These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi Drug substance(s): SAR302503	Study Identifiers: NCT01692366, UTN U1111-1130-3710 Study code: ARD12888

Title of the study: A Phase 2 open-label, dose-ranging study of the efficacy and safety of orally administered SAR302503 in Japanese patients with intermediate-2 or high risk primary myelofibrosis, post-polycythemia vera myelofibrosis, post-essential thrombocythemia myelofibrosis with splenomegaly

Study center(s): This study was conducted at 7 centers. All participating study centers were located in Japan.

Study period:

Date first patient enrolled: 06/Nov/2012 (first signed informed consent)

Date last patient completed: 17/Mar/2014

Phase of development: Phase 2a

Objectives:

Primary Objective

To evaluate the efficacy of daily oral doses of 300 mg, 400 mg, and 500 mg SAR302503, and combined for the response rate defined as the ≥35% reduction of spleen volume as determined by magnetic resonance imaging (MRI) or computed tomography (CT) scan in patients with contraindications for MRI.

Secondary Objectives

- To evaluate the safety of SAR302503 for both pooled (300, 400, and 500 mg) and individual dose populations.
- To evaluate the pharmacokinetics (PK) of SAR302503 after single and repeat doses.
- To evaluate the effect on myelofibrosis (MF)-associated symptoms (key MF symptoms) as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF).
- To evaluate the durability of splenic response.
- To evaluate the effect of SAR302503 on bone marrow with regard to changes on reticulin fibrosis.

Methodology:

This was a Phase 2, multicenter, dose-ranging, open-label study of Japanese patients with intermediate-2 or high-risk primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (post-PV-MF), or post-essential thrombocythemia myelofibrosis (post-ET-MF) who have splenomegaly. Patients were assigned to 1 of 2 SAR302503 dose groups randomly: 400 mg or 500 mg/day at the beginning of the study. A dose reduction to 300 mg was recommended by the efficacy and safety evaluation committee due to safety concerns. Thus, only 300 mg of SAR302503 was allocated to patients enrolled after Protocol Amendment 3. SAR302503 was self-administered once a day, orally in consecutive 28-day cycles, on an outpatient basis.

Sanofi held a teleconference with the United States Food and Drug Administration (US 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. The purpose of this teleconference was to discuss these cases, as well as 14 cases of cardiomyopathy/congestive heart failure, reported across the program, that were shared with the FDA 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 US 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 MF, 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. These provisions were described in Protocol Amendment 4 to this study.

Number of patients:	Planned: Approximately 20
	Randomized: Not applicable
	Treated: 8
	Evaluated: Not applicable
	Safety: 8

Diagnosis and criteria for inclusion:

Japanese patients with intermediate-2 or high-risk PMF, post-PV-MF, post-ET-MF with splenomegaly.

Study treatments

Investigational medicinal product(s): SAR302503

Formulation: Capsules

Route(s) of administration: Orally

Dose regimen: SAR302503 was self-administered orally (300 mg, 400 mg, or 500 mg), once daily, as a single agent, in consecutive, 28-day cycles at the assigned dose level. Bottles containing SAR302503 capsules were dispensed to patients at the beginning of each cycle. Patients were instructed to take SAR302503 either 1 hour before or 2 hours after the ingestion of food (except for an oral antiemetic), ideally after the evening meal. Other than adhering to the requirement for dosing with regard to meals, patients could eat regularly without restrictions. Missed or vomited doses were not made up.

Duration of treatment: At least 1 cycle (28 days).

Duration of observation: The duration of the study for an individual patient included a period to assess eligibility (screening period of 28 days), followed by a treatment period of at least 1 cycle (28 days) of study treatment, and an end-of-treatment visit at least 30 days following the last administration of study drug. In addition, patients were followed for up to 90 days after initiation of thiamine supplementation as provided in protocol amendment 4.

Criteria for evaluation:

As the SAR302503 program was terminated for safety reasons, no efficacy analyses were performed.

Safety criteria were reported adverse events (AEs) and other safety information, such as clinical laboratory data, vital signs, and electrocardiogram (ECG).

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

SAR302503 predose and postdose plasma collections were obtained on Cycle 1 Day 1, Cycle 1 Day 2, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 2, and Cycle 3 Day 1.

Individual SAR302503 plasma concentrations and PK parameters with descriptive statistics are listed in an appendix. Plasma concentrations of SAR302503 were determined by a validated liquid chromatography-tandem mass spectrometry method with a lower limit of quantification of 1.00 ng/mL.

As the study was terminated, no pharmacodynamic (PD) analyses were performed.

Statistical methods:

As the SAR302503 program was terminated for safety reasons, no efficacy analyses were performed.

All AEs (including serious adverse events [SAEs] and adverse events of special interest [AESIs]) were coded to a lower level term (LLT), preferred term (PT), high level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of the Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

The grades for laboratory variables were derived according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scale version 4.03, whenever applicable.

Potentially clinically significant abnormality (PCSA) criteria for vital signs and ECGs, as described in the Statistical Analysis Plan (SAP), were used to flag abnormal changes.

