# STATISTICAL ANALYSIS PLAN

| | |
|---|---|
| **Protocol title:** | **Open-label, single-arm trial to evaluate antitumor activity, safety, and pharmacokinetics of tusamitamab ravtansine (SAR408701) used in combination with ramucirumab in metastatic, non-squamous, non-small-cell lung cancer (NSQ NSCLC) patients with CEACAM5-positive tumors, previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor** |
| **Protocol number:** | **ACT16525** |
| **Compound number (INN/Trademark):** | **SAR408701** |
| **Study phase:** | **Phase 2** |
| **Short title:** | **SAR408701 in combination with ramucirumab in pretreated patients with NSQ NSCLC (CARMEN-LC04)** |
| **Statistician:** | [redacted] |
| **Statistical project leader:** | [redacted] |
| **Date of issue:** | **21-Sep-2023** |

**Regulatory agency identifier number(s):**

| | |
|---|---|
| IND: | 144484 |
| EudraCT: | 2019-003914-15 |
| NCT: | NA |
| WHO: | U1111-1244-1585 |
| EUDAMED: | NA |
| Other: | NA |

Total number of pages: 47

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# VERSION HISTORY

The statistical analysis plan (SAP) v1.0 for study ACT16525 is based on the amended protocol 01 dated 12-Nov-2020. This section summarizes the major changes to the statistical analysis features in the SAP. The first participant was enrolled on 28-Oct-2020. Changes made in SAP v2.0 are based on amended protocol 02 dated 20 December 2022 and were made before the database lock for the CSR after the last participant last visit.

**Table 1 - Major changes in statistical analysis plan**

| SAP Version | Approval Date | Changes | Rationale |
|---|---|---|---|
| 1.0 | 09-Nov-2021 | Updates in definition of screened population, all-treated population, activity population, ATA population and PK population in Section 3. | To clarify the analysis populations and to reflect the actual programming. |
| 2.0 | | To precise this SAP cover only doublet cohort | For clarity |
| | | SAR408701 was replaced by the INN tusamitamab ravtansine | For clarity |
| | | Added disease control rate as a secondary endpoint | For efficacy analysis |
| | | Added subgroups analysis : PD-L1 expression (<50%,≥50%), Prior taxanes (yes,no) and Prior antimicrotubules (yes, no) | For efficacy analysis |
| | | Clarifications added for the definition of duration of IMP exposure | For clarity |
| | | Adverse events: updates section for adverse events of special interest (AESIs) and other adverse events (AEs) of interest | |
| | | Additional safety assessments<br>• Additional analyses for drug-induced liver injury<br>• Updated Schirmer test categories, visual acuity test, and slit-lamp examination | |
| | | Added formula for QTc Fridericia; Deletion of some urinalysis | For clarity |
| | | Update PK analyses | |
| | | Update biomarkers analyses | |
| | | Correction of typographical errors and standardization of wording | For clarity |

# 1 INTRODUCTION

## 1.1 STUDY DESIGN

This is a Phase 2, multicenter, multinational, open-label, single-arm study evaluating tusamitamab ravtansine in combination with ramucirumab in participants with metastatic CEACAM5 positive (CEACAM5 immunohistochemistry [IHC] intensity ≥2+ in ≥50% of tumor cells) nonsquamous non-small-cell lung cancer (NSQ NSCLC) previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor (ICI).

The study will comprise 2 parts: Part 1 (Safety run-in) to assess the tolerability and to confirm the recommended Phase 2 dose (RP2D) of tusamitamab ravtansine in combination with ramucirumab and Part 2, to assess the antitumor activity of tusamitamab ravtansine in combination with ramucirumab.

The screening phase will be performed only in pre-screened participants determined to be CEACAM5 positive by central IHC assessment.

Approximately 30 to 36 participants will be treated from approximately 18 sites in order to achieve a total of 30 participants treated at the RP2D and evaluable for activity.

The cycle duration is 14 days. The median expected duration of study per participant is estimated to be 11 months (up to 1 month for screening, a median of 6 months for study intervention administration, a median of 4 months for end of treatment (EOT) assessments and safety follow-up visit). Participants will continue to receive study intervention until disease progression, unacceptable toxicity, or upon participant's request to stop the study intervention, or Investigator's decision, whichever occurs first.

Protocol amendment 02 dated 20 December 2022 added the evaluation of a new cohort of 6 to 12 participants to assess the safety and tolerability of a new combination of tusamitamab ravtansine (SAR408701) with ramucirumab and pembrolizumab given every 3 weeks (Q3W). This new cohort has not started yet; therefore, the SAP does not cover any details regarding this part of the study.

## 1.2 OBJECTIVES AND ENDPOINTS

**Table 2 - Objectives and endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • **Part 1 (safety run-in):** To assess the tolerability and to confirm the recommended dose of tusamitamab ravtansine in combination with ramucirumab in the NSQ NSCLC population | • **Part 1:** Incidence of study drug-related dose-limiting toxicity (DLT) at Cycle 1 and Cycle 2 (C1D1 to C2D14). Anticipated DLT includes, but is not limited to, corneal toxicity |

