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Sponsor / Company: Sanofi **Drug substance(s):** SAR245408	**Study Identifiers:** NCT01943838, UTN U1111-1132-9056, EudraCT 2012-003368-39 **Study code:** TED12863
Title of the study: A Phase 1 dose-escalation study of the safety and pharmacokinetics of a tablet formulation of SAR245408 polymorph E administered once daily to patients with solid tumors or lymphoma	
Study center(s): 1 study center	
Study period: Date first patient enrolled: 16/Oct/2013 Date last patient completed: 10/Feb/2015	
Phase of development: Phase 1	

Objectives:

Primary objective

- To assess the safety, tolerability, and plasma pharmacokinetics (PK) of SAR245408 given once daily (OD) as a tablet formulation of polymorph E in patients with solid tumors or lymphoma.

Exploratory objectives

- To evaluate the pharmacodynamic (PD) effect of SAR245408 given OD as a tablet formulation of polymorph E in patients with solid tumors or lymphoma.
- To explore the antitumor activity of SAR245408 given OD as a tablet formulation of polymorph E in patients with solid tumors or lymphoma.

Methodology: This was a Phase 1, multicenter, open-label, dose-escalation study with cohort expansion Phase, assessing the safety, tolerability, PK, and PD effect, and exploring the antitumor activity of SAR245408 given OD as a tablet formulation of polymorph E ("SAR245408 tablet-E") in patients with solid tumors or lymphoma.

A modified “3 + 3” dose-escalation design was employed to determine a safe dose of SAR245408 tablet-E (recommended Phase 2 dose for SAR245408 tablet-E ["RP2D tablet-E"]) providing a SAR245408 plasma exposure at least similar to that at the RP2D with the SAR245408 capsule formulation of polymorph A (RP2D capsule-A: 600 mg). Patients were enrolled in sequential cohorts of 3 to 4 and treated with successively higher doses of SAR245408. The decisions on dose-escalation were to be made at the time when at least 3 new patients at a given dose level (DL) were evaluable for dose-limiting toxicities (DLTs). 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 made after the appropriate data (safety and PK) were collected and reviewed by the Study Committee.

At the end of the dose-escalation Phase, additional patients (up to a total of 12 at the selected dose level) were enrolled to further assess safety and PK at the selected dose level and confirm the dose level as RP2D tablet-E.

Patients were to receive SAR245408 tablet-E, given with the morning meal, during two 28-day treatment cycles. Patients were monitored for safety and signs of toxicity. Information collected during Cycle 1 was used to determine the DLTs. Blood samples for PK analysis were collected during Cycle 1 and Cycle 2.

After Cycle 2, patients eligible for treatment continuation were offered to enroll in the treatment-extension Study TED12414. Patients who were not enrolled in the treatment-extension study were followed-up for safety for a minimum of 30 days (± 3 days) after last study drug administration.

Number of patients**:**	Planned: approximately 18 to 24 patients
	Enrolled: 22 patients
	Treated: 18 patients
Evaluated:	
	Pharmacodynamics: 18
	Safety: 18
	Dose-limiting toxicity: 18
	Anti-tumor activity: 18
	Pharmacokinetics: 18

Diagnosis and criteria for inclusion:

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

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

or

- Relapsed or refractory lymphoma for which standard therapies were no longer effective or there were no therapies known to prolong survival.

Study treatments

Investigational medicinal product(s): SAR245408

Formulation: tablet formulations at the strengths of 50 mg or 200 mg

Route(s) of administration: oral

Dose regimen: patients were to take SAR245408 tablet-E with the morning meal OD. The actual dose levels administered were 400 mg and 600 mg.

On Cycle 1 Day 1 and Cycle 2 Day 1, a standardized moderate-fat breakfast was given to the patients 30 minutes prior to SAR245408 administration (patients were monitored in order to finish their breakfast within a time frame of 30 minutes or less); patients had to fast for 4 hours after SAR245408 administration.

