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Sponsor / Company: Sanofi **Drug substance(s):** SAR302503	**Study Identifiers:** NCT01420783, EudraCT 2011-001847-58, UTN U1111-1121-4203 **Study code:** ARD12042
Title of the study: A randomized, phase II, open-label study of the efficacy and safety of orally administered SAR302503 in patients with polycythemia vera (PV) or essential thrombocythemia (ET) who are resistant or intolerant to hydroxyurea	
Study center(s): Thirty three sites had actively participated with the enrollment of patients in 9 countries: Australia, Canada, France, Germany, Italy, South Korea, Spain, United Kingdom, and United States of America.	
Study period: Date first patient enrolled: 17/Oct/2011 Date last patient completed: 19/May/2014	
Phase of development: Phase 2a	

Objectives:

Primary objectives

- To evaluate the efficacy of daily oral doses of 100, 200, and 400 mg SAR302503 in patients with polycythemia vera (PV) and essential thrombocythemia (ET) who are resistant or intolerant to hydroxyurea (per European LeukemiaNet criteria) for:
  - Inducing the absence of phlebotomy and a hematocrit below 45% for a minimum of 3 months in patients with PV, and
  - Reduction of platelet count to $\leq$400 x 10^9/L for a minimum of 3 months in patients with ET.

Polycythemia Vera Dose Expansion Phase and ET Dose Ranging Phase (only 600 mg dose group)

- To evaluate the efficacy of daily oral SAR302503 in patients with PV and ET who are resistant or intolerant to hydroxyurea (per European LeukemiaNet criteria) for:
  - Inducing absence of phlebotomy eligibility beginning at Day 1 of Cycle 4 visit and continuing through Day 1 of Cycle 6 visit in patients with PV, and
  - Reduction of platelet count to $\leq$400 x 10^9/L beginning at Day 1 of Cycle 4 visit and continuing through Day 1 of Cycle 6 visit in patients with ET.

Secondary objectives

- To evaluate the safety of SAR302503.
- To evaluate the efficacy of daily oral SAR302503 in patients with PV who are resistant or intolerant to hydroxyurea (per European LeukemiaNet criteria) for inducing absence of phlebotomy eligibility beginning at Day 1 of Cycle 4 visit and continuing through Cycle 8 (applicable only for PV dose expansion phase).
- To evaluate the efficacy of daily oral SAR302503 in patients with ET who are resistant or intolerant to hydroxyurea (per European LeukemiaNet criteria) for reduction of platelet count to $\leq$400 x 10^9/L beginning at Day 1 of Cycle 4 visit and continuing through Cycle 8.

- To evaluate the efficacy of SAR302503 in inducing complete and partial clinicohematologic responses (per European LeukemiaNet criteria) beginning at Day 1 of Cycle 6 visit and continuing through Cycle 8.
- To evaluate splenic response as measured by spleen volume using magnetic resonance imaging (MRI) or computed tomography (CT) scan for patients with MRI contraindications.
- To evaluate the pharmacokinetics (PK) of SAR302503 after single and repeat doses.
- To evaluate the pharmacodynamics (PD) of SAR302503 as measured by changes in Janus kinase 2 (JAK2)^{V617F} allele burden in those patients with JAK^{V617F} mutation, and signal transducer of activator of transcript 3 (STAT3) phosphorylation inhibition.
- To measure improvement in baseline myeloproliferative neoplasm (MPN)-associated symptoms, as well as overall impact in quality of life, through serial administration of the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF).
- To measure generic health-related quality of life and utility values using the EuroQol EQ-5D™ questionnaire.

Exploratory Objectives

- To evaluate the effects of SAR302503 on histological, cytogenetic, and molecular responses in bone marrow.
- To evaluate the effects on leukocytosis and thrombocytosis.
- Pharmacogenomic analysis related to drug metabolizing enzymes and genes possibly involved in the JAK-STAT pathway or related to MPNs.

Methodology: This was a Phase 2, multicenter, randomized, open-label study of patients with PV or ET who were resistant to or intolerant of hydroxyurea. The study comprises 2 phases: a dose ranging phase and a dose expansion phase. In the dose ranging phase of the study, patients were stratified by diagnosis (ie, PV or ET) and randomized in a 1:1:1 ratio to 1 of 3 SAR302503 dose groups: 100, 200, and 400 mg daily. At the time of Amendment 4 and completion of the randomization, a 600 mg group of up to 15 ET patients was added using a Simon's stage design. Enrollment in the 600 mg ET cohort was closed per Protocol Amendment No 5.