| Objectives | Endpoints |
|---|---|
| • **Part 2:** To assess the antitumor activity of tusamitamab ravtansine in combination with ramucirumab in the NSQ NSCLC population | • **Part 2:** Objective response rate (ORR) defined as proportion of participants with confirmed complete response (CR) or partial response (PR) as best overall response (BOR) determined per response evaluation criteria in solid tumors (RECIST) 1.1 |
| **Secondary** | |
| • To assess the safety and tolerability of tusamitamab ravtansine in combination with ramucirumab | • Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) and laboratory abnormalities according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) V5.0 |
| • To assess the durability of the response to treatment with tusamitamab ravtansine in combination with ramucirumab | • Duration of response (DOR), defined as the time from first documented evidence of CR or PR until progressive disease (PD) determined per RECIST <1.1 or death from any cause, whichever occurs first |
| • To assess anti-tumor activity of tusamitamab ravtansine in combination with ramucirumab on progression-free survival (PFS) and disease control rate (DCR) | • Progression-free survival, defined as the time from the first investigational medicinal product (IMP) administration to the date of the first documented disease progression or death due to any cause, whichever comes first<br>• Disease control rate (DCR), defined as the percentage of participants who have achieved confirmed CR, confirmed PR or stable disease as per RECIST v1.1 |
| • To assess the pharmacokinetic (PK) profiles of tusamitamab ravtansine and ramucirumab when given in combination | • Pharmacokinetic parameters of tusamitamab ravtansine and ramucirumab |
| • To assess the immunogenicity of tusamitamab ravtansine when given in combination with ramucirumab | • Incidence of antitherapeutic antibodies (ATAs) against tusamitamab ravtansine |
| **Tertiary/exploratory** | |
| • To explore circulating carcinoembryonic agent (CEA) as a potential biomarker for activity and to evaluate circulating CEA levels at pre-screening | • Circulating CEA at pre-screening, screening, and during the treatment period |

### 1.2.1 Estimands

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

For all these estimands, the study intervention of interest will be tusamitamab ravtansine in combination with ramucirumab.

**Table 3 - Summary of primary estimands for main endpoints**

| Endpoint Category (estimand) | Endpoint | Estimands | | |
|---|---|---|---|---|
| | | Population | Intercurrent event(s) handling strategy | Population-level summary (Analysis and missing data handling) |
| **Primary safety objective: To assess the tolerability and to confirm the recommended dose of tusamitamab ravtansine in combination with ramucirumab in the NSQ NSCLC population** | | | | |
| Primary endpoint (primary estimand 1) | Study drug-related dose-limiting toxicity at Cycle 1 and Cycle 2, by dose level (if applicable). | DLT-evaluable population | Participants from the DLT-evaluable population will not experience any anticipated intercurrent events before experiencing a DLT at Cycle 1 or at Cycle 2 or before completing the Cycle 2, whichever is earlier. | Incidence of study drug-related DLTs at Cycle 1 and Cycle 2, defined as rate of participants with study-drug related DLTs at Cycle 1 and Cycle 2. |
| **Primary efficacy objective: To assess the antitumor activity of tusamitamab ravtansine in combination with ramucirumab in the NSQ NSCLC population** | | | | |
| Primary endpoint (primary estimand 2) | Confirmed objective response (confirmed CR or PR as BOR), determined according to RECIST 1.1 | All-treated population restricted to participants treated at the RP2D. | Regardless of IMP discontinuation (treatment policy strategy).<br>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.<br>In the absence of confirmed objective response, participants will be considered as non-responders, whatever the reason (including participants with non-evaluable BOR). |

# 2 SAMPLE SIZE DETERMINATION

The safety run-in part aims to establish the RP2D of tusamitamab ravtansine in combination with ramucirumab according to DLTs observed.

Part 2 of this study is designed to obtain preliminary efficacy, safety, and PK data on tusamitamab ravtansine administered in combination with ramucirumab to participants with NSQ NSCLC. As the second part is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design.

Assuming a pre-screening failure rate of 80% and a study screening failure rate of 20%, approximately 225 participants will be pre-screened to achieve a total of up to approximately 36 treated participants, including Part 1 (safety run-in) and Part 2 of the study.

*Sample size of the safety run-in part:*

The actual sample size is expected to vary depending on DLTs observed. It is anticipated that around 6 to 12 DLT-evaluable participants (as defined in Section 3) will be enrolled in the safety run-in part of the study.

*Sample size of Part 2:*

The initial plan is to treat a total of 30 participants evaluable for activity (ie, having at least one post-baseline evaluable tumor assessment, early clinical progression, or death due to disease progression). The 6 participants treated at the RP2D in the safety run-in part will also be evaluable for this second part of the study.

Estimated ORR and 95% exact CIs by number of responders from a sample size of 30 participants evaluable for activity are summarized in Table 4.

**Table 4 - Estimated objective response rate depending on number of responders**

| Number of Responders (N=30) | Objective Response Rate in % (95% Clopper-Pearson CI) |
|---|---|
| 6 | 20.00% (7.71% - 38.57%) |
| 8 | 26.67% (12.28% - 45.89%) |
| 9 | 30.00% (14.73% - 49.40%) |
| 11 | 36.67% (19.93% - 56.14%) |
| 12 | 40.00% (22.66% - 59.40%) |

# 3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

**Table 5 - Populations for analyses**

| Population | Description |
|---|---|
| Pre-screened | All participants who signed the pre-screening informed consent for CEACAM5 assessment of their biopsy. |
| Screened | All participants who signed the screening informed consent for study participation. |
| Enrolled | Participants from screened population who have been allocated to intervention regardless of whether the intervention was received or not. |
| All-treated | All enrolled participants exposed to the study treatment, regardless of the amount of treatment administered. All safety analyses will be performed on this population, which is also the primary population for analysis of all efficacy parameters. |
| DLT-evaluable (Part 1) | All enrolled participants who received 2 cycles with at least 80% of the intended dose for both tusamitamab ravtansine and ramucirumab at each of the two first infusions unless they discontinued the study intervention before the end of Cycle 2 due to a DLT. |
| Activity | All-treated participants who have measurable disease at study entry and at least 1 post-baseline evaluable tumor assessment. Participants with no post-baseline evaluable tumor assessment but with an early clinical 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. |
| PK | All participants from the all-treated population with at least 1 post-baseline PK concentration with adequate documentation of dosing and sampling dates and times. |
| ATA | All participants from the all-treated population with at least 1 post-baseline ATA result (negative, positive, or inconclusive). |
| Population without trial impact (disruption) due to COVID-19 | All treated participants:<br>• Without any critical or major deviation related to COVID-19<br>• And who did not permanently discontinue study intervention due to COVID-19<br>• And who did not permanently discontinue study due to COVID-19 |

ATA = anti-therapeutic antibodies; CEACAM5 = carcinoembryonic antigen-related cell adhesion molecule 5; DLT = dose-limiting toxicity; PK = pharmacokinetic.

