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	**Study Identifiers:** NCT01420770, UTN U1111-1119-2965
Drug substance(s): SAR302503	**Study code:** ARD11936
Title of the study: A Phase 2 Randomized, Open-Label, Dose-Ranging Study of the Efficacy and Safety of Orally Administered SAR302503 in Patients with Intermediate-2 or High Risk Primary Myelofibrosis, Post Polycythemia Vera Myelofibrosis, Post-Essential Thrombocythemia Myelofibrosis with Splenomegaly	
Study center(s): 4 sites in the United States	
Study period: Date first patient enrolled: 29/Aug/2011 Initial data cut-off date (last randomized patient completed 12 cycles): 28/Nov/2012 Date last patient completed: 12/May/2014	
Phase of development: Phase 2	

Objectives:

Primary Objective

- To evaluate the efficacy of daily oral doses of 300, 400, and 500 mg SAR302503 for the reduction of spleen volume as determined by magnetic resonance imaging (MRI).

Secondary Objectives

- To evaluate the safety of SAR302503.
- To evaluate the pharmacokinetics (PK) of SAR302503 after single and repeat doses.
- To evaluate the pharmacodynamics of SAR302503 as measured by (1) changes in $JAK2^{V617F}$ (a mutation in the tyrosine kinase, JAK2, that results in a substitution of valine for phenylalanine at codon 617 of JAK2) allele burden in those patients with $JAK2^{V617F}$ mutation; (2) changes in substrate phosphorylation in the JAK-STAT signal transduction pathway; and (3) the expression of cytokines.
- To measure improvement in baseline myeloproliferative neoplasm (MPN) associated symptoms, as well as overall impact in quality of life (QOL), through serial administration of the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF).
- To measure generic health-related quality of life (HRQL) and utility values using the EQ-5D questionnaire.

Exploratory Objectives

- To evaluate the effects of SAR302503 on leukocytosis and thrombocytosis.

- To evaluate rates of response based on modified International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria for relapse, progressive disease (PD), stable disease (SD), clinical improvement (CI), partial remission (PR), and complete remission (CR).
- To evaluate the effects on body weight.
- To evaluate the effects on transfusion requirements (red blood cells and platelets).
- To evaluate the effects of SAR302503 on histological and cytogenetic responses in bone marrow or cytogenetics in peripheral blood if bone marrow aspirate was not available.
- Pharmacogenomic analysis related to drug metabolizing enzymes and genes possibly involved in the JAK-STAT pathway or related to myeloproliferative neoplasms.
- To evaluate the effect of SAR302503 on spleen volume reduction in patients from the randomized 300 mg arm who had their dose titrated up after the end of Cycle 6 until Cycle 12.

Methodology: This was a multicenter, randomized, open-label study of 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.

Number of patients:	Planned: 30
	Randomized: 31 (10 [300 mg]; 10 [400 mg]; 11 [500 mg])
	Treated/intent-to-treat (ITT) population: 31 (10 [300 mg]; 10 [400 mg]; 11 [500 mg])
Evaluated:	
	Efficacy:
	Spleen volume: 29 (8 [300 mg]; 10 [400 mg]; 11 [500 mg])
	Patient reported outcomes: 27 (9 [300mg]; 10 [400 mg]; 8 [500 mg])
	Pharmacodynamics: 26 (7 [300 mg]; 10 [400 mg]; 9 [500 mg])
	Fibrosis: 27 (7 [300 mg]; 9 [400 mg]; 11 [500 mg])
	Safety/All treated: 31 (10 [300 mg]; 10 [400 mg]; 11 [500 mg])
	Pharmacokinetics: 31 (10 [300 mg]; 10 [400 mg]; 11 [500 mg])

Diagnosis and criteria for inclusion: The main inclusions criteria were diagnosis of primary or post-polycythemia vera or post-essential thrombocythemia myelofibrosis; myelofibrosis classified as high-risk or intermediate-risk level 2; enlarged spleen, palpable at least 5 cm below costal margin in males and females at least 18 years of age and met the terms of the inclusion/exclusion criteria evaluated during the screening period.

