Sponsor: Sanofi **Drug substance(s):** SAR408701 - tusamitamab ravtansine	**Study Identifiers:** IND: 134514 EudraCT number: 2022-001212-39 NCT: NCT05429762 WHO: U1111-1269-6291 **Study code:** TES16382

Title of the study:

Open-label study evaluating the effect of tusamitamab ravtansine on the QTc interval in participants with metastatic solid tumors

Study center(s):

This study was conducted at 7 centers that enrolled 56 participants in 5 countries.

Study period:

Study start date: 03 October 2022

Study completion date: 10 April 2024 (last participant last visit)

Study Status: Terminated (Tusamitamab ravtansine clinical development program is discontinued as CARMEN-LC03 trial did not meet dual primary endpoint of improving progression-free survival. The decision is not related to any safety concern.)

Phase of development: Phase 1

Objectives:

Primary

- To assess the effect of tusamitamab ravtansine on the QTcF

Secondary

- To assess the effect of tusamitamab ravtansine on other cardiac parameters (Heart rate, QT, QTcB, QRS, and PR)
- To evaluate the PK of tusamitamab ravtansine (SAR408701, DM4, Me-DM4)
- To evaluate the clinical safety of tusamitamab ravtansine
- To evaluate ORR by tumor type in participants treated with tusamitamab ravtansine
- To estimate the DOR in participants treated with tusamitamab ravtansine

Methodology:

An open-label study to assess the effect of tusamitamab ravtansine on the QT interval in participants with metastatic colorectal cancer (CRC) regardless of the CEACAM5 expression, NSQ NSCLC with CEACAM5 expression in at least 1% of the tumor cells or gastric/gastroesophageal junction (GEJ) adenocarcinoma with CEACAM5 expression at least 50% of the tumor cells for which, in the judgment of the investigator, no standard alternative therapy was available.

Participants received a tusamitamab ravtansine intravenous (IV) infusion of loading dose at 170 mg/m^2 on Cycle 1 Day 1, followed by 100 mg/m^2 once every 2 weeks (Q2W) from Cycle 2 and in all other cycles.

Number of study participants:

Planned: Approximately 62 participants were screened to achieve 50 treated participants.

Analyzed: A total of 63 participants were screened, and 56 participants were treated and analyzed. All safety analyses were performed on this population. A total of 55 participants were included in Concentration-electrocardiogram (ECG) population which was used for the primary analysis including all enrolled and treated participants with at least 1 change from baseline ECG assessment time-matched (TM) with a pharmacokinetic (PK) concentration during Cycle 1 or 2. By the date of the last visit for the last participant on 10 April 2024, all 56 treated participants had permanently discontinued study treatment with tusamitamab ravtansine. The most frequently reported reason for permanent treatment discontinuation was progressive disease (49 participants). Four participants decided to withdraw from the study treatment for another reason, and 3 participants permanently discontinued study treatment due to 1 or more adverse event (AE).

Diagnosis and criteria for inclusion:

The key inclusion criteria included male or female participants aged ≥18 years had metastatic CRC regardless of the CEACAM5 expression, NSQ NSCLC with CEACAM5 expression in at least 1% of the tumor cells, or gastric/GEJ adenocarcinoma with CEACAM5 expression in at least 50% of the tumor cells for which, in the judgment of the Investigator, did not have standard alternative therapy were enrolled into the study.

Study products

Investigational medicinal product(s):

Formulation: tusamitamab ravtansine (SAR408701) solution for IV infusion.

Non-investigational medicinal product(s)

Diphenhydramine 50 mg or equivalent was given at Cycle 1 Day -1

Duration of study intervention:

This was a single arm study in which participants received treatment with tusamitamab ravtansine until disease progression, unacceptable toxicity, the start of a new anticancer therapy, or the participant's or Investigator's decision to stop the treatment, whichever comes first.

Criteria for evaluation:

Primary

- Change from baseline in the QTcF centrally assessed using a semiautomated reading

Secondary

- Heart rate
- QT interval
- QTcB
- PR interval

- QRS interval
- Tusamitamab ravtansine (SAR408701, DM4, and Me-DM4) concentrations and PK parameters
- Incidence of participants with TEAEs, SAEs and laboratory abnormalities according to the NCI CTCAE v5.0.
- The ORR, defined as the proportion of participants who have a confirmed CR or PR as the best overall response as determined by investigator/local radiologist review per RECIST v1.1 criteria
- The DOR, defined as the time from the first documented evidence of confirmed CR or PR until progressive disease as determined by investigator/local radiologist review per RECIST v1.1 criteria or death (due to any cause), whichever comes first.

Statistical methods:

The ECG endpoint (primary) was the change from baseline (delta) QTcF value. All post dose assessments during Cycle 1 and Cycle 2 (end of infusion (EOI), EOI+2 hours, EOI+4 hours, T24 hours, T48 hours, T72 hours, T168 hours, and start of infusion (SOI) Cycle 2) were included. Descriptive statistics of change from baseline in QTcF and plasma concentrations of SAR408701, DM4, and Me-DM4 was computed by cycle and time points.

