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Sponsor / Company: Sanofi **Drug substance(s):** SAR245409	**Study Identifiers:** NCT01596270, UTN U1111-1123-1488 **Study code:** TED12471
Title of the study: A Phase 1 dose-escalation study of the safety and pharmacokinetics of a tablet formulation of SAR245409 administered daily to patients with solid tumors or lymphoma	
Study center(s): 3 centers in the USA	
Study period: Date first patient enrolled: 19/Jun/2012 Date last patient completed: 15/Oct/2014	
Phase of development: Phase 1	

Objectives:

Primary objective

- To evaluate the safety and tolerability of SAR245409 administered as a tablet formulation on 2 treatment schedules (once daily [QD] and twice daily [BID] dosing) in patients with solid tumors or lymphoma.

Secondary objectives

- To evaluate the plasma pharmacokinetics (PK) of oral administration of SAR245409 given as a tablet formulation on QD and BID treatment schedules in patients with solid tumors or lymphoma;
- To obtain preliminary information on the effect of food on the plasma PK of oral administration of SAR245409 as a tablet formulation in patients with solid tumors or lymphoma.

Exploratory objectives

- To evaluate the pharmacodynamic (PD) effect of SAR245409 administered as a tablet formulation in patients with solid tumors or lymphoma.
- To assess patient-reported disease and treatment-related symptoms in patients with solid tumors or lymphoma receiving SAR245409 as a tablet formulation on QD and BID treatment schedules.
- To evaluate the antitumor activity of SAR245409 administered as a tablet formulation on QD and BID treatment schedules in patients with solid tumors or lymphoma.

Methodology: This was a Phase 1, multicenter, open-label, nonrandomized, dose-escalation study evaluating the safety, tolerability, PK, PD effect, and antitumor activity of SAR245409 single agent given as a tablet formulation in patients with solid tumors or lymphoma.

Continuous daily dosing

Dose-Escalation Phase

A "3 plus 3" dose-escalation design was employed to determine for each treatment schedule (QD or BID dosing) a safe tablet dose providing an SAR245409 plasma exposure comparable to that at the capsule maximum tolerated dose (MTD). The dose-escalation decision was based on study treatment-related dose-limiting toxicities (DLTs) observed during Cycle 1 from at least 3 patients in the DLT-evaluable population and on PK data.

Cumulative toxicities observed in subsequent cycle were also to be considered for dose escalation and dose selection decisions. Patients who were withdrawn during the first cycle of study treatment for any reason other than a DLT were to be replaced.

The initial dose level was 50 mg QD. Based on safety and PK data from the 50 mg QD dose cohort, additional cohorts of 3 or 6 patients were to be treated at successively higher doses in the QD treatment schedule and in the BID treatment schedule in parallel. Decisions to continue the enrollment in subsequent dose level cohort, dose level to be tested, as well as number of patients to be evaluated were to be made after the appropriate data (safety and PK) were collected and reviewed by the Study Committee.

Cohort Expansion Phase

At the dose level determined for the QD and BID treatment schedule in the dose-escalation phase to provide a plasma exposure comparable to that at the capsule MTD, additional patients were to be included in the expansion cohort, up to a total of 15 patients evaluated in each treatment schedule at the selected dose level.

No patients were enrolled in the expansion cohort of the BID dosing regimen following determination of the MTD, as the Sponsor decided not to develop the BID dosing regimen for SAR245409, either as single agent or in combination.

Food interaction investigation

The effect of food on the bioavailability of SAR245409 tablet formulation was evaluated in a subset of patients in the QD expansion cohort. Patients received a single dose of SAR245409 in fasted conditions and a single dose of SAR245409 in fed conditions prior to the start of Cycle 1 of continuous daily dosing. Patients enrolled in the expansion cohort were to participate in the food effect investigation until at least 8 evaluable patients had participated in the food interaction investigation; subsequent patients enrolled were to begin with Cycle 1 of continuous daily dosing.

Treatment continuation

After Cycle 2 of continuous daily dosing, patients eligible for treatment continuation were offered the opportunity to enroll in the treatment-extension study TED12414 provided that they were eligible and gave consent. Patients who did not enroll in the treatment-extension study were followed-up for safety for a minimum of 30 days (±3 days) after last study drug administration.

Following a review of development priorities, it was decided by the Sponsor to terminate the development of SAR245409. The current study report is a synopsis style report accordingly with Sanofi SOP.