Study treatments

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

Formulation: SAR302503 was supplied in bottles as hard capsules containing 100 mg. The drug product consisted of a blend of SAR302503 drug substance and microcrystalline cellulose with a small quantity of sodium stearyl fumarate added as a lubricant to facilitate manufacturing.

Route(s) of administration: Oral (capsules)

Dose regimen: Patients were randomized to 1 of 3 SAR302503 dose groups: 300, 400, or 500 mg/day in a 1:1:1 ratio. SAR302503 was to be self-administered once a day, orally in consecutive 28-day cycles on an out-patient basis.

Duration of treatment: The duration of the study for a patient included a 28-day period to assess eligibility, followed by a treatment period of at least one 28-day cycle, and an end of treatment (EOT) visit at least 30 days following the last administration of study drug.

Duration of observation: The study duration was approximately 16 months, which included a 3-month enrollment period, a 12-month treatment period after the last patient enrolled, and a 30-day follow-up period. Final analysis was performed when the last randomized patient completed the end of Cycle (EOC) 12 visit. Limited information including safety and spleen size by palpation was collected after Cycle 12. Following Sanofi's decision to stop the development of SAR302503, all patients were discontinued from this study and all patients were given to receive thiamine supplementation for 90 days.

Criteria for evaluation:

Efficacy:

Primary efficacy analysis

- Measurement and assessment of reduction in spleen volume on MRI as determined by a central imaging laboratory based on comparison of baseline to Cycle 3 EOC images; reviewers were blinded to dose.

Secondary efficacy analyses

- The proportion of patients who achieved ≥35% reduction in spleen volume from baseline to Cycle 3 EOC and Cycle 6 EOC.
- The percent change in spleen volume based on MRI at Cycle 6 EOC compared to baseline.
- Duration of maintenance of ≥35% reduction in spleen volume relative to baseline, as measured at Cycle 3 EOC, Cycle 6 EOC, Cycle 12 EOC, and EOT. Duration was defined as the time from the date of the first IRC-confirmed response (ie, ≥35% reduction in spleen volume relative to baseline) to PD or death, whichever was earlier.
- Absolute and percent change from baseline to Cycles 3 and 6 EOC and EOT in total symptom score (sum of score of 6 symptoms identified as key symptoms of the disease psychometrically validated to be part of a fit for purpose instrument, the Modified Myelofibrosis System Assessment Form (MF SAF), that was used in the Phase 2, open-label, single arm study of SAR302503 in patients previously treated with ruxolitinib ARD12181 and in the Phase 3 study EFC12153) (ad hoc analysis).
- Response (defined as either a 2-point improvement or resolution of that symptom in patients with a symptom present at baseline) rate for each of the symptoms at Cycle 1 EOC, Cycle 3 EOC, Cycle 6 EOC, at EOT as measured by the MPN-SAF.
- Symptom response rate for total symptom score (defined as proportion of patients who achieved ≥50% reduction in the total symptom score for MPN-SAF) at Cycle 1 EOC, Cycle 3 EOC, Cycle 6 EOC, and EOT (ad hoc analysis).
- Cumulative Distribution Function (CDF) (continuous plot of percent change from baseline on the X-axis and the percent of patients experiencing that change on the Y-axis) of responses between treatment groups at Cycle 1 EOC, Cycle 3 EOC, Cycle 6 EOC, and EOT for the Myeloproliferative Neoplasms Symptoms.
- Proportion of patients having a resolution of total symptom score and of each of the Patient Reported Outcome (PRO) symptoms according to the MPN-SAF.
- Proportion of patients with a ≥50% reduction (response rate) in total symptom score and in each of the PRO symptoms from baseline to Cycles 1, 3, and 6 EOC and end of treatment.
- Comparison of generic HRQL and utility values using the EQ-5D questionnaire at baseline to Cycle 6 EOC and to EOT. Information on the frequency and proportion of the population reporting Level 1 (no problems), Level 2 (some problems) and Level 3 (extreme problems) per item, will be summarized by treatment group. Quantitative description was provided for the single index utility score and the visual analog pain intensity scale (VAS) at baseline and at the end Cycle 6 or EOT, by treatment group. Change from baseline was also described.

