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Sponsor / Company: Sanofi Drug substance(s): SAR302503	Study Identifiers: NCT01523171, UTN U1111-1124-0967, EudraCT 2011-005226-21 Study code: ARD12181
Title of the study: A Phase II, Multicenter, Open Label, Single Arm Study of SAR302503 in Subjects Previously Treated with Ruxolitinib and with a Current Diagnosis of Intermediate or High-Risk Primary Myelofibrosis, Post Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis	
Study center(s): Thirty-six active sites in Canada, Austria, Belgium, France, Germany, Italy, Spain, Netherlands, United Kingdom, and the United States (US)	
Study period: Date first patient enrolled: 30/Apr/2012 Date last patient completed: 29/Apr/2014	
Phase of development: Phase 2	

Objectives:

Primary objective

The primary objective of this study was to evaluate the efficacy of once daily dosing of SAR302503 in subjects previously treated with ruxolitinib and with a current diagnosis of intermediate-1 with symptoms, intermediate-2 or high-risk primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PV MF), or post-essential thrombocythemia myelofibrosis (ET MF) based on the reduction of spleen volume at the end of 6 treatment cycles.

Secondary objectives

To evaluate the effect of SAR302503 on myelofibrosis (MF) associated symptoms as measured by the Modified Myelofibrosis Symptom Assessment Form (MFSAF) diary.

To evaluate the durability of splenic response.

To evaluate the splenic response to SAR302503 by palpation at the end of Cycle (EOC) 6.

To evaluate the splenic response to SAR302503 at the EOC 3.

To evaluate the effect of SAR302503 on the Janus kinase 2 (JAK2)^{V617F} allele burden.

To evaluate the safety and tolerability of SAR302503 in this population.

To evaluate plasma concentrations of SAR302503 for population pharmacokinetic (PK) analysis, if warranted.

Methodology:

This was a Phase 2, multicenter, open-label, single-arm study of SAR302503 at a starting dose of 400 mg/day in patients previously treated with ruxolitinib and with a current diagnosis of intermediate-1 with symptoms, intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF.

With Amendment 4, a 90-day Thiamine Supplementation Period was added either as a therapeutic thiamine treatment for patients with symptoms or as supplemental thiamine for patients without symptoms.

During this study, the SAR302503 Investigational New Drug (IND) was placed on full clinical hold following submission and discussion with the US Food and Drug Administration (FDA) of 5 cases (4 confirmed) consistent with Wernicke's encephalopathy (WE) in patients treated with SAR302503, as well as 14 cases of cardiomyopathy/congestive heart failure reported across the program. After a thorough risk benefit analysis including consultation with the US FDA, study Investigators, independent expert neurologists, and neuroradiologists, 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.

Number of patients:	Planned: 70 (70 evaluable patients)
	Randomized: N/A
	Treated: 97
Evaluated:	
	Efficacy: 83
	Safety: 97
	Pharmacokinetics: 97

Diagnosis and criteria for inclusion:

Major inclusion criteria:

- ≥18 years of age with a diagnosis of PMF, or post-PV MF, or post-ET MF with the MF classified as high risk, intermediate-2 risk level, or intermediate-1 with symptoms.
- Spleen size ≥5 cm below costal margin.
- Previously received ruxolitinib treatment for PMF, post-PV MF, or post-ET MF or PV or ET.
- Signed written informed consent.

Major exclusion criteria:

- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of >2 before the first dose of SAR302503 at Cycle 1 Day 1.
- The following laboratory values within 14 days prior to the initiation of SAR302503: absolute neutrophil count (ANC) <1.0 x 10^9/L, platelet count <50 x 10^9/L, serum creatinine >1.5 x upper limit of normal (ULN), serum amylase and lipase >1.5 x ULN.
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 x ULN.
- Total bilirubin: Exclude if ≥3.0 x ULN; patients with total bilirubin between 1.5-3.0 x ULN must be excluded if the direct bilirubin fraction is ≥25% of the total.
- Patients with prior history of chronic liver disease (eg, chronic alcoholic liver disease, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemachromatosis, non-alcoholic steatohepatitis [NASH]).
- Splenectomy.
- Uncontrolled congestive heart failure, angina, myocardial infarction, cerebrovascular accident, coronary/peripheral artery bypass graft surgery, transient ischemic attack, or pulmonary embolism.
- Subjects with a QTc prolongation >450 ms at screening or prior to study drug administration or patients who need concomitant medicines that are known to prolong QTc (applicable for France only).

