence of the worst grade

- Relationship to study intervention: in case of multiple occurrences with different relationships, if any event is related, then the relationship will be considered as related
- Action taken with the study intervention: in case of multiple occurrences with different actions, 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, the most severe outcome will be tabulated and selected according to the following order of severity: fatal, not recovered or resolved, recovering or resolving, recovered or resolved with sequelae, recovered or resolved, unknown

In addition, analyses on occurrence and recurrence of corneal events will be provided.
An occurrence of corneal event will be defined as one or a group of concomitant corneal events.
A recurrence will be defined as any occurrence of corneal event starting after a previous 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 one recovered or resolved occurrence of corneal event (with or without sequelae), considering the longest duration, and the longest duration of the worst grade among all occurrences 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.

4.7.3 Additional safety assessments

4.7.3.1 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 and prothrombin time (expressed as international normalized ratio [INR]).
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils and eosinophils
- Clinical chemistry:
  - Metabolism: glucose, total protein and albumin.

  - Electrolytes: sodium, potassium, chloride, phosphate and corrected calcium. Corrected calcium (mmol/L) will be derived using the following formula: measured total calcium (mmol/L) + 0.8 × 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.
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase, total and direct bilirubin.
  - Circulating carcinoembryonic antigen (CEA)
- Vital signs: heart rate, temperature, systolic and diastolic blood pressure, weight, ECOG Performance status (PS) and body surface area (BSA)
- ECG variables: PR, QRS, QT and 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 (ULOQ) will be replaced by ULOQ value.

For hematological parameters and some selected coagulation and biochemistry parameters, Sanofi sponsor generic ranges (LLN, ULN) are defined and will be used for grading (see list of parameters in Section 5.5). For other biochemistry and coagulation parameters, grading will be derived using local laboratory normal ranges.

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 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 above, 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

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 (except for liver function).
- 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 or 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:

- 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 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 ULN).

4.7.3.2 Ophthalmological examinations

Schirmer test

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

Visual acuity test

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

Frequency tables on best corrected visual acuity (BCVA) measured during 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 the summary table on all participants, all on-treatment BCVA values are considered.

The worst classification between the laterality will be considered for the worst value of participant either left or right eye then the change from baseline and the last value will be measured from same eye with worst value. 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 baseline value was worse than the values reported during the during the treatment period/treatment-emergent corneal events) 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).

4.8 OTHER ANALYSES

4.8.1 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.

4.8.2 PK analyses (for mPAC Cohort C)

4.8.2.1 Noncompartmental analysis

4.8.2.1.1 Tusamitamab ravtansine

The PK parameters will be calculated using non-compartmental methods from tusamitamab ravtansine concentrations will include, but may not be limited to, those listed in Table 13.

Table 13 - List of PK parameters and definitions

Parameters	After Cycle 1 Day 1 administration	After Cycle 2 Day 15 administration	Definition
C_{eoi}	✓	✓	Concentration observed at the end of IV infusion
C_{max}	✓	✓	Maximum concentration observed after infusion
t_{max}	✓	✓	Time to reach C_{max}
C_{last}	✓	✓	Last concentration observed above the lower limit of quantitation after infusion
t_{last}	✓	✓	Time of C_{last}
AUC_{last}	✓	✓	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to t_{last}

Parameters	After Cycle 1 Day 1 administration	After Cycle 2 Day 15 administration	Definition
AUCtau	✓	✓	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to 14 days
AUC	✓		AUC from time zero extrapolated to infinity according to the following equation: $AUC = AUC_{last}+(C_{last}/\lambda_z)$ Extrapolation should not exceed more than 30% of total AUC. If AUC_{ex} >30%, the value will be reported and not taken into account in descriptive statistics and derived parameters will not be calculated.
CL	✓		Total body clearance of a drug from plasma calculated using the following equation from AUC, after single dose: CL = Dose/AUC
CL_{ss}		✓	Total body clearance of the drug from the plasma after IV administration calculated after repeated dosing, using the following equation: CLss = Dose/AUC0- τ, τ being the dosing time interval (14 days)
V_{ss}	✓		Volume of distribution in the terminal phase calculated according to the following equation: Vss = CL × MRT with MRT = AUMC/AUC(-T_{inf}/2 if infusion) MRT being the Mean Residence Time of a molecule in the body; AUMC is the area under the curve of the moments and T_{inf} is the duration of infusion.
$t_{1/2z}$	✓	✓	Terminal half-life associated with the terminal slope determined according to the following equation: $t_{1/2z} = 0.693/\lambda_z$ Where λ_z is the slope of the regression line of the terminal phase of the plasma concentration versus time curve, in semi-logarithmic scale. Half-life is calculated by taking the regression of at least 3 points on the terminal slope.