Exploratory efficacy analyses

- The proportion of patients with baseline leukocytosis who achieved normalization of leukocyte count at Cycle 2 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, and at EOT.
- The proportion of patients with baseline thrombocytosis who achieved normalization of platelet count at Cycle 2 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, and at EOT.

Rates of clinical response based on modified IWG-MRT criteria for relapse, PD, SD, CI, PR, and CR Cycle 3, EOC, Cycle 6, EOC, Cycle 12 EOC, and at EOT.

- Change in body weight compared to baseline.
- Change in transfusion (red blood and platelets) requirements compared to baseline.
- Change in histology (including cellularity and bone marrow fibrosis) and cytogenetics in bone marrow for every patient from baseline to the end of Cycle 6, at the end of Cycle 12, and at the EOT compared to baseline (at Cycle 3 EOC optional) (local and central assessments). If bone marrow aspirate was not available, cytogenetics could have been performed with peripheral blood. These results will be provided in a separate report in an appendix.
  - At end of Cycles 6 and 12, proportion and 95% CI of patients with a decrease of at least 1 grade from baseline in bone marrow fibrosis.
  - At end of Cycles 6 and 12, proportion and 95% CI of patients with a decrease of at least 2 grades from baseline in bone marrow fibrosis.
- Spleen volume reduction in patients from the randomized 300 mg arm who had their dose titrated up after the end of Cycle 6 until Cycle 12. (There were no patients in this category.)

Pharmacodynamic analyses

- Changes in substrate phosphorylation in the JAK-STAT signal transduction pathway.
- Expression of cytokines was measured at baseline (Cycle 1 Day 1), Cycles 1-3 EOC and at EOT.
- In patients with the $JAK2^{V617F}$ mutation, change in peripheral blood granulocyte $JAK2^{V617F}$ allele burden.

Pharmacokinetics:

Measurement of SAR302503 PK (secondary endpoint) endpoints of maximum plasma concentration observed (C_{max}), time to maximum concentration (t_{max}), and area under the time concentration curve from time 0 to hour 24 (AUC_{0-24}). SAR302503, predose and postdose plasma collections were obtained on Cycle 1 (Day 1, Day 2, and Day 15), Cycle 2 (Day 1 and Day 2), and Cycle 3.

Safety:

Safety (secondary endpoint) evaluation was based on frequency, duration, and severity of treatment-emergent adverse events (TEAEs), changes in clinical laboratory parameters, changes in physical examination findings, vital signs relative to baseline, and changes in Eastern Cooperative Oncology Group (ECOG) performance status score.

Statistical methods: No statistical hypothesis was defined in this study and no statistical testing was planned.

Analysis populations

- Intent-to-Treat (ITT) population: all randomized patients, the primary population for all efficacy parameters. All analyses using this population were based on the treatment assigned by Interactive Voice Response System (IVRS).

