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Sponsor / Company: Sanofi Drug substance(s): SAR302503	Study Identifiers: NCT01585623, UTN U1111-1125-8930 Study code: INT12497
Title of the study: An open-label, two-treatment crossover pharmacokinetic interaction study of repeated doses of SAR302503 on pharmacokinetics of a single dose cocktail of omeprazole, metoprolol, and midazolam used as probe substrates for CYP2C19, CYP2D6, and CYP3A4 activities, respectively, in adult patients with refractory solid tumors.	
Study center(s): 3 centers in the United States	
Study period: Date first patient enrolled: 15/Jun/2012 Date last patient completed: 01/Mar/2013	
Phase of development: Phase 1 pharmacokinetic (PK) interaction study	

Objectives:

Segment 1

Primary:

- To assess the effect of 15-day repeated oral doses of 500 mg SAR302503 on the cytochrome P450 (CYP) activity using a CYP probe cocktail (2C19, 2D6, and 3A4).
- To document the PK of SAR302503 after repeated 500 mg oral daily doses.

Secondary:

- To assess the safety profile of 15-day repeated oral doses of 500 mg SAR302503.
- To evaluate the potential for CYP3A4 enzyme induction and inhibition by SAR302503 after repeated doses with plasma 4β-hydroxycholesterol concentration ratios on Day 14 versus Day -1.

Segment 2

- To characterize the global safety profile including cumulative toxicities.
- To assess preliminary antitumor activity in patients with evaluable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.

Methodology: open-label study with two segments

Segment 1

1-sequence, 2-period, 2-treatment crossover study. Patients were administered a single oral dose cocktail of omeprazole, metoprolol, and midazolam used as probe substrates for CYP2C19, CYP2D6, and CYP3A4 activities, respectively, with or without SAR302503 on Day-1 or with SAR302503 on Day 15.

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

Segment 2

During Segment 2, patients received 500 mg SAR302503 daily, in a 28-day cycle, at the Investigator's discretion until 1 of the following occurs: disease progression, unacceptable toxicity, or withdrawal of consent.

Number of patients:	Planned: 12 Enrolled: 16 Treated: 16 in Segment 1, 10 in Segment 2
Evaluated:	Efficacy: 5 Safety: 16 Pharmacokinetics: 16 (16 on Day -1 for Cocktail alone and 13 on Day 15 for Cocktail + SAR302503)

Diagnosis and criteria for inclusion: Male or female patients, at least 18 years old, with advanced solid tumors that were refractory to standard treatment or for which no standard treatment existed.

Study treatments

Segment 1

Investigational medicinal product(s): SAR302503 (now also known as fedratinib)

Formulation: capsule

Route(s) of administration: oral

Dose regimen: 500 mg once daily from Day 1 to Day 15

Segment 2

Investigational medicinal product(s): SAR302503 (now also known as fedratinib)

Formulation: capsule

Route(s) of administration: oral

Dose regimen: 500 mg once daily, in consecutive 28-day cycles

Non-investigational medicinal product(s): Cocktail containing omeprazole, metoprolol, and midazolam

Formulation: 20 mg capsule; metoprolol: 100 mg coated tablet, midazolam: 1 mg/mL solution for injection

Route(s) of administration: oral

Dose regimen: 20 mg; metoprolol: 100 mg; midazolam: 2 mg; single dose on Day -1 and Day 15

Duration of treatment: Segment 1: 16 days

Segment 2: patients proceeded to Segment 2 on Segment 1 Day 16 at the Investigator's discretion. Patients continued treatment at the Investigator's discretion until 1 of the following occurred: disease progression, unacceptable toxicity, or withdrawal of consent.

Duration of observation: 30 days after last treatment

Criteria for evaluation:

Segment 1

Safety: Safety was evaluated based on the incidence of treatment-emergent adverse events (TEAEs) and changes in clinical laboratory parameters, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, electrocardiogram (ECG), and body weight relative to baseline. Clinical and laboratory adverse events (AEs) were assessed and reported using terminology of the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Pharmacokinetics:

Primary endpoints:

Omeprazole, metoprolol, midazolam: Area under the curve until the last measurable concentration (AUC_{last}) and area under the curve (AUC)

Secondary endpoints:

Omeprazole, metoprolol, midazolam: maximum plasma concentration (C_{max}), time to C_{cmax} (t_{max}), and terminal half-life ($t_{1/2z}$);

SAR302503: C_{max}, t_{max}, Trough plasma concentration (C_{trough}), and area under the curve versus time between 0 and 24 hours (AUC_{0-24H})

The plasma 4β-hydroxycholesterol on Day 14 versus Day -1 concentration ratios will be calculated to evaluate the potential for CYP3A4 enzyme induction and inhibition by SAR302503 after repeated doses.

Segment 2

Safety: Safety was evaluated based on the incidence of TEAEs and changes in clinical laboratory parameters, ECOG performance status, vital signs, ECG, and body weight relative to baseline. Clinical and laboratory AEs were assessed and reported using terminology of the National Cancer Institute - CTCAE Version 4.03.

Efficacy: Overall response rate (ORR).

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Sampling:

Cocktail probe drugs: Blood samples for PK evaluation were collected in Segment 1 at predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours after dosing on Day -1 and Day 15 of Segment 1.

