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Sponsor / Company: Sanofi Drug substance(s): SAR302503	Study Identifiers: NCT1836705, UTN U1111-1115-7323, EudraCT 2012-005642-38 Study code: TES13519
Title of the study: Effect of 14-day repeated oral doses of SAR302503 on ventricular repolarization, compared to 1-day placebo in adult patients with advanced solid tumors	
Study center(s): 10 centers, 2 in Belgium and 8 in the United States of America	
Study period: Date first patient enrolled: 07/May/2013 Date last patient completed: 02/May/2014	
Phase of development: Phase 1	

Objectives:

Primary

To assess the effect of SAR302503 (500 mg) administered as 14-day repeated doses on the corrected QT interval using Fridericia's formula (QTcF) compared to 1-day placebo in patients with advanced solid tumors.

Secondary

Segment 1

To assess the effect of SAR302503 administered as 14-day repeated doses on heart rate, QT, QTc using Bazett's formula (QTcB), population-specific QTc (QTcN), PR and QRS, compared to placebo.

To assess the clinical and laboratory safety of SAR302503.

To document the plasma concentrations of SAR302503 at the time of electrocardiogram (ECG) investigation.

Segment 2

To characterize the global safety profile including cumulative toxicities.

Exploratory

To evaluate the antitumor activity of SAR302503 administered as 500 mg daily repeated dose.

Methodology:

Prospective, multicenter, multinational, and nonrandomized study in patients with histologically or cytologically confirmed advanced solid malignancy, metastatic or unresectable, and for which curative measures did not exist.

The study consisted of 2 consecutive segments:

Segment 1:

Single-sequence, 2-treatment, cross-over study; the study was single-blinded for 1 day between Day 1 (placebo) and Day 15 (SAR302503).

Treatment A (Day 1): Palonosetron (0.25 mg, intravenous [IV], 30 minutes prior to investigational medicinal product [IMP] dosing) + placebo (oral).

Treatment B: Days 2-13: Granisetron (1 mg oral) per Investigator's discretion + SAR302503 (500 mg, once daily [QD], oral, self-administered on non-visit days)

Days 14-15 : Palonosetron (0.25 mg, IV, 30 minutes prior to IMP dosing) + SAR302503 (500 mg, QD, oral)

Segment 2:

Patients progressed to Segment 2 on Day 16 of Segment 1, at the Investigator's discretion.

During Segment 2, patients received SAR302503 500 mg (or a modified dose) daily, in 28-day cycles, until disease progression, unacceptable toxicity, withdrawal of consent, or Investigator's decision to withdraw patient, whichever came first.

Thiamine Supplementation Period

Sanofi held a teleconference with the US Food and Drugs Administration (FDA) Division of Hematology Products on 13 November 2013, following submission of 5 cases (4 confirmed) consistent with Wernicke's encephalopathy (WE) in patients treated with SAR302503 reported across the program. The purpose of the teleconference was to discuss these cases, as well as 14 cases of cardiomyopathy/congestive heart failure that were shared with the Agency prior to the teleconference call. The outcome of this discussion was that the FDA placed the SAR302503 Investigational New Drug (IND) on full clinical hold, since there was insufficient information to minimize the risk of WE. Altogether, a total of 7 cases of WE (from patients enrolled in the fedratinib clinical program) were reported to Sanofi and were shared with the FDA.

After a thorough risk-benefit analysis including consultation with the FDA, study Investigators, independent expert neurologists and neuro-radiologists, the Sponsor determined that the risk to patient's safety outweighed the benefit that SAR302503 would bring to patients. Sanofi agreed; therefore, that the full clinical hold was in the best interest of patient safety, resulting in the termination of all SAR302503 clinical trials including those in myelofibrosis, polycythemia vera, essential thrombocythemia, and solid tumors, and did not pursue lifting the clinical hold that was imposed by the FDA.