For PV and ET patients who completed at least 1 cycle of treatment at their assigned dose level (100, 200, and 400 mg) dose adjustment was performed at the next scheduled visit. The study drug dose was titrated up or down in a 100 mg step to optimize efficacy and to minimize drug toxicity for individual subjects. The maximum allowable dose was 600 mg/day.

Dose Expansion Phase (PV patients only): Following the implementation of Protocol Amendment 4, a 400 mg/day dose was selected to proceed to the dose expansion phase. Fifteen patients were enrolled and treated at this dose level. In patients who had completed at least 1 cycle of treatment at 400 mg/day dose level, dose adjustment could be performed. The study drug dose was titrated up or down in a 100 mg step to optimize efficacy and to minimize drug toxicity for individual subjects. The maximum allowable dose was 600 mg/day.

Patients were to have remained on study treatment for a minimum of 8 cycles in the absence of disease progression or unacceptable toxicity. Patients who completed 8 cycles of therapy and who tolerated study treatment and benefited clinically were allowed to continue treatment. With the implementation of Protocol Amendment No 5 in which enrollment of additional ET patients at the 600 mg dose level was closed, upward dose titration for ET patients was not advised. In total, there were 6 protocol amendments to this study including one that was introduced before the inclusion of any patients. Protocol Amendment 6 was to permanently discontinue patients from further SAR302503 treatment and to follow up patients both for treatment with thiamine administration and for safety for 90 days.

Thiamine supplementation and follow-up for safety

Sanofi held a teleconference with the United States Food and Drug 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. The purpose of this 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 US FDA, study Investigators, independent expert neurologists, and neuroradiologists, 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 (MF), PV, ET, 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, included 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.

The following measures introduced with Amendment 6 were implemented:

In addition to permanently discontinuing patients from further SAR302503 treatment and providing thiamine supplementation and following up for safety, a Data Safety Monitoring Board (DSMB) consisting of a statistician and physicians with expertise in hematology/oncology, radiology, neurology, and cardiology met twice to collectively review data across the program and the safety measures that were put into place. Additional meetings were held with the DSMB experts who specialize in neuro-oncology and neuroradiology to review suspected and confirmed cases of WE. Details were specified in a DSMB charter.

Furthermore, the following events had to be reported as adverse events of special interests (AESIs) to the Sponsor within 24 hours:

- Any grade encephalopathy, confusion, mental status change, 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.

Number of patients**:**	Planned: 90
	Randomized: 81
	Treated: 80 (45 PV patients and 35 ET patients)
Evaluated:	
	Efficacy: Not applicable
	Safety: 80
	Pharmacokinetics: 80

Diagnosis and criteria for inclusion:

Inclusion Criteria

- Patients had a diagnosis of PV or ET according to the revised World Health Organization (WHO) criteria and had been resistant to or intolerant of hydoxyurea (per European LeukemiaNet criteria). After the implementation of the Protocol Amendments 4 and 5, diagnosis of PV or ET had to be, according to the revised WHO 2008 criteria, documented at screening.
  - For PV patients: Hydroxyurea resistance was defined as: after 12 weeks into a course of hydroxyurea therapy at a total daily dose >2 g/day OR at the maximum tolerated dose, if that dose is <2 g/day
    - Need for phlebotomy to maintain hematocrit control <45% OR
    - Platelet count >400 x 10^9/L AND white blood cell (WBC) count >10 x 10^9/L OR
    - Failure to reduce splenomegaly extending >10 cm below the coastal margin by 50%, as measured by palpation.

- Hydroxyurea intolerance was defined as having at least one of the following hematologic parameters and at least one nonhematologic parameter:
    - Absolute neutrophil count (ANC)<1 x10^9/L OR platelet count <100 x 10^9/L OR hemoglobin <10 g/dL at the lowest hydroxyurea dose required to achieve a response (defined as hematocrit control without phlebotomy AND/OR all 3 of platelet count normalization, WBC normalization, and nonpalpable spleen)
    - Leg ulcers or other unacceptable nonhematologic hydroxyurea-related toxicity (such as mucocutaneous manifestations, gastrointestinal symptoms, pnemonitis, or fever at any dose of hydroxyurea defined as one of the following: Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 Grade 3-4, >1 week of CTCAE version 4.03 grade 2, permanent discontinuation of hydroxyurea, interruption of hydroxyurea until toxicity resolved, OR hospitalization due to hydroxyurea toxicity.