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

Participants treated with 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 treated and will be included in the all-treated population.

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

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

# 4 STATISTICAL ANALYSES

## 4.1 GENERAL CONSIDERATIONS

This study is not intended to explicitly test a hypothesis. 95% confidence intervals will be provided for primary and secondary efficacy endpoints.

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

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

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

The study cut-off for analysis of the primary efficacy endpoint, ORR, corresponds to the date on which all evaluable treated participants have had at least 2 post-baseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason, up to approximately 6 months (4 months for 2 tumor assessments and 2 months for confirmation of response, if needed) from the date of the last participant's first IMP administration.

The analysis cut-off date is defined as the date of the database extraction that will be performed for the analysis.

***Observation period***

The observation period will be divided into 4 segments:

- The **pretreatment period** is defined as the period up to the first IMP administration.
  - The **prescreening period** is defined as the period from the pre-screening informed consent or addendum to informed consent (for participants with available CEACAM5 result) to the day before the screening informed consent.
  - The **screening period** is defined as the period from the screening informed consent up to the first IMP administration.
- The **on-treatment period** (ie, **treatment-emergent period**) is defined as the period from the first IMP administration to the last IMP administration + 30 days.
- The **posttreatment 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 5 will be summarized. Reasons for exclusion from the population without trial impact (disruption) due to COVID-19 will be summarized.

Pre-screen failures are defined as participants who consent to participate in the pre-screening phase of the study but are not subsequently screened. The number (%) of pre-screen failures and reasons for pre-screen failures will be provided in the pre-screened 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 study intervention discontinuation, the following definitions will be used:

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

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

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

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

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

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

For all categories of participants (except for the prescreened, screened, not enrolled categories) percentages will be calculated using the number of participants in the all-treated population as the denominator.

Protocol deviations

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

## 4.3 PRIMARY ENDPOINTS ANALYSIS I

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

### 4.3.1 Definition of endpoints

#### *4.3.1.1 Study-drug related DLT at Cycle 1 and Cycle 2*

The primary safety endpoint is studydrug-related DLT in Part 1 at Cycle 1 and Cycle 2 (from C1D1 to C2D14). The list of DLTs to be considered of the study is defined in the protocol (see Table 4 of the study protocol). For analysis purposes, DLTs will be identified based on the AEs reported on the e-CRF DLT page during the DLT observation period in Part 1.

#### *4.3.1.2 Confirmed objective response*

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

The BOR will be derived according to RECIST 1.1 definitions (1, 2) based on the investigator's assessment. The BOR is the best overall response observed from the date of the first administration of IMP until documented disease progression, death, start of an anticancer therapy, or analysis cut-off date, whichever occurs first.

### 4.3.2 Main analytical approach

#### *4.3.2.1 Study-drug related DLT at Cycle 1 and Cycle 2*

The primary safety analysis is based on the primary estimand 1 introduced in Section 1.2.1. It is defined according to the following attributes:

- The endpoint is study-drug related DLT during the DLT observation period, ie, Cycle 1 and Cycle 2, from Cycle 1 Day 1 to Cycle 2 Day 14.
- The treatment condition of interest is tusamitamab ravtansine in combination with ramucirumab, by dose level (if applicable).

- The analysis population is the DLT-evaluable population (defined in Section 3).
- No intercurrent events handling strategy is defined due to the definition of the analysis population. Indeed, participants from the DLT-evaluable population will not experience any anticipated intercurrent event (study intervention discontinuation, study discontinuation, start of an anticancer therapy, or death) before experiencing a DLT at Cycle 1 or Cycle 2, or before completing the Cycle 2, whichever is earlier.
- The population-level summary will include the incidence of DLTs at Cycle 1 and Cycle 2, defined as number and percentage of participants experiencing at least one study-drug related DLT. There will be no missing data in the analysis population.

#### *4.3.2.2 Confirmed objective response*

The primary efficacy analysis is based on the primary estimand 2 introduced in Section 1.2.1. It 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 in combination with ramucirumab.
- The analysis population is the subgroup of participants from the all-treated population (defined in Section 3) treated at the RP2D (ie, excluding participants treated at the starting dose if this differs from the RP2D).
- Intercurrent events:
  - The study intervention discontinuation intercurrent event will be handled with the treatment policy strategy. Confirmed objective response will be assessed based on tumor assessments regardless of study intervention discontinuation.
  - The further anticancer therapy (including further systemic anticancer therapies) intercurrent event will be handled with the "while not initiating further anticancer therapy" strategy. Confirmed objective response will be assessed based on tumor assessments done up to the time of initiation of further anticancer therapy.
- The population-level summary will include the ORR, defined as the rate of participants with confirmed objective response, and two-sided 95% confidence interval 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 the subgroup of participants from the all-treated population treated at the RP2D (ie, excluding participants treated at the starting dose, if this differs from the RP2D).

As a supplementary analysis, confirmed objective response as per RECIST 1.1 will also be summarized on the subgroup of participants from the activity population (defined in Section 3) treated at the RP2D (ie, excluding participants treated at the starting dose if this differs from the RP2D). The same analytical approach as primary efficacy analysis defined in Section 4.3.2.2 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), will be summarized using a waterfall plot on the subgroup of participants from the all-treated population (defined in Section 3) treated at the RP2D (ie, excluding participants treated at the starting dose, if this differs from the RP2D).