Thus, all patients were permanently discontinued from further SAR302503 treatment, and all patients, including those previously discontinued from the study, were given the option to receive thiamine supplementation for 90 days and to be followed for safety for the length of the Thiamine Supplementation Period. Additional adverse event of special interest (AESI) terms (AESI-2) were added in Protocol Amendment 2.

Therapeutic thiamine: All patients with neuropsychiatric or cardiac symptoms consistent with thiamine deficiency were to begin immediate treatment with thiamine at therapeutic dosages in accordance with institutional practice (eg, 500 mg IV infused over 30 minutes 3 times daily for 2 to 3 days, followed by 250 mg to 500 mg IV infused QD for 3 to 5 additional days, and then continued at an oral minimum daily dose of 100 mg for an additional 90 days).

Supplemental thiamine: Thiamine supplementation for patients without symptoms or signs of thiamine deficiency. Patients were to start thiamine daily supplementation immediately at an oral minimum daily dose of 100 mg and were to continue supplementation for at least 90 days.

This abbreviated Clinical Study Report (CSR) synopsis presents key disposition, exposure, PK, and safety data for the 60 patients who entered the study, of which 36 patients entered the Thiamine Supplementation Period. However, sufficient patients had completed Segment 1 to allow the primary pharmacodynamic (PD) endpoint to be evaluated. Therefore the abbreviated report includes the planned primary analysis, to assess the effect of SAR302503 (500 mg) administered as 14-day repeated doses on the corrected QTcF compared to 1-day placebo in patients with advanced solid tumors.

Number of patients:	Planned:	50
	Enrolled:	60
	Treated:	
	Placebo in Segment 1:	60
	SAR302503 in Segment 1:	59
	SAR302503 in Segment 2:	44
	Thiamine:	36
Evaluated:		
	Pharmacodynamics:	31
	Safety:	60
	Pharmacokinetics:	38

Diagnosis and criteria for inclusion:

Main Inclusion Criteria:

Male or female patients at least 18 years of age with histologically or cytologically confirmed advanced solid malignancy that was metastatic or unresectable, and for which standard curative measures did not exist. Patients having provided written informed consent.

Main Exclusion Criteria:

Screening ECG with automatic reading of QTcB or QTcF ≥ 480 msec (within 8 days of Day -1); Significant hypokalemia at screening (K^+ < 3.5 mmol/L within 8 days of Day -1). Significant hypomagnesemia at screening (Mg^{2+} < 0.7 mmol/L witin 8 days of Day -1); or if the patient received (and could not discontinue), or was scheduled to receive a concomitant treatment known to cause QT prolongation, for 2 weeks before Day 1 and for the duration of Segment 1.

Study treatments

Investigational medicinal product(s): SAR302503

Formulation: 100 mg capsules

Route(s) of administration: Oral, 2 hours after completion of meals

Dose regimen:

Segment 1: 500 mg (5 capsules), QD, for 14 days (Days 2 to 15), self-administered except on visit days

Segment 2 (per Investigator's discretion): 500 mg (5 capsules), or modified dose, QD, in consecutive 28-day cycles

Placebo for SAR302503

Formulation: capsules

Route(s) of administration: Oral, 2 hours after completion of breakfast

Dose regimen:

On Day 1 only: 5 capsules

Noninvestigational medicinal product(s): Palonosetron

Formulation: Solution, 0.25 mg/5 mL

Route(s) of administration: Intravenous

Dose regimen: 0.25 mg, QD, on Days 1, 14, and 15 in Segment 1 only

Thiamine

Thiamine was provided and administered by the site.

Duration of treatment:

Segment 1:

One day placebo + 14 days SAR302503.

Segment 2:

Patients progressed to Segment 2, at the Investigator's discretion and were allowed to continue treatment at the Investigator's discretion until disease progression, unacceptable toxicity, withdrawal of consent, or Investigator's decision to withdraw the patient.

Thiamine Supplementation Period:

Following study termination, all patients still alive were given the option to receive oral or IV thiamine as indicated, and as described under methodology, for at least 90 days.