- PV patients, regardless of resistance or intolerance to prior hydroxyurea, had phlebotomy ≥2 weeks and ≤24 weeks prior to screening AND >1 phlebotomy ≤16 weeks prior to screening OR had required a phlebotomy ≤16 weeks to screening AND exhibit hematocrit >45% at screening.
    - For ET patients: Hydroxyurea resistance defined as: after 12 weeks into a course of hydroxyurea therapy at a total daily dose >2 g/day OR at the maximum tolerated dose, if that dose is <2 g/day
        - Platelet count >600 x 10^9/L
    - Hydroxyurea intolerance for ET defined as at least one of the following:
        - Platelet count >400 x 10^9/L and WBC less than 2.5 x 10^9/L at any dose of hydroxyurea
        - Platelet count >400 x 10^9/L and hemoglobin less than 10 g/dL at any dose of hydroxyurea
        - Presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of hydroxyurea
        - Hydroxyurea-related fever.
- Patients must have signed written informed consent.

Exclusion criteria

- <18 years of age.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 3 or 4 at study entry.
- Life expectancy of <6 months.
- Splenectomy
- Active malignancy other than PV or ET, except adequately treated basal cell carcinoma and squamous cell carcinoma of the skin, cervical carcinoma in situ, or other malignancies that have been stable and off therapy for ≥5 years.
- Major surgery therapy within 28 days or radiation within 3 months prior to initiation of study drug.
- Active acute infection requiring antibiotics.
- Known human immunodeficiency virus or acquired immunodeficiency syndrome-related illness.
- Uncontrolled congestive heart failure (New York Heart Association Classification 3 or 4), angina, myocardial infarction, cerebrovascular accident, coronary/peripheral artery bypass graft surgery, transient ischemic attack, or pulmonary embolism within 3 months prior to initiation of study drug.
- Any severe acute or chronic medical, neurological, or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration and, in the Investigator's opinion, would make the patient inappropriate for entry into this study.
- The following laboratory values with 14 days prior to initiation of study drug:
    - Absolute neutrophil count (ANC) <1.5 x 10^9/L
    - Platelet count <50 x 10^9/L
    - Serum creatinine >1.5 x upper limit of normal (ULN)
    - Serum amylase or lipase >1.5 x ULN

- Known active (acute or chronic) hepatitis A, B, or C; and hepatitis B and C carriers.
- Alanine aminotransferase (AST) or aspartate aminotransferase (ALT) >2.5 x ULN.
- Total bilirubin: ≥3.0 x ULN; if total bilirubin is between 1.5 and 3.0 x ULN, the patient must be excluded if the direct bilirubin fraction is ≥25% of the total.
- Prior history of chronic liver disease.
- Radiophosphorus therapy within 3 months.
- Busulphan within 4 weeks, any chemotherapy (except hydroxyurea), immunomodulatory drug therapy (eg, interferon alpha); corticosteroids >10 mg/day; prednisone or equivalent within 7 days, hydroxyurea or angrelide within 24 hours prior to initiation of study drug; and concomitant treatment with or use of drugs or herbals known to be at least moderate inhibitors or inducers of cytochrome P450 (CYP)3A4.

Study treatments

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

Formulation: capsule

Route(s) of administration: SAR302503 was self-administered, orally

Dose regimen: 100 mg, 200 mg, 400 mg, 600 mg (ET patients only), once daily as a single agent, in consecutive 28-day cycles at the assigned dose level.

After completing at least 1 cycle of treatment dose adjustment could be performed (up or down titration in a 100 mg step).

Duration of treatment: The duration of treatment was up to 8 28-day cycles (32 weeks). Treatment could have continued beyond 32 weeks if the patient was deriving benefit and did not experience disease progression, unacceptable toxicity, or meet other study withdrawal criteria.

Duration of observation: The duration of the study for an individual patient included a period to assess eligibility (screening period) of up to 4 weeks (28 days), a treatment period of up to 8 28-day cycles (32 weeks; treatment was allowed to continue beyond 8 cycles), and a follow-up visit 30 days following the last administration of study treatment.

Criteria for evaluation:

Evaluation criteria statement: This report is being written as a synoptic report that includes only a safety evaluation and a PK analysis of SAR302503. Since the study was terminated for safety reasons, the efficacy and PD evaluations originally planned were no longer considered to be relevant and were not performed. The decision to halt clinical trials was announced on 18 November 2013.

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

Secondary endpoints: Safety was evaluated based on the incidence of treatment-emergent adverse events (TEAEs) and changes in clinical laboratory parameters, red blood cell transfusion requirements, ECOG PS, electrocardiogram (ECG), vital signs, and body weight relative to baseline. Clinical and laboratory AEs were assessed and reported using terminology of the National Cancer Institute (NCI) – CTCAE version 4.03. Patients were followed for safety for the length of the thiamine supplementation period (90 days post thiamine initiation).