### 4.3.5 Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, analyses will be performed on the primary efficacy endpoint (defined in Section 4.3.1.2) 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)
- Smoking status (Never, Former and Current)
- PD-L1 expression (<1%, ≥1% and <50%, ≥50%)
- Circulating CEA at baseline (<100, ≥100 µg/L)
- Prior treatment with EGFR, ALK, or ROS1 inhibitors (Yes, No)
- Prior ICI treatment administration (Sequential, Combination with chemotherapy)
- Time from initial diagnosis (<12 months, ≥12 months)
- Brain metastases (Yes, No)
- Number of organs involved (including primary tumor location) (<3, ≥3)
- Tumor burden at baseline, ie, sum of the longest diameters of the target lesions (<100, ≥100 mm)
- Prior taxanes (Yes, No)
- Prior antimicrotubules (including taxanes and vinca-alcaloids) (Yes, No)

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.

## 4.4 SECONDARY ENDPOINTS ANALYSIS

The secondary endpoints detailed in this section are the duration of response and the progression-free survival. Other secondary endpoints analyses are defined in Section 4.7 (AE, SAE, laboratory abnormalities) and Section 4.8 (PK, immunogenicity).

### 4.4.1 Key/Confirmatory secondary endpoint

No key/confirmatory secondary endpoint.

### 4.4.2 Supportive secondary endpoints

#### *4.4.2.1 Definition of endpoints*

##### *4.4.2.1.1 Duration of response*

DOR is defined as the time from the date of first initial occurrence of the confirmed CR or PR to the date of first documentation of objective progressive disease according to RECIST 1.1 (1, 2) or death due to any cause, whichever occurs first.

In the absence of disease progression or death, DOR will be censored at the date of the last evaluable tumor assessment (not showing documented disease progression) performed up to the date of initiation of new anti-cancer therapy.

##### *4.4.2.1.2 Progression-free survival*

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

The analysis of PFS will be based on the following censoring rules:

- If documented disease progression or death is not observed prior to the initiation of a further anti-cancer therapy, then PFS will be censored at the date of the last evaluable tumor assessment performed up to the date of initiation of a further anti-cancer therapy.
- A participant without PFS event (documented disease progression or death) and without any evaluable post-baseline tumor assessment will be censored at the date of the first administration of IMP (Day 1).

#### *4.4.2.1.3 Disease control rate*

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

### *4.4.2.2 Main analytical approach*

#### *4.4.2.2.1 Duration of response*

Analysis of the DOR 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 in combination with ramucirumab.
- The analysis population is the subgroup of participants from the all-treated population (defined in Section 3) treated at the RP2D of tusamitamab ravtansine (ie, excluding participants treated at the starting dose, if this differs from the RP2D) and limited to participants who have 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) intercurrent event will be handled with the hypothetical strategy. DOR will be assessed based on tumor assessments had a further anticancer therapy not being taken. DOR will be assessed based on tumor assessments up to the time of initiation of further anticancer therapy.
  - Two or more consecutive missing/unevaluable tumor assessments immediately before documented PD or death will be handled with the hypothetical strategy. DOR will be assessed based on tumor assessments had 2 consecutive tumor assessments not been missed immediately before documented PD or death. DOR will be assessed based on tumor assessments up to the last evaluable tumor assessment documenting no progression.
- The population-level summary will include the median DOR and associated 95% confidence interval using Kaplan-Meier methods.

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

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

#### *4.4.2.2.2 Progression-free survival*

Analysis of the PFS 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 in combination with ramucirumab.
- The analysis population is the subgroup of participants from the all-treated population (defined in Section 3) treated at the RP2D of tusamitamab ravtansine (ie, excluding participants treated at the starting dose if this differs from the RP2D).
- Intercurrent events:
  - The study intervention discontinuation intercurrent event will be handled with the treatment policy strategy. PFS will be assessed based on tumor assessments regardless of study intervention discontinuation.
  - The further anticancer therapy (including further systemic anticancer therapies) intercurrent event will be handled with the hypothetical strategy. PFS will be assessed based on tumor assessments had a further anticancer therapy not being taken. PFS will be assessed based on tumor assessments up to the time of initiation of further anticancer therapy.
  - Two or more consecutive missing/unevaluable tumor assessments immediately before documented PD or death will be handled with the hypothetical strategy. PFS will be assessed based on tumor assessments had 2 consecutive tumor assessments not been missed immediately before documented PD or death. PFS will be assessed based on tumor assessments up to the last evaluable tumor assessment documenting no progression.
- The population-level summary will include:
  - Kaplan-Meier estimates of the $25^{th}$, $50^{th}$ and $75^{th}$ 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 (documented disease progression or death without documented disease progression) and the number (%) of censored participants and reason for censoring (no baseline tumor assessment, no evaluable postbaseline tumor assessment, alive without documented disease progression, event occurred after 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.

#### *4.4.2.2.3 Disease control rate*

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

- The endpoint is disease control response (confirmed CR or PR or stable disease (SD) as BOR) as per RECIST 1.1.
- The treatment condition of interest is tusamitamab ravtansine in combination with ramucirumab.
- The analysis population is the subgroup of participants from the all-treated population (defined in Section 3) treated at the RP2D of tusamitamab ravtansine (ie, excluding participants treated at the starting dose if this differs from the RP2D).
- 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 2-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.

## 4.5 TERTIARY/EXPLORATORY ENDPOINTS ANALYSIS

Analyses of tertiary/exploratory endpoints (eg, biomarkers) are defined in Section 4.8.

## 4.6 MULTIPLICITY ISSUES

No multiplicity issues are anticipated in this study.