Duration of treatment: Patients were to receive SAR245408 OD during two 28-day treatment cycles unless progressive disease 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.

Duration of observation:

The duration of the study for an individual patient included:

- Screening period: 1 to 28 days
- Study treatment period: two 28-day cycles
- 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 followed up for safety; a follow-up visit was 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.

The total study duration from screening for an individual patient was 58 to 118 days.

Criteria for evaluation:

Safety: Safety and tolerability of SAR245408 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; findings of laboratory parameters (hematology, coagulation, serologies, serum chemistry, and urinalysis); vital signs and Eastern Cooperative Oncology Group (ECOG) performance status; and electrocardiogram (ECG) parameters.

Pharmacokinetics: Noncompartmental analysis was used to calculate the following SAR245408 PK parameters on Cycle 1 Day 1 (after a single oral dose) and on Cycle 2 Day 1 (after repeated daily oral dosing): Maximum plasma concentration observed (C_{max}), first time to reach C_{max} (t_{max}), area under the plasma concentration curve from time 0 to 24 hours (AUC_{0-24}), and area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real time t_{last} (AUC_{last}). In addition, the plasma concentration observed just before treatment administration during repeated dosing (C_{trough}) was obtained on Day 2, Day 8 and Day 15 of Cycle 1 and Day 2 of Cycle 2.

Pharmacodynamics: The following biomarkers were evaluated: pAKT in blood cells, fasting plasma glucose, and C-peptide.
Anti-tumor activity: Tumor assessment, including imaging by computed tomography (CT) or magnetic resonance imaging (MRI), were performed at baseline and at the end-of-treatment visit, and tumor response as per Investigator were collected. Patients showing disease progression at the end-of-treatment visit were not eligible for the treatment-extension Study TED12414. No tumor measurement data were collected in this study.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Pharmacokinetics:

Sampling: Plasma samples for the assessment of SAR245408 PK were collected:

- Predose on Cycle 1 Day 1, Day 2, Day 8, and Day 15;
- Predose on Cycle 2 Day 1 and Day 2;
- 1, 2, 4, 6, 8, and 10 hours postdose on Cycle 1 Day 1 and Cycle 2 Day 1.

Bioanalytical Method: Plasma concentrations of SAR245408 were measured using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification of 1.00 ng/mL.

Pharmacodynamics:

Sampling: Samples for the PD analysis of SAR245408 were collected:

- Predose on Cycle 1 Day 1, Day 2, Day 8, and Day 15;
- Predose on Cycle 2 Day 1 and Day 2;
- 2 and 4 hours postdose on Cycle 1 Day 1;
- 2, 4, 8, and 10 hours postdose on Cycle 2 Day 1.

Pharmacogenomics:

For those patients who signed the optional pharmacogenetic informed consent form (ICF), a blood sample (patients with solid tumor and patients with lymphoma except chronic lymphocytic leukemia [CLL]/small lymphocytic lymphoma [SLL]) or a saliva sample (patients with CLL/SLL) was to be collected at baseline to investigate allelic variants of drug metabolizing enzymes and/or drug transporters as intrinsic factors associated with PK or PD variability of SAR245408. Deoxyribonucleic acid (DNA) was extracted from whole blood or saliva and assayed using a validated Affymetrix DMET Plus Assay method for different allelic variants of drug metabolizing enzymes and transporters.

Statistical methods:

Dose-limiting toxicity

Summary of DLTs was based on the DLT-evaluable population that consisted of all included patients who had complete assessments for DLT evaluation and received at least 75% of the doses of study treatment during Cycle 1, or received partial doses of study treatment but developed DLTs during Cycle 1. Summary of DLTs was provided by dose level. Characteristics of DLTs were listed by patient.