4.8.2.1.2 Gemcitabine

The PK parameters for gemcitabine and dFdU (gemcitabine metabolite) will be calculated using non-compartmental methods from concentrations will include, but may not be limited to, those listed in Table 14.

Table 14 - List of PK parameters and definitions

Parameters gemcitabine and dFdU (gemcitabine metabolite)	After Cycle 1 Day 1 administration	After Cycle 1 Day 1 administration	Definition
C_{max}	✓	✓	Maximum concentration observed after infusion
t_{max}	✓	✓	Time to reach C_{max}
C_{last}	✓	✓	Last concentration observed above the lower limit of quantitation after infusion
t_{last}	✓	✓	Time of C_{last}
AUC_{last}	✓	✓	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to t_{last}
AUC (gemcitabine only)	✓	✓	AUC from time zero extrapolated to infinity according to the following equation: $AUC = AUC_{last} + (C_{last}/\lambda_z)$ Extrapolation should not exceed more than 30% of total AUC. If AUC_{ex} >30%, the value will be reported and not taken into account in descriptive statistics and derived parameters will not be calculated.
CL (gemcitabine only)	✓	✓	Total body clearance of a drug from plasma calculated using the following equation from AUC, after single dose: CL = Dose/AUC
V_{ss} (gemcitabine only)	✓	✓	Volume of distribution in the terminal phase calculated according to the following equation: Vss = CL × MRT with MRT = AUMC/AUC(-T_{inf}/2 if infusion) MRT being the Mean Residence Time of a molecule in the body; AUMC is the area under the curve of the moments and T_{inf} is the duration of infusion.
$t_{1/2z}$ (gemcitabine only)	✓	✓	Terminal half-life associated with the terminal slope determined according to the following equation: $t_{1/2z} = 0.693/\lambda_z$ Where λ_z is the slope of the regression line of the terminal phase of the plasma concentration versus time curve, in semi-logarithmic scale. Half-life is calculated by taking the regression of at least 3 points on the terminal slope.

Individual concentrations and PK parameters of tusamitamab ravtansine, gemcitabine and dFdU (gemcitabine metabolite) will be listed and summarized by dose level (if applicable) using descriptive statistics (such as the number of observations, arithmetic and geometric means,

median, standard deviation, standard error (SE), coefficient of variation (CV), minimum, and maximum).

In addition, individual and mean concentration profiles over time will be plotted by dose level (if applicable).

These descriptive statistics will be provided by PKDM department at Sanofi.

4.8.2.2 C_{trough} and C_{eoi} over cycles

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 the end of infusion (C_{eoi}, C_{eoi+1h} if any) of tusamitamab ravtansine 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 modifications (delay or reduction as defined in Section 4.7.1.2) 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 dose level superimposed in the same figure (if applicable), will be provided throughout the course of treatment.

4.8.2.3 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.

4.8.2.4 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 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.

4.8.3 Biomarker analyses

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

Unless otherwise specified, biomarkers analyses will be performed on participants with available data from the all-treated population.

4.8.3.1 CEACAM5 by IHC

In the pre-screened population, the CEACAM5 expression (prevalence of the three categories [negative, moderate and high expressers] and possibly H-score) will be presented using descriptive statistics.

4.8.3.2 Circulating CEA

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.

4.8.3.2.1 Circulating CEA levels before IMP and CEACAM5 IHC

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. The correlation between the circulating CEA levels (quantitative) and the CEACAM5 expression 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. The time from tumor biopsy collection and circulating CEA assessment (the closest to biopsy) will be also described and investigated in the correlation between circulating CEA levels and IHC CEACAM5 expression.

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

4.8.3.2.2 Circulating CEA levels at baseline and clinical response

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

The circulating CEA level will be presented using descriptive statistics, by response status, part, dose level and overall. The confirmed objective response rate and two-sided 95% confidence intervals using the Clopper-Pearson method will be presented for each circulating CEA subgroups (based on the predefined thresholds) by part, and overall.

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.

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

A graphical visualization (spaghetti plot) will be presented to visualize the relative change from baseline of circulating CEA values for each participant, annotated with the best overall response.

4.8.3.3 Circulating free DNA (cfDNA)

4.8.3.3.1 Relationship between the tumor mutation profiles detected in the cfDNA at baseline with efficacy outcomes

Genomic alterations collected locally from the eCRF at pre-screening will be described. 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 part, dose level and overall in the pre-screened population. The confirmed objective response rate and two-sided 95% confidence intervals using the Clopper-Pearson method will be presented for each gene in the all-treated population.

Circulating-free DNA (cfDNA) centrally assessed will be collected and analyzed in the same way as local data from eCRF.