## 4.7 OTHER SAFETY ANALYSES

All safety analyses will be performed on the all-treated population as defined in Section 3, by dose level (if applicable) and overall, unless otherwise specified, using the following common rules:

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

### 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 interventions is administered.
- Duration of IMP exposure (in weeks) is defined as
(last day of exposure - first day of exposure + 1 day)/7.
  - The first day of exposure is defined as the first administration date with nonzero dose for at least 1 of the IMPs (tusamitamab ravtansine or ramucirumab).
  - The last day of exposure is the day before the theoretical date of the next administration (after the last administration), defined as the maximum between:
    - Last administration date + 14 days - 1 day for tusamitamb ravtansine,
    - Last administration date + 14 days - 1 day for ramucirumab.

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

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

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

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

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

- Number (%) of participants with a cycle delayed >7 days (using maximum delay across all cycles)

- Number (%) of cycles delayed
  - Number (%) of cycles delayed between 3 and 7 days
  - Number (%) of cycles delayed between 8 and 14 days
  - Number (%) of cycles delayed >14 days

#### *4.7.1.2 Tusamitamab ravtansine exposure*

The dose information will be assessed by the following:

- Total number of cycles started.
- Number of cycles started per participant.
- Duration of tusamitamab ravtansine exposure (in weeks) is defined by (date of last administration of tusamitamab ravtansine + 14 days - date of first administration of tusamitamab ravtansine)/7.
- Actual dose (in $mg/m^2$). 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 $mg/m^2$): the cumulative dose is the sum of all actual doses of tusamitamab ravtansine, given from first to last administration.
- Actual dose intensity (ADI in $mg/m^2$/week): defined as the cumulative dose divided by the duration of tusamitamab ravtansine exposure (in weeks).
- Planned dose intensity (PDI in $mg/m^2$/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).
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/m}^2\text{/week)}}{\text{PDI (mg/m}^2\text{/week)}}$.

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

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

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

**Table 6 - Tusamitamab ravtansine dose reduction criteria**

| Actual dose level | Dose level interval |
|---|---|
| Starting dose (100 mg/m$^2$) | >90 mg/m$^2$ |
| Dose level -1 (80 mg/m$^2$) | >72.5 mg/m$^2$ and ≤90 mg/m$^2$ |
| Low dose | >0 mg/m$^2$ and ≤72.5 mg/m$^2$ |

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

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

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

#### *4.7.1.3 Ramucirumab exposure*

The dose information will be assessed by the following:

- Total number of cycles started.
- Number of cycles started per participant.
- Duration of ramucirumab exposure (in weeks) is defined by (date of last administration of ramucirumab + 14 days - date of first administration of ramucirumab)/7.
- Actual dose (in mg/kg). In case of dose interruption, actual dose will be the sum of the actual doses administered before and after the dose interruption.

- Cumulative dose (in mg/kg): the cumulative dose is the sum of all actual doses of ramucirumab, given from first to last administration.
- Actual dose intensity (ADI in mg/kg/week): defined as the cumulative dose divided by the duration of ramucirumab exposure (in weeks).
- Planned dose intensity (PDI in mg/kg/week): corresponds to the planned dose multiplied by the theoretical total number of doses started and divided by the theoretical cycle duration expressed in weeks (ie, 2 weeks per cycle started).
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/kg/week)}}{\text{PDI (mg/kg/week)}}$.

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

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

- Dose reduction: The first administration will not be counted as a dose reduction. For the second and subsequent ramucirumab administrations, dose reduction will be determined using the dose level intervals provided in Table 7, 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 7 - Ramucirumab dose reduction criteria**

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

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

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

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

    - Number (%) of participants with at least 1 dose reduction
    - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with a least 1 dose interruption
- **Cycle** (number of cycles started will be used as denominator)
  - Number (%) of cycles with at least 1 dose modification
    - Number (%) of cycles with at least 1 dose 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 (TEAEs): AEs that developed, worsened or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period.

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

The primary AE analyses will be on TEAEs. Pre-treatment AEs 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 8.

**Table 8 - Sorting of AE tables**

| AE presentation | Sorting rules |
|---|---|
| SOC, HLGT, HLT and PT | By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs |
| SOC and PT | By the internationally agreed SOC order and decreasing frequency of PTs[a, b] |
| SMQ/CMQ and PT | By decreasing frequency of SMQs/CMQs and PTs[a] |
| PT | By decreasing frequency of PTs[a] |

*a* Sorting will be based on the experimental intervention arm at the highest dose.
*b* The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by primary 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 discontinuation of tusamitamab ravtansine
- Any TEAE leading to permanent partial discontinuation of ramucirumab
- Any TEAE related to IMP
- Any Grade ≥3 TEAE related to IMP
- Any treatment-emergent SAE related to IMP
- Any treatment-emergent corneal event (CMQ "Corneal events compound level")
- Any treatment-emergent peripheral neuropathy event TEAE (SMQ "Peripheral neuropathy" [Narrow and Broad])
- Any ocular/visual symptoms TEAE (CMQ "Eye disorders exclude corneal disorders")

The AE summaries of Table 9 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.

**Table 9 - Analyses of adverse events**

| Type of AE | MedDRA levels |
|---|---|
| All TEAE | Primary SOC, HLGT, HLT, and PT |
| | Primary SOC and PT |
| | PT |
| TEAE related to IMP as per Investigator's judgment | Primary SOC and PT |
| TEAE related to tusamitamab ravtansine as per Investigator's judgment | Primary SOC and PT |
| TEAE related to ramucirumab as per Investigator's judgment | Primary SOC and PT |
| Treatment-emergent SAE | Primary SOC, HLGT, HLT and PT |
| | Primary SOC and PT |
| Treatment-emergent SAE related to IMP as per Investigator's judgment | Primary SOC and PT |
| Treatment-emergent SAE related to tusamitamab ravtansine as per Investigator's judgment | Primary SOC and PT |
| Treatment-emergent SAE related to ramucirumab as per Investigator's judgment | Primary SOC and PT |
| TEAE leading to permanent full study intervention discontinuation | Primary SOC and PT |
| TEAE leading to permanent partial discontinuation of tusamitamab ravtansine | Primary SOC and PT |
| TEAE leading to permanent partial discontinuation of ramucirumab | Primary SOC and PT |
| 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 (death as an outcome of the AE as reported by the Investigator in the AE page) | 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, dose reduction and dose omission) | Primary SOC and PT |
| TEAE leading to dose modification of ramucirumab (including dose delay, dose reduction and dose omission) | Primary SOC and PT |
| TEAE leading to dose interruption of tusamitamab ravtansine | Primary SOC and PT |
| TEAE leading to dose interruption of ramucirumab | Primary SOC and PT |

*a* Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs (except for pretreatment AEs) leading to permanent full study intervention discontinuation.