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods: Blood sample for PK were collected at predose during Cycle 1 on Days 1, 2, and 15, during Cycle 2 on Days 1 and 2, and during Cycle 3 on Day 1, and at 1, 2, 3, 4, 6, and 8 hours postdose during Cycle 1 and 2 on Day 1. An additional sample was to be taken in the case of a serious adverse event (SAE). 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. A summary of PK data is provided in this report. As the SAR302503 program was terminated for safety reasons, no PD analyses were performed.

Statistical methods:

Analyses of Efficacy Data: not performed

Analyses of Safety Data:

Safety analysis was based on the all-treated (AT) population. Safety was evaluated based on the incidence of TEAEs and changes in clinical laboratory parameters, red blood cell transfusion requirements, ECOG PS, ECG, vital signs, and body weight relative to baseline. Clinical and laboratory AEs were assessed and reported using terminology of the NCI-CTCAE version 4.03.

Analysis of adverse events:

All AEs were graded according to the NCI-CTCAE version 4.03 scale and coded using the Medical Dictionary for Regulatory Activities Version 17.0.

An overview of TEAEs was summarized. The number and percentage of patients who experienced any TEAE, TEAE leading to permanent treatment discontinuation, TEAE leading to death, Grade 3 and 4 TEAE, and treatment-emergent SAE were summarized for the AT population. All posttreatment AEs were listed by patient. Treatment-emergent adverse events by System Organ Class (SOC) and Preferred Term (PT) were summarized for the AT population. Treatment-related TEAEs were also summarized. Treatment-emergent adverse events leading to treatment discontinuation were summarized by SOC and PT and listed by patient. Treatment-emergent SAEs were summarized by SOC and PT, high group level term (HGLT), high level term (HLT), and PT, and listed by patient. Treatment-related treatment-emergent SAEs were summarized by SOC and PT. Adverse events of special interest were summarized by SOC and PT and listed by patient. Deaths on-treatment and deaths occurring up to 90 days after initiation of thiamine supplementation were listed by patient.

Analyses of laboratory variables:

The number (%) of patients with laboratory abnormalities using the worst grade during the on-treatment period was provided for the following laboratory categories: hematology, liver/renal, electrolytes, metabolism, and pancreatic enzyme.

Lactate dehydrogenase (LDH) and LDH categories (>1 x ULN, >2 x ULN, >5 x ULN) were descriptively summarized by visit. Worst direct bilirubin categories (<1.5 x ULN, >3 x ULN, >10 x ULN) on-treatment were summarized descriptively. Urinalysis (protein and blood) were summarized descriptively by visit. Shift tables matching the grade at baseline and the worst grade during the on-treatment period were produced for the following parameters: ALT, AST, total bilirubin, creatinine, hemoglobin, amylase, lipase, WBC, lymphocytes, neutrophils, platelet count, and potassium.

The number (%) of patients with out of range values during the on-treatment period was provided for all parameters. In addition, all Grade 3 and 4 laboratory results were listed by patient.

Analyses of vital sign variables:

Potentially clinically significant abnormality (PCSA) analyses were performed for vital signs. Descriptive statistics in raw values and change from baseline values were provided by treatment and visit.

Analyses of electrocardiogram variables:

The number (%) of patients with abnormal ECGs was listed.

Analyses of other safety variables:

Eastern Cooperative Oncology Group PS was presented in shift tables. A shift table matching the score at baseline and the worst score during the on-treatment period was also provided.

Description of pharmacokinetic analyses:

Pharmacokinetic parameters including but not limited to maximum concentration (C_{max}), time to reach C_{max} (t_{max}) and area under the curve (AUC_{0-24}), were determined following the first dose (on Cycle 1, Day 1) and multiple doses (Cycle 2, Day 1) of SAR302503. In addition C_{trough} (minimum concentration) values were determined on Cycle 1/Day 2, Cycle 1/Day 15, Cycle 2/Day 1 and Day 2, and Cycle 3/Day 1. The PK population was comprised of patients who received at least 1 full cycle (even partial) of study treatment and had evaluable drug concentration data. Pharmacokinetic parameters were listed and summarized by arithmetic and geometric mean, median, standard deviation (SD), coefficient of variation (CV), minimum, maximum, and number of available observations by treatment. All SAR302503 plasma concentrations were presented in tables as descriptive statistics.

Description of pharmacodynamic analyses: not performed

Description of interim analysis:

Per Protocol Amendment 4, a formal interim safety report had been prepared on 12 August 2013. The cutoff date for this interim safety report was 28 November 2012. This report was prepared after 70 patients were randomized out of which 69 patients were treated with SAR302503; 45 patients continued treatment after data cutoff. This interim report was prepared for regulatory purposes.