The relationship between the change from baseline in QTcF and plasma concentrations were first explored graphically to investigate any potential delayed or sustained effects and the type of modeling to be done. Modeling was done separately for SAR408701, DM4, and Me-DM4 PK concentrations. In addition, models with >1 moiety were tested. In case of a direct and linear relationship between the plasma concentration and delta QTcF, a linear mixed-effects model was performed.

Prediction using change from baseline QTcF at selected concentrations compared with a concentration of zero was calculated from the model (estimates and 90% confidence intervals [CI]). The upper bound of the 90% 2-sided CI was compared with a threshold of 20 msec.

Objective response rate (ORR) by tumor type was summarized for the all-treated population using descriptive statistics and 95% exact CI were provided using the Clopper-Pearson method.

Number and percentage of participants experiencing treatment-emergent adverse events (TEAE) by primary system organ class (SOC) and preferred term (PT) was summarized by National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 Grade (all grades, and Grade $\geqslant$3) for the All-Treated population. Similar summaries were prepared for all types of TEAEs. In addition, groupings of interest were considered to investigate potential proarrhythmic effects.

Number and percentage of participants with potentially clinically significant abnormality (PCSA) in cardiac parameters during the on-treatment period was provided on the all-treated population. In addition, descriptive statistics for cardiac parameters was provided by cycle, visit, and nominal time point.

Summary Results:

Demographic and other baseline characteristics:

The mean (standard deviation [SD]) age of participants in the all group (56 participants) was 59.4 (11.2) years. The number (%) of male and female participants was the same (28 participants for each [50.0%]). The majority of participants (35 participants [62.5%]) were <65 years of age. A total of 21 participants (37.5%) were elderly participants (ie, ≥65 year of age). For race, majority of participants were White (41 participants [73.2%]); for several participants (8 participants [14.3%]) race was not reported (due to country personal data protection laws) and race was unknown for 4 participants (7.1%). The mean body weight was 76.24 kg. The eastern cooperative oncology group (ECOG) performance status for all participants was either '0' or '1' at study entry.

At initial disease diagnosis, of the 56 participants in the All-treated population, 52 participants (92.9%) had a primary tumor type of CRC, 3 participants (5.4%) had NSQ NSCLC, and 1 participant (1.8%) had a gastric tumor type. For the 52 participants with CRC, all cases were metastatic, and most of the participants (43 participants [82.7%]) had 2 or more organs involved. The most frequently reported organs were lung (40 participants [76.9%]), liver (33 participants [63.5%]), and lymph node (19 participants [36.5%]).

Exposure:

The median cumulative dose was 568.49 mg/m^2 with a median actual dose intensity of 54.84 mg/m^2/week and a median relative dose intensity of 99.44%. For overall exposure for the 56 participants, the median number of cycles started per participant was 5 cycles (range: 1 to 24) and the median duration of tusamitamab ravtansine exposure was 10.14 weeks (range: 2.0 to 49.1).

Pharmacokinetic results:

・Following IV infusion, the pharmacokinetics of tusamitamab ravtansine were characterized by a biphasic profile after a peak of concentration generally observed at the end of infusion or within 3 hours after SOI in most of patients. After first administration at 170 mg/m², mean C_{max} and area under the curve (AUC) were 114 µg/mL and 682 µg.day/mL, respectively. After 100 mg/m² administration at Cycle 2, mean C_{max} and $AUC_{0\text{-}14d}$ were 79.5 µg/mL and 468 µg.day/mL, respectively. Overall, a low to moderate variability was observed for all tusamitamab ravtansine PK parameters.

・After administration of tusamitamab ravtansine, DM4 median time to maximum concentration (t_{max}) was around 4 hours. After 170 mg/m² administration mean C_{max} and AUC were 4.75 ng/mL and 11.7 ng.day/mL, respectively. After 100 mg/m² administration at Cycle 2, mean C_{max} and $AUC_{0\text{-}14d}$ were 2.54 ng/mL and 6.48 ng.day/mL, respectively. Overall, a low to moderate variability was observed on DM4 exposure PK parameters (C_{max} and AUCs).

・Me-DM4 was characterized by a high variability on C_{max} and AUCs. After a first administration of tusamitamab ravtansine at 170 mg/m², median t_{max} was around 3 days, with mean C_{max} and AUC of 11.1 ng/mL and 94.6 ng.day/mL, respectively. After 100 mg/m² administration at Cycle 2, median t_{max} was around 1 day with C_{max} and area under curve from zero to Day 14 ($AUC_{0\text{-}14d}$) of 9.68 ng/mL and 73.0 ng.day/mL, respectively.

Electrocardiogram data

・No participants experienced PCSAs of QTcF prolongation of >480 msec during the on-treatment period. One participant had a of PCSA of QTcF prolongation of >450 msec at a single timepoint (value was 452 msec) during the on-treatment period.