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

- Nonhematologic toxicity:
  - Any Grade ≥3 nonhematologic toxicity except asthenia lasting less than 10 days, diarrhea, nausea, or vomiting;
  - Nausea/vomiting or diarrhea was to be considered a DLT in patients who had Grade ≥3 toxicity for >2 days despite receiving optimal prophylaxis and/or treatment
  - Any Grade 4 nonhematologic toxicity
  - Any toxicity resulting in a treatment interruption >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
  - Grade 4 thrombocytopenia; Grade 4 anemia
- A treatment-emergent adverse event (TEAE) that, in the opinion of the Investigator, was of potential clinical significance such that further dose-escalation would expose patients to unacceptable risk.

Safety

Safety was evaluated in the safety population that consisted of all patients who took at least 1 dose of the study treatment. All summaries were performed by dose level. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.

Total incidence (ie, Grade 1 or higher) and incidence of Grade ≥3 of each AE were summarized by system organ class (SOC) and preferred term (PT) 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 treatment-emergent AEs, deaths, SAEs, and AEs leading to treatment discontinuation were summarized similarly.

Treatment-emergent laboratory abnormalities were summarized based on change from baseline (increase of at least 1 grade for graded laboratory abnormalities or change from normal to abnormal for un-graded laboratory abnormalities). Vital signs data were presented in data listings. Appropriate summary statistics were provided for potentially clinically significant abnormalities (PCSAs). Electrocardiogram raw data were listed and changes from baseline were summarized based on number and percentage of patients with PCSAs. Additional safety data including ECOG were presented in listings.

Pharmacokinetics

The PK population was defined as all patients with at least 1 valid PK sample and having evaluable concentration-time data. The concentrations and PK parameters of SAR245408 were summarized for each dose level using descriptive statistics.

Pharmacodynamics

The PD population consisted of all included patients who received at least 1 dose of study treatment and had evaluable biomarker samples.
The PD parameters for SAR245408 were summarized in a descriptive manner with comparison between pre- and posttreatment biomarker data.

Antitumor activity

Tumor response was presented for all treated patients in listings.

Summary:

Population characteristics: A total of 22 patients were registered for this study, of whom 18 patients were enrolled and treated with SAR245408 tablet-E: 6 patients were enrolled at the dose level of 400 mg and 12 patients were enrolled at the dose level of 600 mg (6 out of the 12 patients were enrolled after determination of RP2D tablet-E). All of the 18 patients treated were evaluable for safety, DLT, PK, PD, and antitumor activity.

Four patients discontinued the study treatment: 3 patients discontinued due to disease progression and 1 patient discontinued due to AE. Eight patients completed the study treatment period but were not enrolled into Study TED12414. Five patients completed the study treatment period with stable disease as the overall response and went into the treatment extension Study TED12414. One patient was enrolled in Study TED12414 while the end-of-treatment tumor assessment for TED12863 was not performed. The decision was made by the Investigator and Sponsor jointly in the patient's best interest in terms of safety and potential benefit from study drug.

All patients treated were Caucasians. The median age of patients was 58.5 years (range: 27 to 83 years). The median weight was 76.8 kg. Eleven (61.1%) patients were male and 7 (38.9%) patients were female. All patients had an ECOG performance status of 0 or 1 at baseline.

Fourteen patients (77.8%) had metastatic solid tumor at baseline, and the median time from initial diagnosis to first study drug dose was 4.0 years. Adrenal gland adenocarcinoma was reported in 2 patients; other types of solid tumor were reported in individual patients. Four patients (22.2%) had lymphoma, and the median time from initial diagnosis to first study drug dose was 3.5 years. Mantle cell lymphoma was reported in 2 patients, while other types of lymphoma were reported in individual patients. Seventeen patients (94.4%) received prior anti-cancer therapy; 10 patients (55.6%) underwent prior anti-cancer surgery; 9 patients (50.0%) received prior immunotherapy; 7 patients (38.9%) received prior radiotherapy; 4 patients (22.2%) received biologicals. Median number of regimens in prior systemic treatments was 3.0 (range: 1 to 7 regimens).