Summary:

Population characteristics: A total of 81 patients were randomized into the study. Of those, 80 patients were treated with SAR302503 including 22 with 100 mg, 24 with 200 mg, and 34 with >400 mg. One patient in the 100 mg group was randomized but not treated due to being ineligible for inclusion in the study.

Nineteen patients discontinued from the study due to AEs or disease progression with most patients discontinuing in the >400 mg group (11 patients [10 due to AEs, 1 due to disease progression]). Twenty-five patients requested discontinuation of treatment with 6 patients in the 100 mg group, 7 patients in the 200 mg group, and 12 patients in the >400 mg group, respectively. Among the 100 and 200 mg groups, most patients discontinued due to other reasons associated with lack of treatment efficacy; ie, no response, thrombocytosis, no improvement on hematocrit or platelet count, worsening of symptoms (8 patients in the 100 mg and 8 patients in the 200 mg group).

A total of 81 patients were included in the randomized/intent-to-treat (ITT) population, and 80 patients were included in the AT population. There were 35 males (43.8%) and 45 females (56.3%) treated with SAR302503 in the study, with most patients being Caucasian/white (74 [92.5%]). Demographic characteristics were similar among the dose groups with the exception of age. Patients in the 100 mg group had a median age of 64.0 years (range 33 to 86 years) and patients in the >400 mg group had a median age of 62.5 years (range 30 to 95 years) which was older than patients in the 200 mg group who had a median age of 50.5 years (range 19 to 81 years). Overall, 8 patients were >75 years old. In addition, time since diagnosis had been shorter in the 100 mg group (mean 7.6 years versus 9.37 and 8.41 years in the 200 and >400 mg group, respectively).

All 80 patients had prior medical history recorded at baseline. Overall, the most frequently reported (>10% of patients) types of medical history were drug intolerance (33 patients); fatigue (26 patients); hypertension (25 patients); pruritus (19 patients); headache (13 patients); night sweats and transient ischemic attack (12 patients each); hyperuricemia (10 patients); abdominal pain, skin ulcer, and back pain (9 patients each); and bone pain and drug hypersensitivity (8 patients each). Thirty-seven patients had prior surgical history recorded at baseline. The most frequently reported types of surgical history were appendectomy (8 patients), hysterectomy (7 patients), tonsillectomy (6 patients), and cholecystectomy (5 patients). Fifty-four patients had cardiovascular risk factors at baseline. Overall, the most frequently reported cardiovascular risk factors were vascular disorders (34 patients), nervous system disorders (16 patients), and metabolism and nutrition disorders (13 patients).

Patients were stratified by diagnosis (ie, PV or ET), with a total of 45 patients with PV and 35 patients with ET. Patients were then randomized in a 1:1:1 ratio to 1 of 3 SAR302503 dose groups: 100, 200, and >400 mg daily. Thus, the numbers of patients with PV and ET were well balanced between dose groups. Overall, most patients had an ECOG PS of 0 or 1 (a total of 49 and 29 patients, respectively); ECOG PS was also well balanced between dose groups.

Most median hematologic laboratory values were similar among all dose groups both for ET and PV patients, with the exception of platelet count (high in the ET population as expected) and WBC count (higher in the PV population as expected).

Across dose groups, most of the baseline renal/liver laboratory values were normal and fell within the inclusion criteria guidelines, with the exception of 2 patients who had a protocol deviation (screening ALT concentration of 119 U/L, which was >2.5 x ULN, and ALT concentration of 233 U/L at baseline). Lactate dehydrogenase was abnormal at baseline (>1 x ULN or >2 x ULN) for most patients across dose groups, which was expected in the study population.

All 80 patients received prior anticancer therapy. More patients (50.0%) in the >400 mg group received 1 prior therapy, while more patients (45.8%) in the 200 mg group received 2 prior therapies. The proportion of patients receiving >3 prior therapies was highest for the 100 mg group (40.9%). Other frequently administered anticancer therapies included anagrelide and interferon therapies.

Thiamine supplementation follow-up population

The thiamine supplementation follow-up population (patients who were exposed to at least one dose of study treatment and received thiamine per FDA request) consisted of 68 patients. Of those, 16 were treated with 100 mg, 21 with 200 mg, and 31 received ≥400 mg.

Of the population treated with SAR302503 (n=80 patients), 11 patients refused to take thiamine.

Within this population 1 death occurred prior to implementation of safety follow up. From the 68 patients that received thiamine, 43 (53.8%) were adequately followed (all safety follow-up visits performed), and 25 (31.3%) had an incomplete follow-up.

Safety Results

At the time of study termination the median number of cycles administered was 14 for the 200 mg group, 9.5 for the 100 mg group, and 9 for the ≥400 mg group. The median duration of exposure was 57.2 weeks for the 200 mg group, 40.2 weeks for the 100 mg group, and 34.3 weeks for the ≥400 mg group.