Number of patients**:**

Planned: Approximately 33 to 48 patients

Continuous Daily Dosing Period

QD Dosing Regimen	BID Dosing Regimen
Enrolled: 32	Enrolled: 17
Safety : 32	Safety : 17
Evaluable for DLT: 24	Evaluable for DLT: 15
Pharmacokinetics : 32	Pharmacokinetics: 17
Pharmacodynamics: 32	Pharmacodynamics: 17
Antitumor activity: 31	Antitumor activity: 16

Food Interaction Period:

Enrolled: 11

Safety: 10

Pharmacokinetics: 10

Pharmacodynamics: 10

Diagnosis and criteria for inclusion:

Male or female patients, aged at least 18 years, with either

- A histologically confirmed solid tumor that is metastatic or unresectable and for which standard therapies are no longer effective, or there are no therapies known to prolong survival,

  or

- Relapsed or refractory lymphoma - including chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) - for which standard therapies are no longer effective, or there are no therapies known to prolong survival.

Study treatments

Investigational medicinal product(s): SAR245409

Formulation: tablet formulations at the strengths of 20 mg and 30 mg.

Route(s) of administration: oral

Dose regimen:

Continuous Daily dosing Period:

- *QD Dosing:* initial dose level 50 mg QD, escalated in the successive cohort to 70 mg QD, and then reduced in the successive cohort to 60 mg QD.
- *BID Dosing:* initial dose level 30 mg BID, escalated in successive cohorts to 40 mg BID and to 50 mg BID.

Food interaction investigation:

Patients received a single dose of 50 mg SAR245409 in fasted condition and a single dose of 50 mg SAR245409 in fed condition (standardized moderate-fat breakfast), in a sequence determined as per the randomization list.

Duration of treatment:

Continuous Daily Dosing Period:

Patients were to receive SAR245409 during two 28-day treatment cycles unless progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and/or unacceptable toxicity had emerged.

Patients eligible for treatment continuation after Cycle 2 were offered the opportunity to enroll in the treatment-extension study TED12414.

Food Interaction Period:

Patients were to receive a single dose of 50 mg SAR245409 in fasted condition and a single dose of 50 mg SAR245409 in fed condition, in a sequence determined as per the randomization list.

There was to be a minimum 48-hour (maximum: 4-day) washout period between the two SAR245409 administrations in the food interaction investigation and a minimum 48-hour (maximum: 7-day) washout period between the last SAR245409 administration in the food interaction investigation and the first SAR245409 administration in Cycle 1 of continuous daily dosing.

Duration of observation:

- Screening: 1 to 28 days.
- Study treatment periods:
  - Food interaction investigation period (when applicable): 4 to 11 days;
  - Cycles 1 and 2 of continuous daily dosing period: 28 days for each cycle.

- End-of-treatment visit: no later than 7 days after the last study drug administration.
- Patients not eligible for treatment continuation after Cycle 2 were to be followed up for safety; a follow-up visit was to be performed within 30 ± 3 days after the last study drug administration.
- Patients eligible for treatment continuation after Cycle 2 were offered the opportunity to enroll in the treatment-extension study TED12414.

Criteria for evaluation:

Safety: Safety and tolerability of SAR245409 in patients with solid tumor or lymphoma were assessed through the collection of adverse events (AEs), serious adverse events (SAEs), and DLTs graded with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03; laboratory parameters (hematology, coagulation, serum chemistry, urinalysis, and serum pregnancy test [if applicable]); vital signs; electrocardiogram (ECG) parameters; physical examination findings; ophthalmologic examinations findings; and Eastern Cooperative Oncology Group (ECOG) performance status (PS).

Pharmacokinetics-Continuous Daily Dosing Period:

Bioanalytical Method: Plasma concentrations of SAR245409 were measured using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.00 ng/mL.

Sampling: Plasma samples for the assessment of SAR245409 PK were collected:

- *Continuous Daily Dosing Period*: on Cycle 1, Day 1 and Day 28 at predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose; as well as predose on Cycle 1 Day 2, Day 8, and Day 15.
- *Food Interaction Investigation*: at predose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose in fasted and fed conditions, respectively

Pharmacokinetic Parameters: The following SAR245409 PK parameters were to be calculated:

Continuous Daily Dosing Period: Maximum plasma concentration observed (C_{max}), first time to reach C_{max} (t_{max}), area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the end of the dosing interval (AUC_{tau}), area under the plasma concentration versus time curve extrapolated to infinity (AUC), plasma concentration observed just before treatment administration during repeated dosing (C_{trough}), and other parameters as needed were to be calculated.