Study treatments

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

Formulation: Hard capsules containing 100 mg of investigational medicinal product (IMP) free base (equivalent to 117 mg dihydrochloride monohydrate).

Route(s) of administration: Orally self-administered on an outpatient basis

Dose regimen: The starting dose was 400 mg but a flexible dosing regimen could be employed to optimize efficacy and to minimize drug toxicity for individual subjects; SAR302503 was administered once daily in consecutive 28-day cycles at the assigned dose level ranging from 200 to 600 mg.

Duration of treatment:

Duration of observation: The expected duration of the study for an individual patient was approximately 8 months. The study consisted of Screening, Treatment, and Post-treatment Observation Visits. The Screening Period was up to 28 days, followed by a 6-month (6 cycles of 28 days) Treatment Period, and a Follow-up Visit, which was performed approximately 30 days following the last administration of the IMP. Cut-off date for the analysis of the primary endpoint of response was at the maximum at the end of 6 cycles after the date of first dose of IMP of the last treated subject. After discontinuation of study treatment a 90-day Thiamine Supplementation Period was added.

Criteria for evaluation:

Efficacy:

Primary endpoint

The primary efficacy endpoint response rate (RR) was defined as the proportion of patients who had a ≥35% reduction in volume of spleen from baseline at the EOC 6 as measured by magnetic resonance imaging (MRI) (or computed tomography [CT] scan in patients with contraindications for MRI).

Secondary endpoints

- Symptom Response Rate (SRR), defined as the proportion of patients with a ≥50% reduction from baseline to the EOC 6 in the total symptom score using the modified MFSAF.
- Duration of spleen response, measured by MRI (or CT scan in patients with contraindications for MRI), defined as the time from the date of the first response to the date of subsequent progressive disease or death, whichever was earlier.
- Duration of Response was determined only for patients who have a response; this value was missing for other patients.
- Proportion of patients with a ≥50% reduction in length of spleen by palpation from baseline to at the end of Cycle 6.
- Response rate at the EOC 3 defined as the proportion of patients who have a ≥35% reduction from baseline in volume of spleen at the EOC 3 as measured by MRI (or CT scan in patients with contraindications for MRI).
- Percent change of spleen volume at the EOC 3 and 6 from baseline as measured by MRI (or CT scan in patients with contraindications for MRI).
- The effect of SAR302503 on the $JAK2^{V617F}$ allele burden.

Safety endpoint:

Safety and tolerability of the IMP was evaluated based on the incidence of treatment-emergent adverse events (TEAEs) and changes in clinical laboratory parameters and peripheral blood smear, ECOG PS, electrocardiogram (ECG), and vital signs and by physical examinations.

Pharmacokinetic endpoint:

Plasma concentrations of SAR302503.

Statistical methods:

Due to SAR302503 clinical program and ARD12181 study termination for safety reasons, this summary includes only the primary efficacy endpoint (spleen response at EOC 6), spleen response at EOC 3, and the SRR endpoint, and spleen size by palpation at EOC 6. None of the exploratory endpoints were analyzed.

Analysis of primary efficacy endpoint(s):

The primary analysis of RR in spleen volume at the EOC 6 was defined as ≥35% reduction from baseline.

The RRs and 95% confidence intervals (CI) were provided for the per-protocol (PP) population. The last observation carried forward method was used to impute the missing EOC 6 spleen volume measurement with the Cycle 4 Day 1 spleen volume measurement, except for patients who discontinued prior to EOC 6 due to disease progression.

A subgroup analysis of RR was performed for patients who were resistant or intolerant to ruxolitinib (according to the Investigator's assessment of ruxolitinib treatment failure).

A waterfall plot of the percent reduction in spleen volume from baseline to EOC 6 was provided.