・A total of 7 of 55 participants (12.7%) had PCSAs in the category of an increase in QTcF from baseline of >30 msec to <60 msec.

・No participants experienced PCSAs of (QT interval corrected according to the Bazett's formula) QTcB prolongation of >480 msec during the on-treatment period.

・The bias between the fully automated QTcF measurements and the semi-automatic measurements from the ECG core lab reported QTcF values is acceptable taking into consideration that the slope for the Bland-Altman plot did not exceed ± 0.1 (ie, ± 10 msec per 100 msec) for both the off-drug and on-drug assessments.

・Results from the concentration-QTcF analysis (primary analysis of this study) using TM ECG and PK concentration time points do not suggest any clinically meaningful QTcF prolongation induced by tusamitamab ravtansine, DM4, and Me-DM4. The upper bound of the 90% 2-sided CI of change from average baseline QTcF at Maximum concentration after study treatment (C_{max}) of each Cycle compared with a concentration of "0" was below 20 msec for the primary analysis model including both DM4 and Me-DM4 (DM4 highest 90% CI upper bound = 5.68 and Me-DM4 highest 90% CI upper bound = 4.89), and for the models including only tusamitamab ravtansine (highest 90% CI upper bound = 4.38), DM4 (highest 90% CI upper bound = 5.20) or Me-DM4 (highest 90% CI upper bound = 3.81) PK concentrations. Supplementary analyses evaluating the impact of meals and using TM baseline showed similar results.

・It is not possible to rule out a drug effect on heart rate, as the time profile plot of mean change from baseline heart rate included values above 10 bpm and, looking at the correlation of QTcF and RR, the QTcF might not be completely independent from RR. To

take this uncertainty into consideration, QTcN was calculated with a slope of 0.39 [95% CI: 0.350; 0.425]. Concentration-QTcN analysis (using either average or TM baseline) also showed similar results and conclusions.

· In addition, results from the by-time point analyses for both QTcF and QTcN do not show any clinically meaningful drug effect on the QTc interval. The average largest mean change from baseline (LMCBAV) estimate for QTcF was 2.57 msec [90% CI: 0.309; 4.838] in Cycle 1 and 6.60 msec [90% CI: 3.736; 9.464] in Cycle 2. The LMCB occurred at Day 1 EOI+2 hours in Cycle 1 and at Day 1 EOI in Cycle 2. For both cycles, the upper bound of the 90% 2-sided CI for the LMCBAV was lower than 20 msec. The LMCBAV estimate for QTcN was similar to the LMCBAV estimate for QTcF. The LMCB also occurred at Day 1 EOI+2 hours in Cycle 1 and at Day 1 EOI in Cycle 2. Supplementary analyses using TM baseline showed similar results and conclusions.

· One participant had a PCSA of QT interval >500 msec during the on-treatment period. A total of 4 participants (7.1%) had PCSA heartrate (HR) values of >120 beats/min and increase from baseline ≥20 beats/min.

· A total of 5 participants (8.9%) had PCSA PR interval >200 msec, 1 participant (1.8%) each had PCSA PR interval >240 msec. No participant had PCSA PR interval values ≥25% increase from baseline. A total of 3 participants (5.4%) had PCSA QRS duration >110 msec, 1 participant (1.8%) had PCSA QRS duration >120 msec.

Safety results:

· Of the 56 participants in the All-treated population, 53 participants (94.6%) experienced 1 or more TEAEs. A total of 23 participants (41.1%) experienced at least 1 Grade ≥3 TEAE. The most frequently reported Grade ≥3 TEAE was keratopathy (3 participants [5.4%]). Other Grade ≥3 TEAEs were reported in ≤2 participants.

· One participant (1.8%) had a Grade 5 TEAE (disease progression) with a fatal outcome during the treatment period.

· A total of 12 deaths (21.4%) were reported. Of the 12 deaths, 10 deaths occurred during the post-treatment period and 2 deaths occurred during the on-treatment period. None of the deaths were considered to be related to treatment with tusamitamab ravtansine.

· The most frequently reported TEAEs by PT (≥6 participants [all grades]) were: keratopathy (14 participants), fatigue, diarrhea (13 participants each), nausea (11 participants), peripheral sensory neuropathy, constipation, vision blurred (7 participants each), abdominal pain, asthenia, cough, and edema peripheral (6 participants each).

· In the Cardiac disorders SOC, 1 participant reported a non-serious TEAE of palpitations that was rated as Grade 1.

· Treatment-emergent serious adverse events (SAEs) were reported in 18 participants (32.1%).

· A total of 3 participants (5.4%) experienced 1 or more TEAEs that led to permanent study treatment discontinuation. Treatment-emergent AESI were reported in 4 participants (7.1%).

· No TEAEs were reported that were associated with QT prolongation and none were associated with any other ECG parameters (eg, PR interval, QRS interval, etc.).

Issue date: 23-Jan-2024