Food Interaction Investigation: C_{max}, area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real time t_{last} (AUC_{last}), AUC, t_{max}, and terminal half-life associated with the terminal slope λ_z ($t_{1/2z}$) were to be calculated.

Pharmacodynamics:

Sampling: Samples for the PD analysis of SAR245409 were collected:

- *Continuous Daily Dosing Period* (Plasma and blood cells): Predose and 2, 4, 8, and 12 hours postdose on Cycle 1, Day 1 and on Cycle 1, Day 28, as well as at predose on Cycle 1, Day 15.
- *Food Interaction Investigation* (Plasma): Predose and 1, 2, 4, 8, and 12 hours postdose on Cycle 1, Day 1 and on Cycle 1 Day 3 in fasted and fed conditions, respectively.

Pharmacogenomics: For patients who gave informed consent for participating in the optional pharmacogenetic investigation, a blood sample (as for patients with solid tumor) was collected at baseline (Day -7 to Day -1) to potentially investigate allelic variants of drug metabolizing enzymes and/or drug transporters as intrinsic factors associated with pharmacokinetic or pharmacodynamic variability of SAR245409.

Patient-reported symptoms**:** Patient-reported disease and treatment-related symptoms were assessed using the patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). A subset of 26 symptoms that were deemed most applicable to the cancer diagnoses and treatment in the current study was selected for this study.

Antitumor activity: Tumor assessment was performed per standard of care (including imaging by computerized tomography [CT] or magnetic resonance imaging [MRI] at Investigator's choice) at baseline and at the end-of-treatment visit, and tumor response as per Investigator was collected. Patients showing disease progression at the end-of-treatment visit were not to be eligible for the treatment-extension study TED12414. No tumor measurement data was collected in this study.

Statistical methods:

Dose-limiting toxicity

The DLT-evaluable population consisted of all included patients who had complete assessments for DLT evaluation and received at least 80% of the doses of study treatment during Cycle 1, or received partial doses of study treatment but developed DLTs during Cycle 1.

A DLT was defined as any of the following occurring during the first cycle of study treatment:

- Non-hematologic toxicity:
  - Any Grade ≥3 non-hematologic toxicity except diarrhea, nausea, or vomiting.
  - Nausea/vomiting or diarrhea will be considered a DLT in patients who have Grade ≥3 toxicity for >2 days despite receiving optimal prophylaxis and/or treatment.
  - Any Grade 4 non-hematologic toxicity.
  - Any toxicity resulting in a treatment delay >2 weeks.
- Hematologic toxicity:
  - Grade 4 neutropenia of ≥4 days duration.
  - Febrile neutropenia defined as Grade ≥3 neutropenia associated with a single temperature >38.3°C or a sustained temperature ≥38°C for more than 1 hour; neutropenic infection.
  - All other Grade 4 hematologic AEs.
- A treatment-emergent adverse event (TEAE) that, in the opinion of the Investigator, is of potential clinical significance such that further dose-escalation would expose patients to unacceptable risk

Summary of DLTs was provided by dose/regimen. Characteristics of DLTs were listed by patient.

Safety

The safety population was defined as all patients who took at least 1 dose of the study treatment.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

The safety profile was be based on incidence, severity (as graded by the NCI CTCAE v4.03), and cumulative nature of TEAEs. A TEAE was defined as an AE that newly develop or pre-existing signs/symptoms that worsen in severity or become serious during the on-treatment period. For this study, the on-treatment period was defined as the time from first dose of IMP administration up to 30 days after the last dose of IMP administration. Total incidence (ie, Grade 1 or higher) and incidence of Grade ≥3 of each TEAE were summarized by system organ class and preferred term using frequencies and percentages. For patients with several episodes of the same event during the on-treatment period, the worst grade was used. Drug-related TEAEs, deaths, SAEs, and AEs leading to treatment discontinuation were summarized similarly.

A selection of TEAEs based on Sanofi grouping were summarized, which included those events related to rash or other type of events to be closely monitored. Adverse events of special interest (AESIs), including DLTs, elevated alanine aminotransferase /aspartate aminotransferase ≥Grade 2, pregnancy, symptomatic overdose with IP, asymptomatic overdose with IP, and skin toxicities, were also summarized if different from Sanofi-defined grouping.

Laboratory tests, vital signs, ECG, ECOG PS, physical examinations, and ophthalmologic examinations were also assessed. For each parameter that could be graded with NCI CTCAE version 4.03, number and percentage of patients with laboratory abnormalities (all grades and Grade 3 to 4) using the worst grade during the on-treatment period were provided. For other laboratory parameters, values outside of the normal ranges were identified. For vital signs and ECG data, summary statistics (including mean, median, standard error, minimum and maximum) of the raw data and changes from baseline were calculated.