Analysis of secondary efficacy endpoints:

The SRR was defined as the proportion of subjects with a ≥50% reduction from baseline to the EOC 6 in the total symptom score.

The SRR at Cycle 6 was provided along with the corresponding 95% CI. It was also summarized by the Investigator's assessment of ruxolitinib treatment failure (resistant versus intolerant).

The MFSAF compliance profile over time up to EOC 6 was summarized. A descriptive summary of each of the individual symptoms and the total symptom score at each cycle up to Cycle 6 and changes from baseline was provided. A waterfall plot of the percent reduction in total symptom score from baseline to EOC 6 was provided. For each day a total symptom score was calculated.

The RR in spleen volume at the EOC 3 was provided along with the corresponding 95% CI.

The proportion of patients with a ≥50% reduction by palpation from baseline to the EOC 6 was provided along with the 95% CI.

The percent change of spleen volume at the EOC 3 and 6 from baseline was summarized using descriptive statistics (including the 95% CI).

In the absence of disease progression or death before the analysis cut-off date, the duration of response (DR) was censored at the date of the last valid assessment performed before the analysis cut-off date.

Individual plasma concentration values of SAR302503 were listed by patient, treatment, and nominal time of sample collection. Summary statistics were provided where appropriate.

The all-treated (AT) population was used for the analysis of exposure and safety data. The AT population is a subset of the intention to treat (ITT) patients who took at least 1 dose (even if partial) of study medication.

The characterization of the safety profile of the IMP was based on the incidence of TEAEs, graded and reported using terminology from Common Terminology Criteria for Adverse Events (CTCAE) v4.03, changes relative to baseline, in clinical laboratory parameters, red blood cell and platelet transfusion requirements, vital signs and ECG.

The summary of safety results was provided. Analysis of adverse events (AEs) and laboratory data was descriptive and conducted on the safety population. Summary of safety data was also presented by patient and by cycle. If the Investigator's assessment of causality was missing, the TEAEs were considered as related. Adverse event tables present the number (n) and percentage (%) of patients experiencing an AE. For patients with multiple occurrences of the same event, the one with the maximum CTCAE grade was used.

Thiamine exposure during the Thiamine Supplementation Period was summarized. A descriptive summary was provided for additional safety data reported from the end of the TEAE period (defined as within 30 days of the last SAR302503 dose) to the end of the additional 90-day Follow-up Period.

Summary:

Population characteristics:

A total of 97 patients were enrolled and treated in the study. Study treatment was discontinued in all 97 patients (100%). The 3 main reasons for study treatment discontinuation were “study being terminated by the Sponsor” (63 patients [64.9%]), “AE” (18 patients, [18.6%]), and 8 patients discontinued due to patient decision. Six patients (6.2%) discontinued due to disease progression.

All 97 patients were included in the ITT, AT, and PK populations, 83 were included in the PP population, 90 patients were included in the MFSAF and 81 patients in the thiamine supplementation follow-up population.

Demography and baseline characteristics:

Demographics and baseline characteristics are provided for the AT population.

Overall, the AT population consisted of 54.6% males and 45.4% females who were mostly Caucasian/white (94.8%) and had a median age of 67.0 years. Overall, the median weight was 73.0 kg (range: 47 kg to 105.7 kg).

All 97 patients had prior medical or surgical history recorded at baseline. Overall, the most frequently reported (>20% of patients) conditions were pyrexia (97 patients, 100%), weight decreased (97 patients, 100%), night sweats (60 patients, 61.9%), hyperhidrosis (44 patients, 45.4%), fatigue (32 patients, 33%), hypertension (28 patients, 28.9%), and blood product transfusion dependence (21 patients, 21.6%).

Nearly half of the patients entered the study with an ECOG performance status of 1 (45 patients, 46.4%), and 26 patients (26.8%) had an ECOG status of 0 at study entry.

Of the 97 patients in the AT population, most had a diagnosis of primary MF (53 patients, 54.6%); 25 patients (25.8%) had post-PV, and 19 patients (19.6%) had post-ET. Most patients (47 patients, 48.5%) were classified as having intermediate level 2 MF; 34 patients (35.1%) had high risk MF, and 16 patients had intermediate level 1 with symptoms MF. Overall, the median time from diagnosis of MF disease for patients in this study was 4.08 (0.3 years to 24.5) years.