- Evaluable Patient (EP) population: all randomized and treated patients with a baseline and at least 1 post-baseline MRI (computed tomography [CT] in the case of contraindications for MRI), and who received a minimum of 50% of the targeted dose for 3 cycles. All analyses using this population were based on the actual first dose received.
- Evaluable Patient population for PRO: ITT population with a baseline score >0; analyses were based on treatment assigned by IVRS. Patients without a baseline score >0 were considered nonevaluable for PRO analysis.
- Evaluable patient population for fibrosis: ITT population with a baseline bone marrow fibrosis Grade >0 by local review, with a post baseline assessment evaluable according to local review, and who received a minimum of 50% of targeted dose for 3 cycles; analyses were based on treatment assigned by IVRS. Patients without a baseline score >0 were considered nonevaluable for fibrosis analysis.
- All-treated (AT; safety) population: a subset of the ITT population that took at least 1 dose of study medication for analysis of exposure and safety data based on the dose actually received (initial dose if patient received more than 1 dose level in the study).
- Randomized patients for whom it was unclear whether they took the study medication were included in the safety population as randomized.
- Nonrandomized but treated patients were not included in the safety population; their safety data were presented separately, as applicable.
- PK population: received at least 1 full cycle of study treatment and had evaluable drug concentration data.
- Pharmacodynamic population: received at least 1 full cycle of study treatment and had evaluable pharmacodynamic biomarkers' concentration data.

Primary endpoint analysis

Descriptive statistics (n, mean, median, standard deviation [SD]) and 95% confidence intervals (CI) were provided for the percent change from baseline in spleen volume based on MRI at Cycle 3 EOC.

Secondary, exploratory, and supportive efficacy analyses

Descriptive summary statistics and 95% CI by treatment group were provided of all secondary, exploratory, and supportive endpoints.

Safety analyses

Safety analyses were summarized by descriptive statistics and were performed on the safety population. Analysis of adverse events and laboratory data was performed by treatment group, by patient, and by cycle. Vital signs measurements were summarized by treatment group and as potentially clinically significant abnormalities (PCSAs).

Interim and final analyses

No formal interim analysis was planned. However, at Cycle 3 EOC, the primary endpoint and relevant secondary efficacy endpoints were analyzed while the study was ongoing.

Randomization and blinding

Treatment assignment was done centrally via an IVRS. Eligible patients were randomly assigned (open-label) to 1 of the 3 doses (ie, 300, 400, and 500 mg) in a 1:1:1 ratio.

Summary:

Population characteristics:

Demographics and baseline patient characteristics were relatively well-balanced across the treatment groups. Of the 31 patients in the ITT population, 51.6% (16/31) were men and 48.4% (15/31) were women with a median age of 63.0 years (median range: 57.0 to 67.0 years), 58.1% (18/31) were <65 years of age, 16.1% (5/31) were ≥75 years old, 58.1% (18/31) had primary MF of high risk status, 89.7% (26/29) had the mutant JAK2 allele, and 93.5% (29/31) were not red blood cell (RBC) transfusion-dependent. Median spleen volume at baseline was 2394 mL (11x normal) for all patients (2602.50 mL 300 mg, 2468.00 mL 400 mg, 1616.00 mL 500 mg group). A majority of patients, 62.5% (15/24), had only 1 prior anticancer therapy for MF; 29.2% (7/24) had ≥3 therapies; the most prevalent prior anticancer therapy for MF was hydroxyurea (83.3%, 20/31).

Extent of exposure

Median number of cycles administered and duration of exposure per patient were lower in the 300 mg group (12 cycles, 48.2 weeks) than the 400 mg (14 cycles, 56.2 weeks) and 500 mg (13.0 cycles, 52.2 weeks) groups.

Thiamine

A total of 22 patients entered the thiamine supplement period. The total number of patient-weeks of exposure to thiamine was 187.1 and median duration of exposure to thiamine was 15 weeks.

Efficacy results:

Primary efficacy endpoint

Primary endpoint (ITT population): As shown in Table 1, clinically meaningful mean (SD) reductions from baseline in spleen volume, as measured by MRI, were seen at Cycle 3 EOC: 30.30% (12.60%) reduction from a median baseline volume of approximately 2600 mL in the 300 mg group (8 patients), 33.14% (18.96%) reduction from a median baseline volume of approximately 2500 mL in the 400 mg group (10 patients), and 43.34% (19.01%) reduction from a median baseline volume of approximately 1600 mL in the 500 mg group (11 patients).