Treatment compliance (>80% of intended dose) was good in all dose groups with a compliance of 100% in the ≥400 mg group, 95.8% in the 200 mg group, and 95.5% in the 100 mg group.

Adverse Events

Seventy-nine patients had at least 1 TEAE (all grades), including 21 (95.5%) in the 100 mg group and all patients in the 200 and ≥400 mg group (24 and 34 patients, respectively). The most common TEAEs (reported in ≥10 patients) in all dose groups (all grades) were nausea (43 patients), diarrhea (40 patients), vomiting (27 patients), headache (20 patients), fatigue (17 patients), constipation (14 patients), muscle spasms and asthenia (13 patients each), abdominal pain (11 patients) and dizziness, pruritus, oedema peripheral and lipase increased (10 patients each).

Sixty-seven patients had at least 1 treatment-related TEAE with 17 patients in the 100 mg group, 18 patients in the 200 mg group, and 32 patients in the ≥400 mg group. The most common treatment-related TEAEs (reported in ≥10 patients) in all dose groups (all grades) were nausea (36 patients), diarrhea (28 patients), vomiting (24 patients), and muscle spasms (10 patients).

One patient in the 100 mg group had a nonserious event of accidental overdose reported during Cycle 6 and again in Cycle 9. No action was taken with the study treatment, and the event was considered to be resolved.

Another nonserious event of accidental overdose was reported for 1 patient in the 400 mg group, occurring during Cycle 1 and again in Cycle 5. No action was taken with the study treatment, and the event was considered to be resolved. The events were not associated with any AEs or symptoms.

Clinical laboratory data

Most hematologic abnormalities were Grade 1 or 2. No Grade 3 or 4 anemia was observed in any dose group; however, Grade 3 and 4 lymphopenia were observed in 3 out of 22 (13.6%), 5 out of 24 (20.8%) and 7 out of 34 (20.6%) patients, respectively in the 100, 200, and ≥400 mg dose groups. Grade 3 and 4 thrombocytopenia were reported in 1 patient each in the 100 and 200 mg dose group and Grade 3 and 4 neutropenia were reported in 3 out of 22 (13.6%), 1 out of 24 (4,2%), and 2 out of 34 (5.9%) patients, respectively in the 100, 200 and ≥400 mg dose group. One case of Grade 3 leukopenia was reported in patients in the 100 mg group.

Table 1 provides the number of patients with out of range hematology values (at least one value in a row >50%)

Table 1 - Clinical laboratory data – number (%) of patients with out of range hematology value during the on treatment period – All treated populations

Laboratory parameter n/N1 (%)	100 mg (N=22)	200 mg (N=24)	≥400 mg (N=34=
Basophils >ULN	16/22 (72.7%)	16/24 (66.7%)	22/34 (64.7%)
Eosinophils >ULN	13/22 (59.1%)	13/24 (54.2%)	14/34 (41.2%)
Hematocrit <LLN	11/22 (50.0%)	12/24 (50.0%)	23/34 (67.6%)
Ery Mean Corpuscular Volume >LLN	13/22 (59.1%)	14/24 (58.3%)	16/34 (47.1%)
Monocytes <LLN	10/22 (45.5%)	13/24 (54.2%)	18/34 (52.9%)
Monocytes >ULN	20/22 (90.9%)	21/24 (87.5%)	21/34 (61.8%)
Erythrocytes <LLN	8/22 (36.4%)	10/24 (41.7%)	23/34 (67.6%)
Erythrocytes >ULN	13/22 (59.1%)	13/24 (54.2%)	13/34 (38.2%)

The number (n) represents the subset of the total number of patients who met the criterion in question at least once during treatment. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline.
ULN=upper limit of normal; LLN=lower limit of normal

Grade 3 ALT and AST increased were reported in 2 out of 21 and 1 out of 21 (9.5% and 4.8%, respectively) patients in the 100 mg group and Grade 3 ALT increased in 1 out of 34 (2.9%) patient in the ≥400 mg group; all cases were transitory and reversible except one case with unknown outcome. No other Grade 3 or 4 liver or renal test results had been reported.

Grade 3 or 4 hyperkalemia was reported in 3 out of 22 (13.6%) patients in the 100 mg group, 6 out of 24 (25.0%) patients in the 200 mg group, and 3/34 (8.8%) patients in the ≥400 mg group. In addition, 1 patient in each dose group experienced Grade 3 or 4 hyponatremia and hypo- as well as hypercalcemia were reported for 1 out of 34 patients each in the ≥400 mg group.