Median hemoglobin concentration at baseline was 9.83 g/dL (range: 6.8 to 15.3 g/dL) for all patients at baseline; 51 patients (52.6%) had a hemoglobin concentration below 10 g/dL. Median platelet count was 147.00 x 10^9/L (range: 48.00 x 10^9/L to 929.0 x 10^9/L) for all patients; 32 patients (33.0%) had a platelet count between 50 x 10^9/L and 100 x 10^9/L at baseline. Blood blasts were >1% in most patients (59 patients, 60.8%).

Most of the baseline renal/liver laboratory values were normal and fell within the inclusion criteria guidelines, with the exception of 3 patients who had protocol deviations.

Most of the baseline pancreatic enzyme laboratory values were normal and fell within the inclusion criteria guidelines, with the exception of 1 patient who had a protocol deviation.

The median spleen volume at baseline was 2893.50 mL (range: 737.0 to 7815.0 mL), which is consistent with the study population of patients with MF (normal spleen volume is 215 mL); the median spleen length was 18.00 cm (range: 5.0 to 36.0 cm).

Per the protocol, all 97 patients had prior treatment with ruxolitinib. The majority of patients (n=76) had received at least 2 prior anticancer therapies, with 7 (15.5%) patients receiving 4 or more prior anticancer therapies. The most common anticancer therapy, besides ruxolitinib, was hydroxycarbamide (66 patients, 68.0%).

The study population consisted of patients with MF that were resistant to ruxolitinib or patients with MF who were intolerant to ruxolitinib according to the Investigator’s assessment. For the AT population, 64 patients had MF that was resistant to ruxolitinib, and 32 patients had MF that was intolerant to ruxolitinib.

Prior medications other than anticancer therapy were taken by 94 (96.9%) patients. Overall, the most common types of prior medications (received by >25% of patients) included analgesics (51 patients, 52.6%); antithrombotic agents and ophthalmologicals (42 patients each, 43.3%); drugs for acid related disorders and topical products for joint and muscular pain (40 patients each, 41.2%); anti-gout preparations (39 patients, 40.2%); stomatological preparations (37 patients, 38.1%); homeopathic preparations (32 patients, 33.0%); antianemic preparations (27 patients, 27.8%); and psycholeptics, corticosteroids for systemic use, and antidiarrheals, intestinal anti-inflammatory (26 patients each, 26.8%).

Efficacy results:

- The primary efficacy endpoint, patient RR, was evaluable in 83 patients (PP population). Of these 83 patients, 46 (55.4%) achieved a ≥35% reduction in spleen volume from baseline at the EOC 6.
- For the secondary endpoint of SRR at the EOC 6, 23 of 90 patients (25.6%) achieved a ≥50% reduction in modified MFSAF total symptom scores from baseline to the EOC 6.
- For the secondary endpoint the proportion of patients who had a ≥50% reduction in spleen size by palpation from baseline at the EOC 3 and 6, 33 of the 97 (34.0%) patients had achieved this threshold at the EOC 3 and 30 patients (30.9%) achieved the threshold at the EOC 6.
- For the secondary endpoint of RR at the EOC 3, 39 of 83 patients (47.0%) met the criteria for RR.
- For the secondary endpoint of percent change in spleen volume from baseline to the EOC 6, the median percent change in spleen volume was a 34.01% reduction.

Safety results:

Extent of exposure: Overall, the median number of cycles was 6.0 (range: 1 to 20 cycles), and the median duration of exposure was 24.4 weeks (range: 1 to 79 weeks). Most patients received a maximum dose of 400 mg (64 patients, 66.0%); 17 (17.5%) patients and 15 (15.5%) patients had an upward titration dose of 500 mg and 600 mg, respectively. Eighty-one (83.5%) patients were exposed to thiamine during the Thiamine Supplementation Period, and the mean duration of exposure was 15.55 weeks (range 1.1 to 25.7 weeks).