Safety results: The mean (standard deviation [SD]) duration of study treatment per patient was 7.1 (1.15) weeks, and the median duration of study treatment per patient was 7.9 weeks (range: 3 to 8 weeks). Sixteen patients (88.9%) received 2 cycles of the study treatment and 2 patients (11.1%) received only 1 cycle. The mean (SD) relative dose intensity for SAR245408 was 85.4% (19.11%) in the overall safety population, 91.7% (20.41%) in the 400 mg OD dose cohort, and 82.2% (18.51%) in the 600 mg OD dose cohort.

A total of 6 patients were enrolled and treated at the dose level of 400 mg OD, with no DLT reported. Out of the first 3 patients enrolled and treated at the dose level of 600 mg OD, 1 DLT of Grade 3 rash maculo-papular was reported. Three additional patients were enrolled and treated at the dose level of 600 mg OD, with no DLT reported. To further investigate the recommended dose for Phase 2 studies (RP2D), 6 additional patients were enrolled and treated at the dose level of 600 mg OD, with 1 patient experiencing DLTs of Grade 4 lipase increased and Grade 3 rash generalized. The dose level of SAR245408 600 mg OD was considered safe, given that the DLT rate (2/12) was <1/3 in all of the DLT-evaluable patients. Based on the safety and PK data, 600 mg OD was selected as the RP2D for SAR245408. The Study Committee made a joint decision that no further dose-escalation was to be carried out.

All of the 18 patients treated experienced at least 1 TEAE. Frequent all grades TEAEs included: constipation (reported in 6 patients [33.3%]), fatigue, nausea, vomiting (reported in 5 patients [27.8%] each), decrease appetite, dry skin (reported in 4 patients [22.2%] each), dermatitis acneiform, diarrhea, pyrexia, and tumor pain (reported in 3 patients [16.7%] each).

Treatment-emergent AEs that were assessed by the Investigator to be related to the IMP were reported in 17 patients (94.4%). Frequent related TEAEs (all grades) included: decreased appetite, dry skin, nausea, vomiting (reported in 4 patients [22.2%] each), and fatigue (reported in 3 patients [16.7%]).

Grade ≥3 TEAEs were reported in 9 patients (50.0%) and all events were isolated occurrences. Grade ≥3 related TEAEs were reported in 5 patients (27.8%), including decreased appetite, vomiting, blood alkaline phosphatase (ALP) increased, lipase increased, photosensitivity reaction, rash maculo-papular, rash generalized, and hypertension.

There was no notable imbalance between the dose cohorts in the TEAEs. The frequent TEAEs observed in this study were generally expected based on the clinical experience with SAR245408 to date.

Eight patients (44.4%) experienced at least 1 serious TEAE. Four patients (22.2%) experienced 1 or more serious TEAEs associated with the infections and infestations SOC. No individual serious TEAE by preferred term was reported by more than 1 patient. Related serious TEAEs were reported in 1 patient from the 400 mg OD dose cohort (Grade 3 vomiting) and 1 patient from the 600 mg OD dose cohort (Grade 4 lipase increased), respectively.

One patient from the 600 mg OD dose cohort died due to a serious fatal Grade 5 sepsis secondary to a serious Grade 3 skin infection. The events of skin infection and sepsis were considered to be unrelated to SAR245408.
One patient from the 600 mg OD dose cohort experienced a serious Grade 4 lipase increased leading to permanent discontinuation of SAR245408. One patient from the 600 mg OD dose cohort experienced a nonserious Grade 3 rash maculo-papular leading to dose reduction. Five patients (27.8%) experienced TEAEs leading to dose delay, including gamma-glutamyltransferase (GGT) increased, abdominal infection, skin infection, rash generalized, and rash maculo-papular.

Six patients (33.3%) experienced protocol-defined adverse event of special interests (AESIs) of skin adverse events, including rash maculo-papular, dermatitis acneiform (reported in 2 patients [11.1%] each), rash pruritic, and rash generalized (reported in 1 patient [5.6%] each). No pregnancy or overdose of the IMP was reported in this study. Grade ≥3 AESIs included Grade 3 rash maculo-papular and Grade 3 rash generalized, each reported in 1 patient from the 600 mg OD dose cohort.