Grade 3 or 4 hypoglycemia was reported in 2 out of 24 (8.3%) patients in the 200 mg group and in 2 out of 34 (5.9%) patients in the ≥400 mg group and 1 patient each experienced Grade 3 or 4 hyperglycemia in the 100 and 200 mg dose groups, respectively.

Grade 3 serum amylase increase was reported in 1 out of 21 (4.8%) patients in the 100 mg group and 1 out of 34 (2.9%) in the ≥400 mg group. Grade 3 or 4 lipase increase was reported in 2 out of 21 and 1 out of 21 (9.5% and 4.8%, respectively) patients in the 100 mg group, and Grade 3 lipase increase was reported in 1 out of 24 (4.2%) patients in the 200 mg group and in 6 out of 33 (18.2%) patients in the ≥400 mg group. Elevations of lipase were more common in the ≥400 mg group. All cases were transitory and reversible, with the exception of 1 that was part of the patient's medical history.

Vital signs, physical findings, and other safety observations

A small number of patients across all dose groups had systolic blood pressure (BP) >160 mmHg and an increase from baseline of >20 mmHg, including 2 (9.5%) in the 100 mg group, 5 (20.8%) in the 200 mg group and 5 (14.7%) in the ≥400 mg group. No patient had a change in diastolic BP or heart rate. Overall, changes in vital signs from baseline were not clinically meaningful.

No clinically significant changes in ECGs from baseline to the end of treatment were reported for any patient. Most patients across all dose groups had ECOG PS of 0 or 1 at both baseline and end of treatment.

Deaths, serious adverse events and other significant adverse events

Twenty-two patients experienced at least 1 serious TEAE with 7 patients in the 100 mg group, 7 patients in the 200 mg group, and 8 patients in the >400 mg group. Out of those 9 serious TEAEs had been judged as treatment related with 1 TEAE in the 100 mg group, 3 TEAEs in the 200 mg group, and 5 TEAEs in the >400 mg group. One case of WE was reported in the 200 mg dose group:

A 67-year-old female patient received her first dose of SAR302503 on 08 October 2012, and her last dose was on 02 November 2013 (a total of 14 cycles). No dose interruptions or reductions were reported. On 30 September 2013, the patient had one episode of binocular diplopia with episodic memory disorder, repetitive language, and difficulty in performing everyday tasks. The patient consulted her neurologist due to worsening symptoms. On 02 October 2013 (Cycle 13, Day 17) serious

Grade 3 WE was reported leading to hospitalization. A brain CT scan showed bilateral thalamic hypoattenuation and Arnold-Chiari type 1 malformation. The patient was suspected to have a vertebrobasilar stroke of undetermined etiology. In addition, she was evaluated by an ophthalmologist, who found no papilledema or ocular pathology.

A venous angiogram showed appreciating permeability in the entire brain dural sinus, cerebral and supraaortic sinus, while the CT angiogram and scanning acoustic tomography revealed permeability of carotid and vertebral axes without evidence of obstruction of large veins. A vascular MRI also showed good enhancement and permeability of cerebral dural sinus.

Clinical examination showed good general condition. Neurologic examination revealed that the patient was oriented to person and space, but disoriented in time. The clinical features included impaired episodic memory for recent events and altered calculation, repetitive language, apraxia, and difficulty in performing everyday tasks. An examination of cranial nerves showed no alterations. Motor system examination revealed normal tone and tropism and full muscle balance. No abnormal movements were observed.

The patient received multiple medications including thiamine. No action was taken with the investigational medicinal product (IMP). During hospitalization, the patient remained stable; she had persistent mild horizontal nystagmus with bilateral extreme look and alteration of the higher cognitive functions, consciousness with temporary disorientation, impaired episodic memory, and alteration of calculation. On 15 October 2013, the event of WE was considered resolved. No information regarding the patient's discharge was provided.

The brain MRI on 05 November 2013 further confirmed the diagnosis of WE. The patient fully recovered from the event on an unknown date in March 2014.

The IMP was permanently discontinued during Cycle 14 due to nonserious Grade 3 pyrexia and serious Grade 3 vomiting. The Investigator considered the event of WE as not related to SAR302503, the sponsor considered the event of WE to be related to the IMP. All suspected cases of WE were reviewed independently by 2 of the DSMB members. Based on patient profile, Council for International Organizations of Medical Sciences (CIOMS) forms, and MRI images, they concluded that this was a classic case of WE.