## Analysis of deaths

In addition to the analyses of deaths included in Table 9 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods by study period and main 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 of date of death/period),
    - Grade 5 TEAE with a fatal outcome during the treatment-emergent 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 posttreatment period).
- Deaths in nonenrolled 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) will be defined using eCRF and other AEs of interest will be selected for analyses as indicated in Table 10. Number (%) of participants experiencing at least 1 TEAE will be provided overall for AESI, and for each other event of interest, by SOC and PT (if applicable). The DLTs observed during the DLT-observation period will be listed in the DLT-evaluable population. Tables will be sorted as indicated in Table 8.

**Table 10 - Selections for AESIs and other AEs of interest**

| AESIs and other AEs of interest | Selection |
|---|---|
| **AESIs** | eCRF AESI specific tick box on the AE page |
| DLT during DLT observation period | eCRF specific DLT page |
| **Other AEs of interest** | |
| Any AE meeting DLT criteria beyond the DLT observation period | AEs reported on the eCRF DLT page outside the DLT observation period |
| Corneal events | CMQ “Corneal events compound level” containing the PTs included in both SOC “Eye disorders” and SMQ “Corneal disorders” (Narrow) |

| AESIs and other AEs of interest | Selection |
|---|---|
| Ocular/visual symptoms (excluding corneal disorders) | CMQ "Eye disorders exclude corneal disorders" containing PTs included in SOC "Eyes disorders" and excluding PTs in SMQ "Corneal disorders" (Narrow) |
| Cardiac conduction defects | SMQ "Conduction defects" (Narrow) |
| Peripheral neuropathy events | SMQ "Peripheral neuropathy" (Narrow and Broad) |
| Colitis events (excluding infective) | CMQ "Colitis (excluding infective)" containing PTs included in HLT "Colitis (excl infective)" |
| Hypersensitivity events | SMQ "Hypersensitivity" (Narrow) and adverse event occurring on the day or the day after the infusion |
| Hepatic disorders adverse events | SMQ "Hepatic Disorders" (Narrow and Broad) |
| Hematological adverse events | SMQ "Haematopoietic cytopenias" (Narrow and Broad) |
| AE related to COVID-19 illness | SMQ "COVID-19" (Narrow) |

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

In addition, a summary table of corneal events will be displayed by grade.

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

- Number (%) of participants by worst grade.
- Cycle of first onset of corneal event regardless of the grade.
- Cycle of first onset of corneal event with the worst grade.
- Relationship to the study intervention: in case of multiple events 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 events 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 events 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 is defined as one or a group of concomitant corneal events. A recurrence is defined as any new 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 1 recovered or resolved occurrence of a 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 1 recurrence, considering the shortest time among all recurrences by participant.

Beside the AE categorized as ocular/visual AEs, all ocular symptoms (coded term) recoded in the eCRF will be reported as a descriptive analysis. The same analysis will be done separately on ocular symptoms associated with treatment-emergent corneal events (CMQ).

### 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 and platelets and coagulation: hemoglobin, hematocrit, red blood cell (RBC) count, platelet count, prothrombin time (expressed as international normalized ratio [INR]) and activated partial thromboplastin time (aPTT),
  - White blood cells: white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, basophils and eosinophils.
- Clinical chemistry:
  - Metabolism: glucose, total protein, and albumin,
  - Electrolytes: sodium, potassium, 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) and urea,
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total and direct bilirubin,
  - Circulating carcinoembryonic antigen (CEA).

- Urinalysis:
  - Urine dipstick: proteins,
  - Urinalysis: proteins assessed on 24 hour urine collection.
- Vital signs: heart rate, systolic and diastolic blood pressure, weight and ECOG Performance Status (PS).
- ECG variables: PR, QRS, QT and corrected QTcF (according to Fridericia).
- $QTcF=QT/RR^{0.33}$.

where RR interval (in seconds) = 60/HR, and HR = heart rate in beats per minute (from the ECG form).

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

For hematological parameters and 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 5.4). For other coagulation and biochemistry 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 treatment-emergent period. These analyses will be performed using local measurements.

For QRS and QTcF 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 the NCI-CTCAE scale is not applicable, such as 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).

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

For laboratory variables, vital signs and ECG variables above, the incidence of participants with at least 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) will be displayed.

For laboratory variables graded by NCI-CTCAE,

- The number (%) of participants with abnormal laboratory tests at baseline will be presented by grade.
- The number (%) of participants with an abnormal laboratory test 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 test abnormalities, the baseline status will be provided according to multiples of the upper limit of normal (ULN) for each test.

For laboratory variables graded neither by NCI-CTCAE nor by PCSA, the number (%) of participants with laboratory test results outside normal ranges will be provided.

***Additional analyses for drug-induced liver injury***

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

- For each liver function test (eg, ALT), participants having experienced a PCSA will be summarized considering worst on-treatment value.
- An Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH)-like plot of peak bilirubin/ULN versus peak or /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 Ocular examinations*

***Schirmer test***

Participants reported Schirmer's test will be classified into 3 classes at baseline: normal (≥10 mm), mild (<10 and >5 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 for the participants with corneal events (CMQ) during the treatment-emergent period and for the participants without an event.