The number of patients with potentially clinically significant abnormalities (PCSA) for each parameter was summarized. Physical and ophthalmologic examinations were summarized by number and percentage of patients with any abnormality during the TEAE period for each of the assessments.

Patient-reported symptoms were analyzed by the frequency, severity, interference, and presence at each assessment point and over time. In addition, the frequency of each symptom was cross tabulated with the severity to explore the impact of the symptom when it occurred.

Pharmacokinetics

The PK population was defined as all patients with at least one valid pharmacokinetic sample.

SAR245409 PK parameters were to be summarized using descriptive statistics. For the food interaction investigation only, the difference between food conditions was to be assessed on log-transformed C_{max}, AUC_{last}, and AUC with a linear mixed effects model. Estimate and 90% confidence interval (CI) for the geometric means ratio between fed and fasted food conditions were to be provided for C_{max}, AUC_{last}, and AUC.

Pharmacodynamics

The PD population consisted of all included patients who received at least 1 dose of study treatment and had evaluable concentration-time data.

Pharmacodynamic parameters for SAR245409 were summarized using descriptive statistics.

Antitumor activity

The antitumor activity population consisted of patients who received at least 1 dose of study treatment and either had postbaseline tumor response data or had no postbaseline tumor response data due to symptomatic deterioration or death.

Tumor response was listed by patient.

Summary:

Patient Disposition: In the QD dosing regimen, 32 patients were enrolled and treated: 3 patients in the 50 mg QD dose cohort, 12 patients in the 70 mg QD dose cohort, and 17 patients in the 60 mg QD dose cohort (10 patients out of which participated in the food interaction investigation prior to the continuous daily dosing period). Out of the 32 patients treated, 14 patients (43.7%) completed the study treatment period, and 18 patients (56.3%) permanently discontinued the study treatment. The main reason for treatment discontinuation was disease progression (13 patients, 40.6%), and other reasons for treatment discontinuation included adverse events (3 patients, 9.4%) and patient's decision to withdraw consent (2 patient, 6.3%).

In the BID dosing regimen, 17 patients were enrolled and treated: 4 patients in the 30 mg BID dose cohort, 6 patients in the 40 mg BID dose cohort, and 7 patients in the 50 mg BID dose cohort. Out of the 17 patients, 10 patients (58.8%) completed the study treatment period, and 7 patients (41.2%) permanently discontinued the study treatment. The main reason for treatment discontinuation was disease progression (5 patients, 29.4%), and other reasons for treatment discontinuation included adverse events (1 patients, 5.9%) and patient's decision to withdraw consent (1 patient, 5.9%).

Population characteristics:

Demographics:

Out of the 32 patients treated on the QD dosing regimen, 17 patients (53.1%) were female, 26 patients (81.3%) were white, and 29 patients (90.6%) were non-Hispanic. The median age of patients was 56.0 years (range: 35 to 78 years). At baseline, 25 patients (78.1%) had an ECOG PS of 1, while the other 7 patients (21.9%) had an ECOG PS of 0.

Out of the 17 patients treated on the BID dosing regimen, 10 patients (58.8%) were female, 13 patients (76.5%) were white, and 16 patients (94.1%) were non-Hispanic. The median age of patients was 62.0 years (range: 29 to 78 years). At baseline, 13 patients (76.5%) had an ECOG PS of 1, and 4 patients (23.5%) had an ECOG PS of 0.

Disease Characteristics:

All the 32 patients treated on the QD dosing regimen had metastatic solid tumor at baseline. The most common tumor types at initial diagnosis were lung cancer (8 patients, 25.0%) and colon cancer (6 patients, 18.8%). Thirty patients (93.8%) had received at least 1 prior regimen of anti-cancer therapy, and the median (range) number of regimens was 3 (1 to 12) regimens.

All the 17 patients treated on the BID dosing regimen had solid tumor at baseline. All patients but 1 presented with metastatic disease. The most common tumor types at initial diagnosis were colon cancer (4 patients, 23.5%), breast cancer (3 patients, 17.6%), and lung cancer (3 patients, 17.6%). All (100%) of the 17 patients had received at least 1 prior regimen of anti-cancer therapy, and the median (range) number of regimens was 4 (1 to 17) regimens.

Of note, no patients with relapse or refractory lymphoma were enrolled in the current study.