SAR302503: Blood samples for PK evaluation were collected in Segment 1 at predose on Day -1 and Day 14; at predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 24 hours after dosing on Day 15 of Segment 1.

Assays: Plasma concentrations were determined using validated liquid chromatography - tandem mass spectrometry (LC-MS/MS) methods with lower limits of quantification (LLOQ) of 0.100 ng/mL for SAR302503, 5.00 ng/mL for metoprolol and omeprazole, and 0.05 ng/mL for midazolam, respectively.

Statistical methods:

Pharmacokinetics (Segment 1)

Pharmacokinetic parameters of each treatment were summarized using descriptive statistics.

For log-transformed C_{max}, AUC_{last}, and AUC, the effect of repeated doses of SAR302503 on a single dose of omeprazole, metoprolol, and midazolam PK parameters were analyzed using a linear mixed effects model (fixed terms for treatment and gender).

Point estimates and 90% confidence intervals (CIs) for the geometric mean ratios of the cocktail coadministered with SAR302503 versus cocktail alone were provided for C_{max}, AUC_{last}, and AUC.

Individual 4β-hydroxycholesterol concentration data were listed and summarized using descriptive statistics by day, and individual Day 14 / Day -1 ratios were calculated and listed for each patient and also summarized using descriptive statistics. The log-transformed concentration was analyzed using a linear mixed model (with fixed terms for day and gender). The point estimate and 90% CI for the difference of mean log-transformed concentration between Day -1 and Day 14 was provided and then converted to the geometric mean ratio between Day -1 and Day 14 by the antilog transformation.

Safety (Segment 1 and 2)

Safety assessments were based upon the review of individual data and descriptive statistics. Individual values were flagged for potentially clinically significant abnormalities (PCSAs). Treatment-emergent adverse events were tabulated.

Safety assessment period:

- For patients who continued to Segment 2, safety data up to the day when the first dosing started in Segment 2 were collected in Segment 1. After that, safety data were collected in Segment 2.
- For patients who did not continue to Segment 2, safety data were collected in Segment 1 up to the follow-up visit, 30 days post dose.

Efficacy (segment 2)

The number and percentage of patients with an objective response (OR) according to RECIST1.1 were summarized by descriptive statistics.

Summary:

Population characteristics: A total of 16 patients were enrolled and treated, and all of them had at least 1 day of PK assessment for omeprazole, metoprolol, and midazolam; therefore, all were included for the PK population. Thirteen out of 16 patients completed Segment 1 treatment as planned. Ten patients continued into Segment 2 of the study.

There were 10 male and 6 female patients enrolled in the study with a mean body weight of 77.5 kg. The mean age was 64.6 years. The ECOG status was rated at 0 or 1 in all patients. All patients had metastatic disease and received prior anticancer therapies.

Safety results: All 16 patients experienced at least 1 TEAE (all grades) related to SAR302503, and all 16 patients reported at least 1 system organ class gastrointestinal disorder TEAE. The most common TEAEs (all grades) regardless of relationship to study treatment were nausea and fatigue (each in 12 [75.0%] patients), vomiting (11 [68.8%] patients), blood creatinine increased (7 [43.8%] patients), constipation and diarrhea (each in 6 [37.5%] patients), and decreased appetite and dehydration (each in 5 [31.3%] patients). One patient died within 30 days of the end of study treatment due to multiple organ failure related to disease. Eight patients had serious TEAEs, none of which was considered by the Investigator to be drug-related. One patient had a drug-related TEAE leading to treatment discontinuation. The safety profile was consistent with the known safety profile of SAR302503.

Pharmacokinetic results: Coadministration of 500 mg once-daily doses of SAR302503 for 15 days with a single-dose cocktail containing omeprazole (20 mg), metoprolol (100 mg), and midazolam (2 mg) resulted in the following conclusions:

- Repeated doses of SAR302503 increased the mean AUC_{last}, and AUC of omeprazole by 2.57-fold (90% CI: 1.94-3.41) and 2.82-fold (90% CI: 2.26-3.53), respectively.
- Repeated doses of SAR302503 increased the mean C_{max}, AUC_{last}, and AUC of metoprolol after a single 100 mg oral dose by 1.60-fold (90% CI: 1.25-2.05), 1.81-fold (90% CI: 1.30-2.53), and 1.77-fold (90% CI: 1.27-2.74), respectively.
- Repeated doses of SAR302503 increased the mean C_{max}, AUC_{last}, and AUC of midazolam after a single 2 mg oral dose by 1.82-fold (90% CI: 1.49-2.21), 4.01-fold (90% CI: 3.19-5.05), and 3.84-fold (90% CI: 2.62-5.63), respectively.
- Repeated doses of SAR302503 decreased the endogenous plasma 4β-hydroxycholesterol concentrations, with the mean Day 14/Day -1 ratio of plasma 4β-hydroxycholesterol of 0.59 (90% CI: 0.54-0.66) suggesting a net inhibition of CYP3A by SAR302503, which is in agreement with the observed midazolam results.
- SAR302503 plasma concentrations appeared to reach steady state by Day 14 after once-daily oral doses at 500 mg.

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