Table 1 - Percent change in spleen volume by central imaging MRI/CT review at the end of Cycle 3 - ITT population

	SAR302503		
	300 mg (N = 10)	400 mg (N = 10)	500 mg (N = 11)
Number	8	10	11
Mean (SD)	-30.30 (12.60)	-33.14 (18.96)	-43.34 (19.01)
Median	-25.77	-31.34	-39.32
Min : Max	-47.1 : -13.5	-55.0 : 1.5	-72.9 : -17.2
95% CI	(-40.83 to -19.77)	(-46.70 to -19.58)	(-56.11 to -30.57)

Results for secondary, exploratory, and supportive efficacy endpoints

Spleen volume

- The proportion of patients in the ITT population with ≥35% reduction in spleen volume at end of Cycle 3 was higher in the 400 mg (50.0%, 5/10) and 500 mg (63.6%, 7/11) groups than the 300 mg group (30.0%, 3/10).
- The proportion of patients in the ITT population with ≥35% reduction in spleen volume at Cycle 6 EOC was higher in the 400 mg (60.0%, 6/10) and 500 mg (54.5%, 6/11) groups compared with the 300 mg group (30.0%, 3/10).
- The mean percent changes in spleen volume based on MRI at Cycle 6 EOC in the ITT population were 26.56% at 300 mg (N=8), 37.24% at 400 mg (N=10), and 41.06% (N=11) at 500 mg.
- The response of at least 35% reduction in spleen volume was durable; the response rate was maintained for a median of 251 to 255 days across the 3 treatment groups.

Reductions in spleen volume at the end of Cycle 3 in the evaluable patient population confirmed the results observed in the ITT population.

Spleen length

- The percent changes in spleen length determined by palpation were consistent with and ran parallel to the treatment effect observed when reduction in spleen volume was measure by MRI.

Patient Reported Outcome (PRO)

MPN-SAF

- Improvement from baseline was observed at all SAR302503 doses in total symptom score and in each of the 6 key PRO symptoms (filling up quickly when you eat, abdominal discomfort, abdominal pain, itching, night sweats, bone pain).
- Among the 6 key PRO symptoms, the highest responses (at least 2 point improvement from baseline or resolution of a baseline Grade 1 symptom) as measured by MPN-SAF in the evaluable population across all timepoints were seen for night sweats (56% to 90.0%) in all treatment groups. Maximum response rates at Cycle 3 EOC were 66.7% (9/9) for itching in the 300 mg group, 60.0% (6/10) for night sweats in the 400 mg group, and 50.0% (4/8) for abdominal discomfort in the 500 mg group. Maximum response rates at Cycle 6 EOC were 44.4% (4/9) for filling up quickly when you eat and itching in the 300 mg group, 70.0% (7/10) for filling up quickly when you eat and night sweats in the 400 mg group, and 75.0% (6/8) for abdominal pain and abdominal discomfort in the 500 mg group.
- The rate of change in total symptom score as a function of the cumulative percent of patients in each treatment group demonstrated that the 400 mg treatment group had the highest cumulative percent responders at almost all levels of total symptom score change from baseline.
- Symptom response rates of ≥50% reduction in total symptom score at Cycle 3 EOC and Cycle 6 EOC for the ITT population with evaluable baseline symptoms were 44.4% (4/9) and 33.3% (3/9) in the 300 mg group, 40.0% (4/10) and 60.0% (6/10) in the 400 mg group, and 37.5% (3/8) at both timepoints in the 500 mg group.
- Total symptom score for the EP population for QOL showed maximum median absolute (percent) decreases from baseline of 13.0 (57.0%) at 300 mg, 20.5 (69.7%) at 400 mg and 8.0 (44.8%) at 500 mg.

EQ-5D

- Health status, as measured by EQ-5D, improved from Cycle 1 to 6 in the 400 mg and 500 mg groups. No meaningful change was seen in the 300 mg group.