Safety results:

Overall exposure:

The safety analysis was performed in 32 patients treated on the QD dosing regimen. The median (range) duration of treatment was 5.93 (0.9 to 8.1) weeks (8.00 [7.9 to 8.1] weeks for patients in the 50 mg QD dose cohort, 6.00 [1.3 to 8.0] weeks for patients in the 60 mg QD dose cohort, and 2.00 [0.9 to 8.1] weeks for patients in the 70 mg QD dose cohort). The median relative dose intensity was 71.43% (100% for the 50 mg QD dose cohort, 75.00% for the 60 mg QD dose cohort, and 25.00% for the 70 mg QD dose cohort).

A total of 17 patients were treated on the BID dosing regimen and evaluated for safety. The median (range) duration of treatment was 7.71 (0.9 to 8.1) weeks (4.71 [0.9 to 8.1] weeks for patients in the 30 mg BID dose cohort, 7.50 [4.0 to 8.0] weeks for patients in the 40 mg BID dose cohort, and 8.00 [1.0 to 8.0] weeks for patients in the 50 mg BID dose cohort). The median relative dose intensity was 82.88% (57.66% for the dose level of 30 mg BID, 92.79% for the dose level of 40 mg BID, and 71.17% for the dose level of 50 mg BID).

Dose-Limiting Toxicities:

For the QD dosing regimen, the dose of 60 mg QD was selected as the MTD; the maximum administered dose (MAD) was 70 mg QD. At the 60 mg dose level (QD MTD), additional patients were included, up to a total of 15 DLT-evaluable patients. Overall, at the QD MTD, no DLT-evaluable patients experienced a DLT during Cycle 1. At the QD MAD, 2/6 DLT-evaluable patients (33.3%) experienced a DLT during Cycle 1: both were serious Grade 3 fatigue.

For the BID dosing regimen, the dose of 40 mg BID was selected as the MTD; the MAD was 50 mg BID. At the BID MTD, 1/6 DLT-evaluable patients (16.7%) experienced a DLT during Cycle 1: 1 serious Grade 3 fatigue. At the BID MAD, 2/6 DLT-evaluable patients (33.3%) experienced a DLT during Cycle 1: 1 nonserious Grade 3 rash maculo-papular and 1 nonserious Grade 3 rash macular.

Treatment-Emergent adverse events:

In the QD dosing regimen, during the continuous daily dosing period, 31 (96.9%) out of the 32 patients treated experienced at least 1 TEAE. The most common TEAEs by preferred term (PT) were diarrhea (12 patients, 37.5%), nausea (12 patients, 37.5%), dyspnea (8 patients, 25.0%), fatigue (8 patients, 25.0%), decreased appetite (7 patients, 21.9%), and vomiting (7 patients, 21.9%). Grade ≥3 TEAEs were reported in 14 patients (43.8%) from all dose levels. The following Grade ≥3 TEAEs were reported in at least 2 patients: disease progression (4 patients, 12.5%), anemia (3 patients, 9.4%), fatigue (2 patients, 6.3%), dyspnea (2 patients, 6.3%), and hyponatremia (2 patients, 6.3%). Other Grade ≥3 TEAEs were single occurrences. Twenty patients (62.5%) experienced at least 1 TEAE related to the IMP. Grade ≥3 related TEAEs were fatigue (2 patients, 6.3%), alanine aminotransferase increased (1 patient, 3.1%), anemia (1 patient, 3.1%), hypophosphatemia (1 patient, 3.1%), and hypokalemia (1 patient, 3.1%). During the food interaction investigation, 3/10 patients (30.0%) experienced at least 1 TEAE when receiving the IMP in fed condition, with no Grade ≥3 TEAE reported; 2/10 patients (20.0%) experienced at least 1 TEAE when receiving the IMP in fasted condition, and 1 TEAE of Grade 3 hypertension was reported. No TEAE related to the IMP was reported in the food interaction investigation.

In the BID dosing regimen, all (100%) of the 17 patients treated experienced at least 1 TEAE. The most common TEAEs by PT were diarrhea (8 patients, 47.1%), fatigue (8 patients, 47.1%), decreased appetite (7 patients, 41.2%), nausea (6 patients, 35.3%), cough (5 patients, 29.4%), and vomiting (5 patients, 29.4%). Grade ≥3 TEAEs were reported in 6 patients (35.3%) from all dose levels. The following Grade ≥3 TEAEs were reported in at least 2 patients: disease progression (2 patients, 11.8%) and hyponatremia (2 patients, 11.8%). Other Grade ≥3 TEAEs were single occurrences. Twelve patients (70.6%) experienced at least 1 TEAE related to the IMP. Grade ≥3 related TEAEs, all of which were single occurrences, included fatigue, nausea, rash maculo-papular, rash macular, anemia, dehydration, hyperglycemia, and hyponatremia.