***Visual acuity test***

Analyses are done on the best corrected visual acuity 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 on BCVA (at least one line decrease), the worst outcome on the last BCVA value will be displayed: Recovered to baseline, Not recovered to baseline, Lost to follow-up or dead with ongoing corneal events.

Of note, 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 is considered for the worst value, the worst change from baseline and the last separately even if not measured on the same eye. If the worst absolute value is the same for both eyes, then the eye with the worst change from baseline is considered, and if identical, then the eye with the worst last value is considered.

Participants whose baseline visual acuity had been reported in naked eye instead of BCVA (ie whenever 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 PK analyses

PK analyses will be performed on the PK population as defined in Section 3.

#### *4.8.1.1 Tusamitamab ravtansine*

##### *4.8.1.1.1 Noncompartmental analysis at Cycle 1 and Cycle 4 in Part 1 (safety run-in)*

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 11.

**Table 11 - List of PK parameters and definitions**

| Parameters | Cycle 1 | Cycle 4 | 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 $t_{last}$ |
| AUCtau | ✓ | ✓ | Area under the plasma concentration versus time curve calculated using the trapezoidal method from time 0 to 14 days |

| Parameters | Cycle 1 | Cycle 4 | Definition |
|---|---|---|---|
| AUC | ✓ | | AUC from time zero extrapolated to infinity according to the following equation:<br>$AUC = AUC_{last}+(C_{last}/\lambda_z)$<br>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:<br>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:<br>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:<br>Vss = CL × MRT<br>with MRT = AUMC/AUC(-$T_{inf}$/2 if infusion)<br>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:<br>$t_{1/2z} = 0.693/\lambda_z$<br>Where $\lambda_z$ 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 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.

#### *4.8.1.1.2 Population PK analysis*

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

#### *4.8.1.1.3 $C_{trough}$ over cycles*

$C_{trough}$ is defined as a sample collected before dosing. All concentration values below the LLOQ will be treated as zero in individual listing and respective descriptive statistics. Geometric mean will not be computed in case at least one concentration is below LLOQ.

Individual observed predose concentrations ($C_{trough}$) and concentrations observed at end of infusion ($C_{eoi}$, $C_{eoi+1h}$ if any) will be tabulated and summarized with standard descriptive statistics by dose level (if applicable) and by visit.

For the descriptive statistics, $C_{trough}$ following any dose reduction or preceding dose delay 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 (if applicable), will be provided throughout the course of treatment.

#### *4.8.1.2 Immunogenicity impact on PK*

The impact of immunogenicity on PK will be assessed graphically by plotting individual $C_{trough}$ profiles of participants with treatment-emergent ATA along with mean (±SD) $C_{trough}$ profile of participants without treatment-emergent ATA over cycles. In addition, for participants with treatment-emergent ATA, each ATA positive, negative and inconclusive sample status will be flagged. A boxplot for participants without treatment-emergent ATA will also be displayed at each timepoint along with individual concentrations for participants with treatment-emergent ATA. A flag for ATA positive, negative and inconclusive sample status will also be used.

Descriptive statistics of $C_{trough}$ for participants without treatment-emergent ATA will be provided by cycle.

#### *4.8.1.3 Ramucirumab*

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

Individual observed predose concentrations ($C_{trough}$) and concentrations observed at end of infusion ($C_{eoi}$) will be tabulated and summarized with standard descriptive statistics by dose level (if applicable) and by visit.

For the descriptive statistics, $C_{trough}$ following any dose modification (delay or reduction as defined in Section 4.7.1.2) will be excluded. $C_{eoi}$ will be excluded following dose reduction.

A graphical representation of mean $C_{trough}$ (±SD) profile over time will be provided throughout the course of treatment.

#### *4.8.1.4 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 the number of observations, arithmetic and geometric means, median, standard deviation, coefficient of variation, minimum and maximum) for tusamitamab ravtansine. A listing will also be provided.

### 4.8.2 Immunogenicity analyses

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

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

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

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

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

***Participant's ATA status***

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

***Kinetics of ATA response***

- Kinetics of ATA response will be derived for participants with treatment-induced/boosted ATA.**Time to onset of ATA response** is defined as the time period between the first IMP administration and the first treatment-induced/boosted ATA.
- **Duration of ATA response** is defined as the time between the first treatment-induced/boosted ATA and the last treatment-induced/boosted ATA, irrespective of negative samples or positive samples not reaching the boosted threshold in-between. ATA duration will be summarized only for participants with persistent ATA response.
  - **Persistent ATA response** is defined by treatment-induced/boosted ATA with a duration of ATA response of at least 16 weeks.
  - **Transient ATA response** is defined by treatment-induced/boosted ATA with a duration of ATA response of less than 16 weeks, and the last sample is not treatment-induced/boosted.
  - **Indeterminate ATA** 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.

### 4.8.3 Biomarker analyses

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

Biomarker data will be collected, if available, at prescreening including PD-L1 status by immunohistochemistry (IHC), type of sample (fresh or archived tumor biopsy), tumor mutation/gene alteration status (eg, EGFR, ALK, ROS, MET, RET, BRAF) and circulating CEA.

CEACAM 5 IHC is assessed at prescreening for eligibility of participant for screening to determine if the participant is positive according to the protocol definition: membrane staining at ≥2+ intensity of ≥50% of tumor cells. In case of re-assessment of CEACAM5 IHC, the most recent tumor tissue samples assessed for CEACAM5 expression will be used for baseline characteristics. All these parameters including type of sample (fresh or archived tumor biopsy) will be described.

#### *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*

Biomarkers analyses described in this section will be performed on participants with available data from the pre-screening population.