Duration of observation:

Segment 1:

From 7 to 10 weeks (including screening) for patients who did not continue on Segment 2.

Segment 2:

Patients progressed to Segment 2 at the Investigator's discretion and were allowed to continue treatment at the Investigator's discretion until disease progression, unacceptable toxicity, withdrawal of consent, or Investigator's decision to withdraw the patient (end-of-study planned 30 ± 3 days after the last dose).

Thiamine Supplementation Period:

Following study termination, all patients still alive were given the option to receive thiamine treatment or supplementation for 90 days and to be followed for safety for the length of the Thiamine Supplementation Period.

Criteria for evaluation:

Pharmacodynamics: Pharmacodynamic (PD) parameters were obtained from continuous Holter 24-hour (Day -1) or 25-hour (Days 1 and 15) monitoring, which were centrally read by an ECG reading center (semi-automatic reading) and triplicate measurements at each prespecified timepoint were extracted. Electrocardiogram interval parameters (RR, PR, QRS, and QT) were obtained from the global superimposed median beat across the 10 seconds. The parameters received from the ECG reading center were: the primary PD parameter QTcF and secondary parameters: respiratory rate (RR), heart rate (HR), pulse rate (PR), QRS, QT, and QTcB. In addition, a population-specific correction formulae, QTcN, was also derived.

Safety: The safety profile was assessed from adverse event (AE) reports, the findings of physical examination (preferably by the same physician), ECG, Holter reports (in Segment 1), and laboratory tests, and were based on incidence, severity (as graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v.4.03).

Pharmacokinetics: Pharmacokinetic (PK) parameters were calculated, using noncompartmental methods from plasma SAR302503 concentrations obtained after 14-day repeated dose administrations in Segment 1. The parameters included maximum plasma concentration observed (C_{max}), plasma concentration observed just before treatment administration during repeated dosing (C_{trough}), time to reach C_{max} (t_{max}) and the area under the plasma concentration versus time curve calculated using the trapezoidal method over the 24-hour dosing interval (AUC_{0-24}).

Statistical methods:

Sample size determination:

The sample size determination for this study, determined for Segment 1 only, was based on a non-inferiority approach in a single-sequence crossover design. Assuming a within-subject standard deviation (SD) of raw QTcF at 1 single timepoint of 12 milliseconds (msec), a sample size of 36 evaluable patients would have 85% power to ensure that the upper bound of the 2-sided 90% confidence interval (CI) of the largest time-matched mean difference (LTMMD) in QTcF between SAR302503 and placebo among the 8 time points (T1H, T2H, T3H, T4H, T5H, T6H, T8H, and T24H) was less than 20 msec using the conservative estimate of a true mean difference of 10 msec in a flat scenario. As a result, the study was planned to enroll up to 50 patients to account for dropouts and non-evaluable patients.

Analysis populations:

The safety population included all enrolled patients who were administered IMP.

The PD population was a subset of the safety population, including patients who did not withdraw from Segment 1 before Day 15 (Holter Day) and who fulfilled all inclusion criteria, and had no important deviations related to the IMP or non-IMP or to Holter or ECG data (including intake of any QT-prolonging drugs or moderate or strong inhibitors or inducers of CYP3A4).

The PK population was a subset of the safety population, including patients who did not withdraw from Segment 1 before Day 15 (Holter Day) and who fulfilled all inclusion criteria and had no important deviations related to IMP or to the intake of the prohibited concomitant medications that are moderate or strong inhibitors or inducers of CYP3A4.

Pharmacodynamic analyses (Segment 1 only)

Primary analysis:

All the PD analyses were performed using the PD population.

The primary analysis assessed the LTMMD between SAR302503 and placebo in QTcF using all assessments between T1H (ie, after Palonosetron and SAR302503 or placebo administration) and T24H. A linear repeated measures mixed effects model was used on the raw QTcF values taking into account all the timepoints (ie, T1H, T2H, T3H, T4H, T5H, T6H, T8H, and T24H) and including data from placebo and SAR302503 treatments. The model included treatment, gender, time, treatment-by-time interaction term as fixed effects and patient nested within gender as random effect (using the SAS® PROC MIXED procedure).