Deaths:

In the QD dosing regimen, a total of 7 deaths occurred during the study. Five patients (15.6%) died during the on-treatment period (within 30 days after the last dose of the IP): 4 patients died due to disease progression and 1 patient died due to a treatment emergent SAE of small intestinal obstruction secondary to disease progression (not related to the IMP). During the post-treatment follow-up period, 1 patient died due to a treatment emergent SAE of respiratory failure (not related to the IMP); another 1 patient died due to an unknown reason.

In the BID dosing regimen, a total of 4 deaths occurred during the study. Two patients (11.8%) died during the on-treatment period: both due to disease progression. During the post-treatment follow-up period, 2 patients (11.8%) died: both due to unknown reasons.

Serious Adverse Events:

In the QD dosing regimen, during the continuous daily dosing period, 13 (40.6%) out of the 32 patients treated experienced at least 1 treatment emergent SAE. Treatment emergent SAE reported in ≥2 patients from all dose cohorts were disease progression (4 patients), fatigue (2 patients), and pyrexia (2 patients). Related treatment emergent SAEs were fatigue (2 patients), pyrexia (2 patients), alanine aminotransferase increased (1 patient), and blood creatinine increased (1 patient). No SAE was reported during the food interaction investigation.

In the BID dosing regimen, 5 (29.4%) out of the 17 patients treated experienced at least 1 treatment emergent SAE. Treatment emergent SAE reported in ≥2 patients from all dose cohorts were disease progression (2 patients). Related treatment emergent SAEs were fatigue (1 patient) and abdominal pain (1 patient).

Treatment-Emergent Adverse Events leading to treatment discontinuation:

In the QD dosing regimen, during the continuous daily dosing period, 3 patients (9.4%) were permanently discontinued from the study treatment due to TEAEs: 1 patient due to hematochezia, 1 patient due to hyperbilirubinemia, and 1 patient due to alanine aminotransferase increased and aspartate aminotransferase increased. No patient was permanently discontinued from the study treatment due to TEAEs during the food-interaction period.

In the BID dosing regimen, only 1 patient (5.9%) was permanently discontinued from the study treatment due to a TEAE of abdominal infection.

Treatment-Emergent Adverse Events leading to Dose Reductions or Dose Delays

In the QD dosing regimen, 2 patients (6.3%) experienced TEAEs leading to dose reductions of the IMP: 1 patient with hypophosphatemia and 1 patient with blood creatinine increased. Eight patients (25.0%) experienced TEAEs leading to dose delay of the IMP; most of the events were single occurrences, except for pneumonia (2 patients, 6.3%) and fatigue (2 patients, 6.3%).

In the BID dosing regimen, 1 patient (5.9%) experienced 2 TEAEs that led to dose reduction: rash macular and alanine aminotransferase increased. Six patients (35.3%) experienced TEAEs leading to dose delay of the IMP, and all of these events were single occurrences.

Selected TEAEs by Sanofi Grouping:

In the QD dosing regimen, during the continuous daily dosing period, selected TEAEs in the drug hypersensitivity grouping were reported in 3 patients (9.4%), liver toxicity TEAEs were reported in 4 patients (12.5%), rash TEAEs were reported in 8 patients (25.0%), and pulmonary toxicity TEAEs were reported in 4 patients (12.5%). None of the rash TEAEs was of Grade ≥3. The following patients experienced Grade ≥3 selected TEAEs:

- One patient experienced a serious Grade 4 pneumonia (pulmonary toxicity grouping) and a serious Grade 5 (fatal) respiratory failure (pulmonary toxicity and drug hypersensitivity groupings); both events were considered as not related to the IMP.
- One patient experienced a nonserious Grade 3 alanine aminotransferase increased (liver toxicity grouping); the event was considered as related to the IMP.

During the food interaction investigation, only 1 patient (10.0%) experienced a nonserious TEAE of Grade 1 wheezing (drug hypersensitivity and pulmonary toxicity groupings); the event was considered as not related to the IMP.