Twelve patients (66.7%) experienced selected AEs based on sanofi-defined toxicity grouping method. Selected TEAEs in the drug hypersensitivity grouping were reported in 5 patients (27.8%), liver toxicity TEAEs were reported in 3 patients (16.7%), and rash TEAEs were reported in 7 patients (38.9%). No lens retinal disease or pulmonary toxicity TEAE was reported.

Grade ≥3 selected TEAEs included: blood ALP increased and GGT increased (reported in 1 patient from the 400 mg OD dose cohort), photosensitivity reaction and rash maculo-papular (reported in 1 patient from the 600 mg OD dose cohort), and rash generalized (reported in another patient from the 600 mg OD dose cohort).

Hematological abnormalities were common in this study. Seventeen patients (94.4%) had anemia, 12 patients (66.7%) had lymphopenia, 6 patients (33.3%) had leukopenia, 5 patients (27.8%) had thrombocytopenia, and 1 patient (5.6%) had neutropenia. Grade 3 to 4 hematology abnormalities were reported only in the SAR245408 600 mg QD cohort, including lymphopenia (5 patients [27.8%]), anemia (2 patients [11.1%]), and thrombocytopenia (1 patient [5.6%]).

Common biochemistry abnormalities included: hyperglycemia (13 patients [72.2%]), alkaline phosphatase increased (9 patients [50.0%]), hyponatremia (7 patients [38.9%]), and hypocalcemia (6 patients [33.3%]). To be noted, one patient from the 600 mg QD dose cohort experienced a nonserious TEAE of Grade 2 hyperglycemia that was considered as related to the IMP. Elevations of alanine aminotransferase and aspartate aminotransferase were reported in 5 patients (27.8%) and 4 patients (22.2%), respectively, and all were Grade 1. Grade 3 to 4 biochemistry abnormalities included ALP increased, hyponatremia, hypophosphatemia, and lipase increased. All of these Grade ≥3 biochemistry abnormalities were isolated occurrences, and no imbalance between dose cohorts were noticed.

There were no safety issues identified in the data from vital signs or ECG assessments. Weight decrease of ≥5% from baseline was reported in 4 patients (22.2%) and increase of ≥5% from baseline was reported in 1 patient (5.6%). Blood pressure and heart rate abnormalities were all isolated occurrences, and hypertension was reported as TEAE in 2 patients (11.1%). Two patients (11.1%) had a QRS interval ≥120 ms at baseline and during the study. Three patients had a borderline QTcF interval based on absolute values and 2 patients had a borderline QTcF interval based on change from baseline. Two patients had a prolonged QTcF interval based on absolute values and 1 patient had a prolonged QTcF interval based on change from baseline. No patient had a QTcF interval >500 ms. None of these abnormal ECG assessments was reported as a TEAE.

Overall, the safety profile experienced with the 600 mg OD dose of SAR245408 was consistent with the known safety profile of the product, and therefore the dose of 600 mg can be used as the RP2D.

Pharmacokinetic results: SAR245408 PK following a single oral dose (Cycle 1 Day 1) and repeated OD dose (Cycle 2 Day 1) showed an increase in plasma exposure values (C_{max} and AUC_{0-24}) in Cycle 2 at both dose levels (SAR245408 400 mg and 600 mg tablet-E), indicating accumulation with repeated dosing. SAR245408 PK after repeated OD dose for 28 days showed an increase in plasma exposure values, with an accumulation of 6.21 and 2.98-fold (AUC_{0-24}) for 400 mg and 600 mg dose, respectively. After a 1.5-fold increase in dose (400 mg to 600 mg), the plasma exposure (C_{max} and AUC_{0-24}) increased by ~2-fold following a single dose (Cycle 1, Day 1) but was comparable in both dose levels following repeated dosing (Cycle 2, Day 1) suggesting potential saturable absorption. SAR245408 was slowly absorbed in both the dose groups evaluated with a median t_{max} ranging from 4.98 to 6.99 hours. A high inter-patient variability was observed in SAR245408 exposure (C_{max} and AUC_{0-24}) with a CV% up to 66% and 58% for C_{max} and AUC_{0-24} respectively, as shown in the tables below. Based on visual inspection of the mean plots for trough concentrations (C_{trough}) during Cycle 1 and Cycle 2, SAR245408 appeared to reach steady-state after 15 days of daily dosing in Cycle 1 and remained at steady state during Cycle 2. The range of exposures (C_{max} and AUC_{0-24}) after repeated doses of 600 mg tablet-E was within the range of historical data at steady state of both the 400 mg tablet-A and 600 mg capsule-A.