Secondary analyses:

Mean estimates (with the corresponding 2-sided 90% CI) of pairwise SAR302503 versus placebo comparison at each timepoint were obtained using linear contrasts within the previous mixed model framework. No multiplicity adjustment was made.

Estimates and 2-sided 90% CIs for mean difference in QTcF between SAR302503 at the time of each individual C_{max} of SAR302503 and placebo (at the same time corresponding to the individual C_{max} of SAR302503) were also estimated, using a linear mixed effects model.

Heart rate, QT, QTcB and QTcN, PR, and QRS intervals were secondary analysis endpoints and were analyzed similarly to QTcF.

Safety analyses:

For safety data, the observation period was divided into 3 periods: pretreatment, on-treatment, and posttreatment. The Pretreatment Period was defined as the time from when the patients gave informed consent up to and including Day -1. The On-treatment Period was defined as from Day 1 (included) up to 30 days after the last dose of IMP, and was divided into 2 periods: (1) for Treatment A (Day 1), (2) for Treatment B (Day 2 to 30 days after last dose of IMP). The Posttreatment Period was defined as starting 31 days after the last dose of IMP to study closure. For the thiamine supplementation population, the subset of the Posttreatment Period for safety data collected from the later of (a) 31 days after the last SAR302503 dose or (b) beginning of the Thiamine Supplementation Period, up to the end of the Thiamine Supplementation Period, was used for safety analyses.

The safety analyses were performed using the safety population, or the thiamine supplementation population (only for safety data collected from the later of (a) 31 days after the last SAR302503 dose or (b) beginning of Thiamine Supplementation Period, up to the end of the Thiamine Supplementation Period). Safety analyses were performed for Segments 1 and 2 combined for the safety population except for ECG analyses (focused on Segment 1), and analyses of the post-treatment period (focused on the thiamine

supplementation population).

Adverse events were graded according to NCI-CTCAE v4.03. Adverse events were classified by system organ class (SOC)/preferred term (PT) according to the Medical Dictionary for Regulatory Authorities (MedDRA), (version 17.0). Prior and concomitant medications were coded using the World Health Organization Drug Dictionary (WHO-DD March 2014 version). The primary focus of AE reporting was on treatment-emergent adverse events (TEAEs). Pre- and posttreatment AEs were described separately. In addition, follow-up AEs were summarized separately.

Other safety analyses included summaries for hematology and chemistry, vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], HR, weight, RR and body temperature), ECGs, Holter reports (rhythm and conduction analysis), physical examination and Eastern Cooperative Oncology Group (ECOG) performance status scores results.

Pharmacokinetic analyses:

Pharmacokinetic parameters were determined using noncompartmental methods from plasma SAR302503 concentrations obtained after 14-day repeated dose administrations in Segment 1. They included descriptive statistics and graphs for: C_{max}, C_{trough}, t_{max}, and AUC_{0-24}.

Summary:

This study enrolled 60 patients, of whom 59 were treated with SAR302503. Sixteen (26.7%) patients discontinued during Segment 1 and 44 patients (73.3%) were enrolled and treated in Segment 2. In November 2013, the 16 patients continuing in the On-treatment Period of the study were permanently discontinued from further SAR302503 following full clinical hold of the IND. All patients still living, regardless of time since treatment discontinuation, were given the option to receive further safety follow-up and thiamine supplementation for 90 days, and 36/42 received thiamine.

Population characteristics:

In the enrolled population in Segment 1 (N=60), 31 (51.7%) patients were female. The mean age of patients was 60.8 years (range: 32 to 80 years).

In the PD population (N=31), 12 (38.7%) patients were female. The mean age of patients was 62.6 years (SD: 9.8).

Pharmacodynamic results:

The target sample size (N= 36) of the PD population (N=31) was not reached.