In the BID dosing regimen, selected TEAEs in the drug hypersensitivity grouping were reported in 4 patients (23.5%), 1 TEAE pf lens retinal disease was reported in 1 patient (5.9%); liver toxicity TEAEs were reported in 3 patients (17.6%), rash TEAEs were reported in 6 patients (35.3%), and pulmonary toxicity TEAEs were reported in 4 patients (23.5%). None of the liver toxicity or lens retinal disease TEAEs was of Grade ≥3. The following patients experienced Grade ≥3 selected TEAEs:

- One patient experienced a serious Grade 4 respiratory failure (pulmonary toxicity and drug hypersensitivity groupings); the event was considered as not related to the IMP.
- One patient experienced a nonserious Grade 3 rash maculo-papular and another patient experienced a nonserious Grade 3 rash macular (rash grouping); both events were considered as related to the IMP.

Other Adverse Events of Special interest:

No pregnancy, symptomatic overdose with IMP, or asymptomatic overdose with IMP was reported in this study.

Laboratory Results:

Hematology:

In the QD dosing regimen, during the on-treatment period, anemia was reported in 26 patients (81.3%), lymphocyte count decreased was reported in 23 patients (71.9%), white blood cell decreased was reported in 11 patients (34.4%), and platelet count decreased was reported in 7 patients (21.9%). Grade 3 hematologic abnormalities included lymphocyte count decreased in 11 patients (34.4%), anemia in 3 patients (9.4%), and platelet count decreased in 1 patient (3.1%). The only Grade 4 hematologic abnormality was lymphocyte count decreased in 1 patient (3.1%).

In the BID dosing regimen, during the on-treatment period, anemia was reported in 17 patients (100%), lymphocyte count decreased was reported in 13 patients (76.5%), white blood cell decreased was reported in 7 patients (41.2%), platelet count decreased was reported in 7 patients (41.2%), and neutrophil count decreased was reported in 2 patients (11.8%). Grade 3 hematologic abnormalities included lymphocyte count decreased in 5 patients (29.4%), anemia in 1 patient (5.9%), and platelet count decreased in 1 patient (5.9%). The only Grade 4 hematologic abnormality was lymphocyte count decreased in 1 patient (5.9%).

Clinical Chemistry:

In the QD dosing regimen, common clinical chemistry abnormalities (reported in >20% of the patients) during the on-treatment period were hyperglycemia (22 patients, 68.8%), hypoalbuminemia (18 patients, 56.3%), alkaline phosphatase (ALP) increased (17 patients, 53.1%), aspartate aminotransferase (AST) increased (13 patients, 40.6%), alanine aminotransferase (ALT) increased (11 patients, 34.4%), and creatinine increased (7 patients, 21.9%). Grade 3 clinical chemistry abnormalities included hypoalbuminemia in 1 patient (3.1%), ALP increased in 1 patient (3.1%) and ALT increased in 1 patient (3.1%).

In the BID dosing regimen, common clinical chemistry abnormalities (reported in >20% of the patients) during the on-treatment period were hyperglycemia (15 patients, 88.2%), hypoalbuminemia (11 patients, 64.7%), ALP increased (9 patients, 52.9%), AST increased (8 patients, 47.1%), and ALT increased (7 patients, 41.2%). Grade 3 clinical chemistry abnormalities included hyperglycemia in 2 patients (11.8%), hypoalbuminemia in 1 patient (5.9%), and ALP increased in 1 patient (5.9%).

- One patient had ALT and AST increases of >3 x upper limit of normal (ULN) and concurrent total bilirubin values >2 x ULN with elevated ALP, which was consistent with the presence of documented liver metastases.

Electrolytes:

In the QD dosing regimen, common electrolytes abnormalities (reported in >20% of the patients) during the on-treatment period were hyponatremia (16 patients, 50%), hypocalcemia (10 patients, 31.3%), hypomagnesemia (10 patients, 31.3%), hypophosphatemia (10 patients, 31.3%), and hypokalemia (7 patients, 21.9%). Grade 3 electrolytes abnormalities included hyperkalemia in 1 patient (3.1%), hypokalemia in 2 patients (6.3%), hypermagnesemia in 1 patient (3.1%), hyponatremia in 5 patients (15.6%), and hypophosphatemia in 3 patients (9.4%). No Grade 4 electrolytes abnormalities were reported.

In the BID dosing regimen, common electrolytes abnormalities (reported in >20% of the patients) during the on-treatment period were hyponatremia (9 patients, 52.9%), hypocalcemia (6 patients, 35.3%), and hypophosphatemia (4 patients, 23.5%). Grade 3 electrolytes abnormalities included hyponatremia in 4 patients (23.5%) and hypophosphatemia in 1 patient (5.9%). The only Grade 4 electrolytes abnormality reported was hypocalcemia in 1 patient (5.9%).