Mean ± SD (Geometric Mean) [CV%] of Plasma SAR245408 Pharmacokinetic Parameters on Day 1 Cycle 1

PK Parameters	Plasma SAR245408	
	SAR245408 400 mg OD	SAR245408 600 mg OD
N	6	12
C_{max} (ng/ml)	24200 ± 13600 (19500) [56.0]	50100 ± 19900 (43000) [39.8]
t_{max}[a] (hr)	6.99 (2.08 - 9.85)	4.98 (2.00 - 9.92)
AUC_{last}[b] (ng•hr/ml)	168000 ± 104000 (132000) [61.6]	333000 ± 134000 (286000) [40.3]
AUC_{0-24} (ng•hr/ml)	441000 ± 242000 (360000) [55.0]	909000 ± 349000 (790000) [38.4]

a Median (Min - Max)

b t_{last} for AUC_{last} estimation was 10 hrs for all patients

Mean ± SD (Geometric Mean) [CV%] of Plasma SAR245408 Pharmacokinetic Parameters on Day 1 Cycle 2

PK Parameters	Plasma SAR245408	
	SAR245408 400 mg OD	SAR245408 600 mg OD
N	6	11[d]
C_{max} (ng/ml)	106000 ± 69900 (83800) [65.7][f]	140000 ± 48800 (131000) [34.9][g]
t_{max}[a] (hr)	6.79 (4.00 - 24.5) [f]	6.00 (1.00 - 24.3)[g]
AUC_{last}[e] (ng•hr/ml)	1040000 ± 567000 (925000) [54.3][b]	1100000 ± 459000 (1010000) [41.7] [d]
AUC_{0-24} (ng•hr/ml)	2740000 ± 1580000 (2380000) [57.8] [b]	2710000 ± 1160000 (2450000) [42.9] [c]

a Median (Min - Max)
b n=5, 1 patient not included in calculation of summary statistics
c n=9, 2 patients not included in calculation of summary statistics
d n=11, 1 patient not included in calculation of summary statistics
e t_{last} for AUC_{last} estimation was 10 hrs for all patients
f 1 patient had only one PK measurement during Day 1 of Cycle 2 and that concentration value was considered as C_{max} and time as tmax by default
g 1 patient had only one PK measurement during Day 1 of Cycle 2 and that concentration value was considered as Cmax time and time as t_{max} by default

Pharmacodynamic results: Modulation of phosphorylated AKT (pAKT) level in platelet rich fraction was used to document the PD impact of SAR245408 on the PI3K pathway. Modulation of the PI3K pathway was observed when SAR245408 concentration reached at least 184 mM in 2 out of 6 patients in the 400 mg OD cohort and in 3 out of 8 patients in the 600 mg OD cohort.

Impact on fasting plasma glucose and C-peptide levels was used to document the PD impact of SAR245408 on the PI3K pathway. Due to food intake after 2 hours after dose administration, we were unable to document any modulation by SAR245408 of plasma glucose and C-peptide levels.

Antitumor activity results: Three out of the 6 patients in the 400 mg OD dose cohort and 2 out of the 12 patients in the 600 mg OD dose cohort had stable disease as the overall response. These 5 patients were enrolled into the treatment-extension Study TED12414. Other patients had progressive disease as the overall response.

Issue date: 12-Apr-2016