Adverse event evaluation: All 97 patients had at least 1 TEAE (all grades); Grade 3 or 4 TEAEs were reported by 61 (62.9%) patients. Thirty-three (34.0%) patients had treatment-emergent serious adverse events (SAEs). Seven (7.2%) patients had a TEAE that led to death on study; 4 cases were due to disease progression and 3 were due to AEs. The most common non-hematologic TEAEs (reported by ≥10% of patients) (all grades) were gastrointestinal disorders including diarrhoea (60 patients, 61.9%), nausea (54 patients, 55.7%), and vomiting (40 patients, 41.2%). The most common hematologic TEAEs (reported by >10 patients) (all grades) were anaemia (47 patients, 48.5%) and thrombocytopenia (26 patients, 26.8%). Thirty-seven patients (38.1%) experienced Grade 3 or 4 anaemia and 21 patients (21.6%) Grade 3 or 4 thrombocytopenia. No Grade 5 hematologic TEAEs were reported.

Anti-infectives for systemic use were given to 54 (55.7%) patients in the study.

During the Thiamine Supplementation Period, 33 (40.7%) follow-up AEs were reported from which 7 (8.6%) were Grade 3 or 4. The most common AEs (reported by ≥10% of patients) (all grades) were anaemia and thrombocytopenia (10 patients, 12.3% each). From those, 5 AEs were graded as 3 or 4. Further Grade 3 or 4 follow-up AEs included pain, traumatic haematoma, and gamma-glutamyltransferase increased.

Overall, 33 (34.0%) patients had treatment-emergent SAEs (any grade), of which 22 (22.7%) patients had a Grade 3 or 4 event, and 7 (7.2%) patients had a Grade 5 event.

The primary system organ classes (SOCs) in which treatment-emergent SAEs were most frequently reported were infections and infestations (8 patients, 8.2%), respiratory, thoracic and mediastinal disorders (8 patients, 8.2%), cardiac disorders (5 patients, 5.2%), blood and lymphatic system disorders (4 patients, 4.1%), metabolism and nutrition disorders (4 patients, 4.1%), and injury, poisoning and procedural complications (4 patients, 4.1%).

There was no Grade 3 or 4 follow-up SAE in the thiamine supplementation follow-up population, however, there was 1 patient who experienced 2 SAEs (confusional state and cognitive disorder) that were both rated as <Grade 3 or 4.

Overall, 19 (19.6%) patients had at least 1 TEAE leading to permanent treatment discontinuation, and 47 (48.5%) patients had at least 1 TEAE leading to dose modification.

There was 1 case of suspected WE: A 62-year old male patient consulted for slight forgetfulness and was admitted to hospital to perform an urgent brain MRI. It was noted that the patient was well oriented, with no neurological alteration or any sign of encephalopathy. This case was evaluated independently by external experts who concluded that MRI findings were not consistent with WE. The final diagnosis of the event was encephalopathy from which the patient fully recovered.

Deaths: Seven patients died on treatment, and 11 patients died more than 30 days after the last dose of study treatment. Out of those 7 patients on treatment, 3 patients died due to TEAEs of pneumonia, shock, and acute respiratory failure (cardiopulmonary arrest due to acute respiratory failure).

Of those 11 patients that died after their last dose of study treatment, 9 patients died due to disease progression and 2 patients due to an unknown cause.

Five patients died in the thiamine supplementation follow-up population. Out of those 3 patients died due to disease progression, and 2 patients died due to unknown cause.

Laboratory evaluations: In almost all patients who had thiamine and magnesium levels evaluations done during the Follow-up Period, thiamine and magnesium levels were reported either within normal range or above the ULN.

There were very few patients with Grade 4 abnormalities in laboratory parameters, and there were no increases in the percentages of patients with laboratory abnormalities in the Thiamine Supplementation Period.

Overall, changes in vital signs and ECGs from baseline were small and not clinically meaningful.

Pharmacokinetic results:

Mean (standard deviation [SD]) plasma SAR302503 C_{trough} at Cycle 2 Day 1 were 1150 (653) ng/mL at 400 mg in MF patients who were previously treated with ruxolitinib. Pharmacokinetic profile was consistent with what has been seen with the compound in MF patients.

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