4.8.3.4 To explore potential sets of biomarkers from tumor DNA and RNA analyses as potential biomarkers of response to tusamitamab ravtansine

The same tumor biopsy as the one sent for CEACAM5 assessment at pre-screening may be used for additional tumor DNA and/or RNA analyses, if enough relevant data is collected.

Tumor DNA data from the TSO500 (+CEACAM5) panel will be generated. These data will be analyzed similarly to cfDNA data. For key genes, the concordance between tumor DNA and cfDNA can be investigated.

RNAseq data will be also generated, and may be used to evaluate the abundance of expression of specific genes in this targeted population (ie, CEACAM5 high expression based on IHC), and explore patterns on response to tusamitamab ravtansine.

4.8.3.5 CEACAM5 expression on circulating tumoral cells (CTCs)

CEACAM5 expression on CTCs have been analyzed for some samples for feasibility purpose. A listing will be provided with the subject ID and associated level of CEACAM5 detected on CTCs.

4.9 INTERIM ANALYSES

An interim analysis based on the number of responses observed in the Activity population for the patients in the mPAC Cohort C will be performed.

The study cut-off for the interim analysis corresponds to the date when the first 15 treated evaluable participants in Cohort C have had at least 2 post-baseline tumor assessments or

experienced confirmed objective response or have discontinued the study for any reason.
For participants with 2 post-baseline tumor assessments and occurrence of response at the second post-baseline tumor assessment, the confirmatory assessment will also be included.

For Cohort C, if 1 or 0 confirmed response is observed among the first 15 treated participants evaluable for activity, the cohort will be closed.

In addition, the study analysis will then be conducted in three steps for each cohort.

- The first step analysis will be conducted for each cohort when all treated evaluable participants of the cohort have had at least 2 post-baseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. The study cut-off for the first-step analysis can be up to approximately 20 weeks after the date of the first IMP administration of the last participant of the cohort: 16 weeks for 2 tumor assessments and at least 4 weeks if a confirmation of response is needed.
- The second step analysis will be based on the study cut-off for secondary efficacy endpoints including DOR and PFS (final cut-off date), 6 months after the study cut-off for the primary analysis. The primary analysis of ORR and DCR will also be updated at that time.
- The final analysis will be conducted at the end of the study. Only safety analyses will be updated at this time.

For the interim analysis and 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 interim analysis, or 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 as applicable. The following additional rules will apply at interim analysis, 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 prematurely discontinue the study intervention at analysis cut-off date will be analyzed as “ongoing” in the disposition summary.
  - Their treatment-emergent (TE) period, and concomitant medication period will end at the analysis cut-off date.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADC:	antibody drug conjugate
ADI:	actual dose intensity
AE:	adverse event
AESIs:	adverse events of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATAs:	antitherapeutic antibody
AUC:	area under the curve, area under the curve
BCVA:	best corrected visual acuity
BOR:	best overall response
BSA:	body surface area
BUN:	blood urea nitrogen
CEA:	carcinoembryoonic agent
CEACAM5:	carcinoembryonic antigen-related cell adhesion molecule 5
cfDNA:	circulating free DNA
CI:	confidence interval
COVID-19:	coronavirus disease 2019
CR:	complete response
CTCs:	circulating tumoral cells
CV:	coefficient of variation
DCR:	disease control rate
DNA:	deoxyribonucleic acid
DOR:	duration of response
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
e-CRF:	electronic case report form
EGFR:	estimated glomerular filtration rate
EOT:	end-of-treatment
HGLT:	high level group term
HLGT:	high-level group term
HLT:	high-level term
ICI:	immune checkpoint inhibitor
IHC:	immunohistochemistry
IMP:	investigational medicinal product
INR:	international normalized ratio
IRT:	interactive response technology
LLN:	lower limit of normal
LLOQ:	lower limit of quantitation
LLT:	lower-level term
MedDRA:	Medical Dictionary for Regulatory Activities

NCI-CTCAE: National cancer institute common terminology for adverse events
ORR: objective response rate
PCSA: potentially clinically significant abnormalities
PD: progressive disease
PDI: planned dose intensity
PFS: progression-free survival
PR: partial response
PS: performance status
PT: preferred term
Q1: quartile 1
Q2W: every 2 weeks
Q3: quartile 3
RBC: red blood cells
RDI: relative dose intensity
RECIST: response evaluation criteria in solid tumors
RNA: ribonucleic acid
SAEs: serious adverse event
SAP: statistical analysis plan
SD: standard deviation
SE: standard error
SOC: system organ class
TE: treatment-emergent
TEAE: treatment-emergent adverse event
TKI: tyrosine kinase inhibitor
TNBC: triple-negative breast cancer
ULN: upper limit of normal
ULOQ: upper limit of quantification
WBC: white blood cell
WHO-DD: World Health Organization-drug dictionary