An individual data listing was provided for additional safety data reported from the end of the treatment-emergent adverse event (TEAE) period (defined as within 30 days of the last SAR302503 dose) to the end of the additional 90-day follow-up period.

Treatment-emergent adverse events were AEs reported during the on-treatment period (first administration of investigational medicinal product [IMP] through last administration of SAR302503 + 30 days).

Adverse events of special interests were:

- Pregnancy
- Symptomatic overdose with SAR302503
- Second malignancies
- Grade 3 and 4 thrombocytopenia (platelet count <25 × 10^9/L) according to CTCAE version 4.03
- Grade 3 and 4 anemia
- Grade 3 and 4 hyperlipasemia
- Grade 3 and 4 hyperamylasemia
- Grade 3 and 4 alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin elevations
- Development of transfusion dependence (transfusion dependence is defined as receiving >2 units of red blood cell [RBC] transfusions per month over 3 months)

In addition, the following events were deemed AESIs with Protocol Amendment 4, and were to be reported to the Sponsor within 24 hours:

- Any grade encephalopathy, confusion, mental status changes, delirium, convulsions, cognitive impairment, memory loss/impairment, amnesia, hallucinations, neuropathy (including sensory and motor), ataxia, nystagmus, and diplopia.
- Any grade cardiac failure or cardiomyopathy.
- Any grade signs or symptoms of suspected thiamine deficiency.

No interim analysis was planned or performed.

Summary:

Eight patients were treated in this study: 3 patients with 300 mg, 2 with 400 mg, and 3 with 500 mg. All 8 patients were included in the intent-to-treat (ITT) and safety populations.

Overall, the mean and median age was 66 years, with a range of 53 to 76 years. The majority of patients were male (6/8), and all patients were Asian. The majority of patients had an Eastern Cooperative Oncology Group performance status of 0 (4/8) or 1 (3/8). Five patients had post-ET-MF, and 5 patients were in the high-risk group.

As the SAR302503 program was terminated for safety reasons, no efficacy or PD analyses were performed.

All patients had at least 1 TEAE. No deaths were reported. While the numbers of patients in each dose group were too small to draw conclusions, increased incidence and severity of TEAEs appeared to be associated with an increased SAR302503 dose.

Gastrointestinal disorders (nausea, vomiting, and diarrhea) were most commonly reported; however, most were Grade 1 or 2. At least 1 Grade ≥3 gastrointestinal TEAE was reported for 6 patients: 1 of 3 patients in the 300 mg group, 2 of 2 patients in the 400 mg group, and 3 of 3 patients in the 500 mg group. The only Grade ≥3 TEAE reported for more than 1 patient overall was anemia (3 patients).

All patients had at least 1 treatment-related TEAE. The incidence and type of treatment-related TEAEs was similar to that for all TEAEs.

Four patients were discontinued due to TEAEs: 2 of 2 patients in the 400 mg group and 2 of 3 patients in the 500 mg group. Treatment-emergent adverse events leading to discontinuation were Grade ≥3 in both patients in the 400 mg group and neither patient in the 500 mg group. At least 1 serious TEAE was reported for 6 patients: 1 of 3 patients in the 300 mg group, 2 of 2 patients in the 400 mg group, and 3 of 3 patients in the 500 mg group. All but 1 of these patients (in the 500 mg group) had Grade ≥3 serious TEAEs.

Of note, one patient in the 400 mg group had serious TEAEs of Grade 3 drug induced liver injury in Cycle 1 and recurring with rechallenge at a lower dose (200 mg) in Cycle 3. SAR302503 was permanently discontinued, and the event resolved.

No individual serious TEAEs or TEAEs leading to discontinuation were reported for more than 1 patient.

Hematological abnormalities of anemia, thrombocytopenia, lymphopenia, and prolonged activated partial thromboplastin time were reported for 5 or more of the 8 patients overall. With the exception of anemia and lymphopenia, the majority of abnormalities were Grade 1 or 2.

Abnormalities in ALT, AST, alkaline phosphatase, and creatinine were reported for 4 or more of the 8 patients overall; however, most abnormalities were Grade 1 or 2. Hyperuricemia was reported for 5 of the 8 patients, all of which were Grade 3 or 4.

Hyperglycemia and hyperalbuminemia were reported in 7 and 6 patients, respectively. There was no Grade 3 or 4 metabolic function abnormalities.

Hyperkalemia was reported for 6 patients and hyponatremia was reported for 4 patients, but the majority of electrolyte function abnormalities were Grade 1 or 2.

There were no remarkable clinically significant abnormal changes from baseline in vital sign or ECG measurements.

In summary, safety concerns led to reduction of the SAR302503 doses used in this study. Additional safety concerns led to discontinuation of all SAR302503 studies. In the 8 Japanese patients with MF treated with SAR302503 in this study (3 received 300 mg daily, 2 received 400 mg daily, and 3 received 500 mg daily), there were no patterns indicative of safety concerns that have not already been identified with this compound.

Issue date: 27-Feb-2015