There was no significant effect on QTcF following SAR302503 treatment in cancer patients. The estimated LTMMD for the QTcF interval observed at T4H was 4.32 msec (90% CI: 1.16; 7.49). The upper bound of the 2-sided 90% CI was lower than 20 msec. Supportive information was provided by a secondary analysis; the mean difference estimate at t_{max} was -2.54 msec (90% CI: -5.93, 0.84).

There was no significant effect of SAR302503 on HR, QTcN, QTcB, uncorrected QT interval, PR interval, or QRS duration compared to placebo. There was no effect of SAR302503 on HR compared to placebo either at T3H, the time of LTMMD (LTMMD estimate was 0.48 bpm [90% CI: -2.33; 3.30]) or at the time of t_{max} (mean difference estimate versus placebo was -0.41 bpm [90% CI: -3.25, 2.43]). The LTMMD for QTcN (4.30 msec [90% CI: 1.24; 7.35]) was similar to that for QTcF. For the uncorrected QT interval, the LTMMD estimate was 11.27 msec (90% CI: 5.03; 17.51). The LTMMD estimate for PR interval between SAR302503 and placebo was 4.28 msec (90% CI: 1.71; 6.85). The LTMMD estimate for QRS duration between SAR302503 and placebo was 1.43 msec (90% CI: 0.14; 2.72).

Safety results:

The mean (SD) duration of exposure to SAR302503 in the overall study was 4.7 (3.6) weeks with a range of <1 to 15 weeks. The majority of patients (35 out of 60) received SAR302503 for <1 to 4 weeks and the median cumulative dose was 13 700 mg.

The mean (SD) duration of exposure to thiamine was 12.54 (5.44) weeks with a range of 0.7 to 21.9 weeks. The largest proportion of patients (41.7%) received thiamine for 9 to 14 weeks and the median cumulative dose was 9200 mg.

Most patients (96.6%) who received SAR302503 had at least 1 TEAE with the most common being gastrointestinal events.

At the time of database lock, a total of 31 patients who received SAR302503 had died, (9 On-treatment and 22 Posttreatment). Most deaths were due to progressive disease (n=26), 3 on-treatment deaths were due to serious TEAEs (treatment-related WE; treatment-related hemoptysis; and nontreatment-related pneumonia aspiration), and 2 poststudy deaths were recorded as due to: "other-cancer"; and "unknown cause".

Serious adverse events (SAE) were reported in 27 patients (45.8%) treated with SAR302503, of whom 18 (30.5%) had a nonfatal SAE. The SAEs with the highest incidences were in the SOCs of Gastrointestinal disorders and General disorders and administration site conditions. No SAEs were reported in the Thiamine Supplementation Period.

Ten patients (16.9%) discontinued SAR302503 treatment due to a TEAE. In 9 patients, the events were considered related to treatment. The events were fatal in 3 patients while the events were treatment-related Grade 4 (gastric perforation and gamma-glutamyl transpeptidase [GGT] increased) in 2 other patients. Only nausea and vomiting (each n=2 [3.4%]) lead to treatment discontinuation in more than 1 patient.

Adverse events of special interest were reported in 21 patients (35.6%) treated with SAR302503 and all 21 had at least one Grade 3-4 AESI. Most of these patients also had other serious or significant events. No AESI were reported during the Thiamine Supplementation Period. Only the fatal case of WE was identified as AESI-2.

No patients had an increase in QTcF, QTcB, or QTcN >60 msec, and there were no notable changes during SAR302503 treatment in safety ECG, rhythm and conduction analysis, or vital signs. Grade 3-4 GGT increased, lymphopenia, hypermagnesemia, anemia, and lipase occurred in >15% of patients.

Pharmacokinetic result

The mean ±SD C_{max} and AUC_{0-24} of SAR302503 were 4570 ± 3550 ng/mL and 68400 ± 49 600 ng•h/mL, respectively, in adult patients with advanced solid tumors after QD oral doses at 500 mg on Day 15.

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