The PK parameters on Cycle 1, Day 1 at 200 mg were higher than mean values with C_{max}=595 ng/mL (mean = 500 ng/mL), and AUC_{0-24} = 4740 ng.h/mL (mean AUC_{0-24} = 3480 ng.h/mL). The following PK results were measured at Day 1 of Cycle 2 at 200 mg:

C_{max}=1280 ng/mL, C_{trough}=706 ng/mL, AUC_{0-24}=22 200 ng.h/mL with linear extrapolation =55 500 ng.h/mL at 500 mg. The estimated PK exposures of the patient at 500 mg were higher than mean steady state PK exposures at 500 mg in MF patients (CSR ARD11936: mean C_{max}=2830 ng/mL and mean AUC_{0-24}=44 500 ng.h/mL).

Three (13.6%) patients in the 100 mg group, 4 (16.7%) in the 200 mg group and 10 (29.4%) in the ≥400 mg group had at least 1 TEAE leading to permanent treatment discontinuation. Out of those, 1 in the 100 mg group, 4 in the 200 mg group, and 9 patients in the >400 mg group had been assessed as treatment-related. Seven (31.8%) patients in the 100 mg group, 6 (25.0%) in the 200 mg group, and 18 (52.9%) in the ≥400 mg group had at least 1 TEAE leading to dose modification.

No patient in this study died on-treatment. One patient died due to disease progression 42 days after her last SAR302503 100 mg dose. Seven (31.8%) patients in the 100 mg group, 6 (25.0%) in the 200 mg group, and 18 (52.9%) in the ≥400 mg group had at least 1 TEAE leading to dose modification.

Safety results in the thiamine supplementation follow-up population

Within the thiamine supplementation period thiamine was administered for ≥15 weeks to 21 (30.9%) patients, for 9 to 14 weeks to 34 (50%) patients, for 5 to 8 weeks to 1 (1.5%) patient and for 1 to 4 weeks to 2 (2.9%) patients.

Within the thiamine supplementation period there had been no patients with a serious follow-up AE. One patient experienced ataxia in the thiamine follow-up period that was recorded as an AESI. There had been no patients with new peripheral neuropathy and no patients with cardiac failure in the thiamine supplementation period. Twenty-one patients had a follow-up AE out of which 1 (head discomfort) was rated as Grade 3 or 4. Most hematologic abnormalities in the thiamine-supplemented population were Grade 1 or 2. Only 1 Grade 3 or 4 lymphopenia was observed in the dose group. The most frequent abnormalities reported were anemia (n=16 [45.7%]) and lymphopenia (n=9 [26.5%]).

All patients had ECOG PS of 0 or 1 during the thiamine supplementation period. There had been no clinically meaningful changes in vital signs or ECG in the thiamine supplementation period.

Biochemistry

There was no case of ALT or AST increase reported in the thiamine supplementation period. One case of Grade 3 or 4 hyperglycemia and 1 case of Grade 3 or 4 elevated serum creatinine was reported in the thiamine-supplemented population. No cases of serum amylase or lipase increased were reported among the thiamine-supplemented population.

Thiamine and magnesium levels were determined at 3 different time points within the follow-up period.

For almost all patients who had the evaluation done, thiamine and magnesium levels were reported either within normal ranges or above ULN. Thiamine and magnesium levels out of range are presented in Table 2.

Table 2 - Thiamine and magnesium out of range by follow-up visit – follow-up population

	All (N=68)	
Magnesium level (mmol/L)		
EOT/Early discontination/Initial Follow-up visit[a]		
Number	12	
High	0	
Low	0	
Normal	12	(100%)
Follow-up visit (14-33 days after initiation of thiamine)		
Number	19	
High	0	
Low	0	
Normal	19	(100%)
Follow-up visit (90 +/- days after initiation of thiamine)		
Number	31	
High	0	
Low	1	(3.2%)
Normal	30	(96.8%)
Thiamine level (nmol/L)		
EOT/Early discontination/Initial Follow-up visit[a]		
Number	13	
High	4	(30.8%)
Low	0	
Normal	9	(69.2%)
Follow-up visit (14-33 days after initiation of thiamine)		
Number	17	
High	13	(76.5%)
Low	0	
Normal	4	(23.5%)
Follow-up visit (90 +/- days after initiation of thiamine)		
Number	21	
High	16	(76.2%)
Low	0	
Normal	5	(23.8%)

Pharmacokinetic results

Following once-daily oral doses of 100, 200, 400, and 600 mg, SAR302503 was absorbed with a median t_{max} of 2 to 4 hours.

On Cycle 1 Day 1, SAR302503 exposure increased in a greater than dose proportional manner from 100 mg to 600 mg. There was accumulation after repeated dosing. However, further conclusions on Cycle 2 Day 1 were not drawn since dose was titrated up or down in a 100 mg step to optimize efficacy and to minimize drug toxicity for individual subjects.

Pharmacodynamic results

Pharmacodynamic analyses had not been performed due to termination of the study.

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