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
1	01-Oct-2021	Added the word “confirmed” for CR and PR for DCR and DOR definitions	To clarify
		Removed specifications of interim analysis planning for the mPAC Cohort B	To remove the interim analysis for the mPAC Cohort B
		Updated definition of activity population	To clarify

Amendment Number	Approval Date	Changes	Rationale
2	25-Jul-2022	Removed mention of interim analysis for mBC Cohort A	The mBC Cohort A stopped enrollment
		mPAC Cohort C and corresponding analyses added	To evaluable Tusamitamab ravtansine in combination with gemcitabine in participants with pancreatic adenocarcinoma

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

Demographics, baseline characteristics, medical and 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, [65-75[, ≥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)
- ECOG PS (0,1)
- Weight in kg as quantitative variable
- BSA in m^2 as quantitative variable
- Primary tumor site (Head, body, tail, head and body, body and tail)

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, histology or histopathology type, mBC subtype (TNBC/non-TNBC), specific mutations and local protein expression (Her2 status, ER status, PgR status), TNM, staging, time from initial diagnosis to first administration of IMP (in years).

Specific disease status at study entry includes extent of diseases, number and type of organs involved (including primary tumor location), time from relapse to first administration of IMP, circulating CEA (<100 µg/L, ≥100 µg/L and <80 µg/L, ≥80 µg/L).

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 the 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 received 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. The summaries will be sorted by decreasing frequency of anatomic category (ATC) based on the overall incidence in the "All group". In case of equal frequency, alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

Premedications

As defined in Section 6.1 of the study protocol, participants receive premedications prior to IMP administration to prevent related allergic reactions to tusamitamab ravtansine. 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 and radiotherapy.

- Number (%) of prior anticancer therapies including neoadjuvant/adjuvant/radiosensitizer and advanced regimen
- Number (%) of participants with intent:
  - neoadjuvant and adjuvant and chemoradiotherapy and advanced
  - neoadjuvant or adjuvant and advanced
  - chemoradiotherapy and advanced,
  - neoadjuvant or adjuvant or chemoradiotherapy only
  - advanced only
- Number (%) of prior anticancer therapies in the advanced setting.

A regimen in the advanced setting consists of a single agent, combination, or a sequential therapeutic strategy with several drugs, given until a PD is documented.

Adjuvant/neoadjuvant treatment for a participant who relapsed with metastatic disease during or within 6 months of treatment will be considered as first line treatment 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, Anti VEGF/VEGFR (anti-angiogenic), BRAF kinase inhibitors, ALK inhibitors, RAS/RAF/MEK/ERK signaling pathway inhibitors, ROS1 inhibitors
    - Immune checkpoint inhibitor (ICI)
    - Others
  - Chemotherapy: Taxane, anthracyclines, platinum, pemetrexed, antimicrobules, gemcitabine, fluoropyrimidine (5-FU or capecitabine), others
  - Antibody drug conjugate (ADC)
  - Hormonal therapy for breast
  - Others
- Prior immune checkpoint inhibitor: Single or Combination with chemotherapy
- Summary of last prior anticancer therapy:
  - Time from completion of last regimen to first administration of IMP (in weeks)
  - Main treatments of last regimen:
    - ICI monotherapy
    - ICI in combination with chemotherapy
    - ICI and other biologics and small molecules
    - No ICI: Chemotherapy (Taxane, anthracyclines), Biologics, or Chemotherapy, or hormonal therapy, and Biologics
  - Best response to the last regimen
  - Reason for discontinuation of the last line
  - Sensitivity to previous lines (<4 months, 4 to 6 months, >6 months):
    - To first line (duration of first line prior anti-cancer therapy other than adjuvant/neoadjuvant) for both mPAC cohorts
    - To second line (duration of second line prior anti-cancer therapy) for both mPAC cohorts
    - To last line (duration of last line prior anti-cancer therapy) for all cohorts
    - To Taxane therapy for all cohorts
- Prior surgery: number (%) of participants with any prior surgery (including biliary stent), type of surgery and time from the last surgery to the first administration of IMP (in months).
- Prior radiotherapy: number (%) of participants with any prior radiotherapy, intent, analgesic intent if palliative and time from last dose of radiotherapy to first administration of IMP (in months).

Further anticancer therapies after discontinuation of 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 on-treatment 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

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 (3) are provided in tables below.

Table 15 - 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
Erythrocytes (RBC) count	M	10^12/L	4.5	5.9
Erythrocytes (RBC) count	F	10^12/L	4	5.2
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 16 - 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
Potassium	mmol/L	3.5	5
Sodium	mmol/L	136	145
Protein	g/L	55	80
Urea	mmol/L	3.6	7.1

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act16432-16-1-9-sap

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