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.

##### *4.8.3.2.2 Potential biomarker for activity*

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 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).

The correlation between the circulating CEA levels (quantitative) and the tumor burden at baseline will be also assessed and visualized graphically.

##### *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.

## 4.9 INTERIM ANALYSES

No formal interim analysis is planned in this study.

The study analysis will be conducted in 2 steps.

The first analysis step will be conducted when all evaluable treated participants have had at least 2 post-baseline tumor assessments, experienced confirmed objective response, or have discontinued the study for any reason. This study cut-off will occur approximately 6 months after the date of the first IMP administration of the last participant: 4 months for 2 tumor assessments and 2 months if a confirmation of response is needed.

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

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

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 the first 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 discontinued 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 |
| AESI: | adverse event of special interest |
| ALP: | alkaline phosphatase |
| ALT: | alanine aminotransferase |
| aPTT: | activated partial thromboplastin time |
| AST: | aspartate aminotransferase |
| ATA: | antitherapeutic antibody |
| AUC: | area under the curve |
| BCVA: | best corrected visual acuity |
| BOR: | best overall response |
| BSA: | body surface area |
| BUN: | blood urea nitrogen |
| CEA: | carcinoembryonic agent |
| CEACAM5: | carcinoembryonic antigen-related cell adhesion molecule 5 |
| CI: | confidence interval |
| COVID-19: | coronavirus disease 2019 |
| CR: | complete response |
| CV: | coefficient of variation |
| DLT: | dose-limiting toxicity |
| DOR: | duration of response |
| ECG: | electrocardiogram |
| ECOG: | Eastern Cooperative Oncology Group |
| e-CRF: | electronic case report form |
| EOT: | end of treatment |
| HLGT: | high-level group term |
| HLT: | high-level term |
| ICI: | immune checkpoint inhibitor |
| IHC: | immunohistochemistry, immunochemistry |
| IMP: | investigational medicinal product |
| INR: | international normalized ratio |
| LDH: | lactate dehydrogenase |
| 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 Criteria for Adverse Events |
| NSQ NSCLC: | non-squamous non-small cell lung cancer |
| ORR: | objective response rate |

PCSA: potentially clinically significant abnormalities
PD: progressive disease
PDI: planned dose intensity
PD-L1: programmed death-ligand 1
PFS: progression-free survival
PK: pharmacokinetic
PR: partial response
PS: performance status
PT: preferred term
Q1: quartile 1
Q3: quartile 3
RBC: red blood cells
RDI: relative dose intensity
RECIST: response evaluation criteria in solid tumors
RP2D: recommended Phase 2 dose
SAE: serious adverse event
SAP: statistical analysis plan
SD: standard deviation
SE: standard error
SMQ: standardized MedDRA queries
SOC: system organ class
TEAE: treatment-emergent adverse event
TKI: tyrosine kinase inhibitor
ULN: upper limit of normal
ULOQ: upper limit of quantitation
WBC: white blood cells
WHO-DD: World Health Organization-drug dictionary

## 5.2 APPENDIX 2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

***Demographics, baseline characteristics, medical surgical history***

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

Demographic and baseline characteristics

- Age in years as quantitative variable and in categories (<65, [65-75[, ≥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

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, histopathology type, 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 (both including and excluding primary tumor location), PD-L1 expression (<1%, ≥1%), smoking status (current, former, never) and smoking habits (in pack-years).

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

***Prior or concomitant medications***

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

- Prior medications are those the participant received prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to any IMP from the first administration of IMP to the last IMP intake + 30 days.
- Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was 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. 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 ramucirumab administration to prevent from infusion related allergic reactions to tusamitamab ravtansine and/or ramucirumab. Premedications are defined as non-investigational medicinal products and are reported on a specific e-CRF page.

Number (%) of participants treated with dexamethasone and number (%) of participants treated with Histamine H1 antagonist after 4 cycles will be provided. In addition, number of cycles of participants treated with Histamine H1 antagonist will be summarized as a quantitative variable.

### *Anticancer therapies*

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

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

  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-angiogenic, BRAF kinase inhibitors, ALK inhibitors, RAS/RAF/MEK/ERK signaling pathway inhibitors, ROS1 inhibitors
    - Immune checkpoint inhibitor (ICI): anti-PD1/PD-L1, CTL4A inhibitors
    - Others
  - Chemotherapy: platinum, pemetrexed, antimicrotubules, gemcitabine, others
  - Antibody drug conjugate (ADC)
  - Others
- Prior immune checkpoint inhibitor: Sequential or Combination with chemotherapy

- Summary of last prior anticancer therapy:
  - Time from completion of last regimen to first administration of IMP (in months)
  - Main treatments of last regimen:
    - ICI monotherapy
    - ICI in combination with chemotherapy
    - ICI and other biologics and small molecules
    - No ICI: Chemotherapy, Biologics, or Chemotherapy and Biologics
  - Best response to the last regimen
  - Reason for discontinuation of the last line
- Prior surgery: number (%) of participants with any prior surgery related to cancer, type of surgery and time from the last surgery to the first administration of IMP (in years)
- Prior radiotherapy: number (%) of participants with any prior radiotherapy related to cancer, intent, analgesic intent if palliative and time from last dose of radiotherapy to first administration of IMP (in years)

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

## 5.3 APPENDIX 3 DATA HANDLING CONVENTIONS

### Unscheduled visits

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

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

## 5.4 APPENDIX 4 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 12 - 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 |

| Parameter | Gender | Unit | LLN | ULN |
|---|---|---|---|---|
| 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 13 - Generic ranges for biochemistry parameters**

| Parameter | Unit | LLN | ULN |
|---|---|---|---|
| Albumin | g/L | 35 | 55 |
| Blood Urea Nitrogen (BUN) | 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 |

# 6 REFERENCES

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