Vital Signs:

In the QD dosing regimen, during the continuous daily dosing period, PCSA values for heart rate were reported for ≥120 bpm and increase from baseline ≥20 bpm in 6 patients (18.8%); PCSA values for systolic blood pressure (SBP) were reported for ≥160 mmHg and increase from baseline ≥20 mmHg in 7 patients (21.9%) and for ≤95 mmHg and decrease from baseline ≥20 mmHg in 6 patients (18.8%); PCSA values for diastolic blood pressure (DBP) were reported for ≥110 mmHg and increase from baseline ≥10 mmHg in 1 patient (3.1%). Weight decrease ≥5% from baseline was reported in 10 patients (31.3%) and increase ≥5% from baseline was reported in 2 patients (6.3%). During the food interaction investigation, PCSA values for SBP were reported for ≥160 mmHg and increase from baseline ≥20 mmHg in 2 patients (20.0%).

In the BID dosing regimen, PCSA values for heart rate were reported for ≥120 bpm and increase from baseline ≥20 bpm in 2 patients (11.8%) and ≤50 bpm and decrease from baseline ≥20 bpm in 1 patient (5.9%); PCSA values for SBP were reported for ≥160 mmHg and increase from baseline ≥20 mmHg in 2 patients (11.8%); PCSA values for DBP were reported for ≤45 mmHg and decrease from baseline ≥10 mmHg in 1 patient (5.9%). Weight decrease ≥5% from baseline was reported in 5 patients (29.4%) and increase ≥5% from baseline was reported in 1 patient (5.9%).

Electrocardiogram:

In the QD dosing regimen, PCSA for heart rate ≥120 bpm and increase from baseline ≥20 bpm were reported in 1 patient (3.1%), PCSAs of borderline QTcF (431 to 450 ms for male; 451 to 470 ms for female) were reported in 5 patients (15.6%), PCSAs of prolonged QTcF (>450 ms for male, >470 ms for female; <500 ms) were reported in 3 patients (9.4%), PCSAs of borderline QTcF increase (30 to 60 ms) from baseline were reported in 3 patients (9.4%), PCSAs of PR interval ≥220 ms and increase from baseline ≥20 ms were reported in 2 patients (6.5%).

In the BID dosing regimen, PCSAs for heart rate ≥120 bpm and increase from baseline ≥20 bpm were reported in 2 patients (11.8%), PCSAs of borderline QTcF (431 to 450 ms for male; 451 to 470 ms for female) were reported in 2 patients (11.8%), PCSA of prolonged QTcF (>450 ms for males, >470 ms for females; < 500 ms) was reported in 1 patient (5.9%), PCSAs of borderline QTcF increase (30 to 60 ms) from baseline were reported in 2 patients (11.8%), and PCSA of QRS width ≥120 ms was reported in 1 patient (5.9%).

Ophthalmological examination:

In the QD dosing regimen, among the patients with available ophthalmological examination results, 2 patients had a normal to abnormal change: 1 patient (6.3%) in the cornea and 1 patient (6.3%) in the retina.

In the BID dosing regimen, among the patients with available ophthalmological examination results, 1 patient (10.0%) had a normal to abnormal change in the lens.

Pharmacokinetic results: As the sponsor decided to terminate the development of SAR245409, the planned final statistical PK analyses were not performed. A listing of individual plasma concentrations of SAR245409 is presented in the bioanalytical report.

Pharmacogenomic Results: Pharmacogenomic samples for drug metabolizing enzymes and/or drug transporters were analyzed, but data was not statistically analyzed. The report for the pharmacogenetic assay methodology is provided in the study report appendices.

Pharmacodynamic results: Evaluation of mechanism-of-action related biomarkers, including p-AKT, t-AKT levels in platelet rich pellets, plasma fasting glucose, and plasma fasting C-peptide, are provided in the translational medicine report and associated appendices.

Antitumor Activity results: In the QD dosing regimen, out of the 31 patients evaluable for antitumor activity, 9 patients had stable disease as the overall objective response: 3 patients in the 50 mg QD dose cohort, 2 patients in the 60 mg QD dose cohort, and 4 patients in the 70 mg QD dose cohort. The other 22 patients had progressive disease as the overall objective response. In the BID dosing regimen, out of the 16 patients evaluable for antitumor activity, 8 patients had stable disease as the overall objective response: 2 patients in the 30 mg BID dose cohort, 3 patients in the 40 mg BID dose cohort, and 3 patients in the 50 mg BID dose cohort. The other 8 patients had progressive disease as the overall objective response.
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