Clinical activity - IWG-MRT

- Clinical activity based on response rates of modified IWG-MRT criteria using the spleen volume assessment of the site radiologist demonstrated a response at each dose level. Maximum clinical improvement rates were 63.6% (7/11) at 500 mg Cycle 6 EOC, 70.0% (7/10) at 400 mg group Cycle 12 EOC, and 10% (1/10) at 300 mg group Cycles 3, 6, 12 EOC.

Weight

- Median weight gain was seen in the 400 and 300 mg groups (maximum 4.73% 400 mg Cycle 13 [N=8] and 12.27% 300 mg Cycle 15 [N=2]). Median loss in body weight was seen in the 500 mg group (maximum 12.67% at Cycle 15; N=5).

Transfusion dependence

- The 2 patients who were RBC transfusion dependent at baseline remained transfusion dependent during treatment. Between 10% and 30% of patients across treatment groups who were RBC transfusion independent at baseline became transfusion dependent during treatment.
- The overall rate of platelet transfusions was low across the study.

Leukocytosis and thrombocytosis

At the end of Cycle 6 (Cycle 7 Day 1), the 300 mg group had a lower percentage of patients with normalization of leukocytosis (2 patients) than in the 400 mg and 500 mg groups (4 patients in each group).

- At the end of Cycle 6 (Cycle 7 Day 1), 1 of 3 patients in the 300 mg group had normalization of thrombocytosis, which was lower than in the 400 mg group; no cases of normalization were seen at this timepoint for the 500 mg group. Among patients who experienced normalization of thrombocytosis, the effect occurred earlier in the 400 mg and 500 mg groups.

Pharmacodynamics

- Nonsignificant reductions in $JAK2^{V617F}$ allele burden were seen in all treatment groups. Maximum median percent change from baseline in each treatment group by end of Cycle 12 was -0.4% to -8.2%.
- A time-dependent, but not dose-related, inhibition of STAT3 phosphorylation was seen in all treatment groups at 2 hours post dose on Cycle 1 Day 1. Similar levels of maximum inhibition were also achieved at steady state for PK of SAR302503 (Cycle 1 Day 15 and Cycle 2 Day 1).
- Expression of 28 of 97 cytokines was regulated (either up or down by ≥1.5-fold, adjusted false discovery rate $p<0.05$) at the end of Cycle 1, 2 or 3 following SAR302503 treatment in the overall patient population (n=29) and 19 were regulated at the end of all 3 cycles, indicating early and continued modulation.
- Numerically, the 300 mg dose was less effective than the 400 mg and 500 mg doses of SAR302503 as shown by the following:
  - The response rate, as determined by central review, was lower than the other 2 treatment groups.
  - There was consistently less activity with the 300 mg dose than with the 400 mg and 500 mg doses as determined by reduction in spleen volume at the end of Cycles 3 and 6.

- The 300 mg dose group had a lower mean percent decrease in spleen volume than the 400 mg and 500 mg dose groups.
- Based on the IWG-MRT criteria evaluated by the site radiologist, spleen volume findings were consistent with the central review whereas, the 300 mg dose group achieved less clinical improvement at end of Cycles 3, 6 and 12 compared with the 400 mg and 500 mg dose groups.
- Of the 4 patients in the 300 mg group who discontinued from study treatment prematurely and who had spleen volume data at the end of Cycle 3, 3 patients did not achieve a ≥35% response.
- Fewer patients in the 300 mg group achieved normalization of baseline leukocytosis on Cycle 7 Day 1 (end of Cycle 6). Compared with the 400 mg and 500 mg groups combined.
- At the end of Cycle 6 (Cycle 7 Day 1), normalization of baseline thrombocytosis was observed in a third of patients in the 300 mg group compared with all patients in the 400 mg group; no cases of normalization were seen at this timepoint for the 500 mg group.

The changes in EQ-5D were nonsignificant in the 300 mg group compared with improvement in the 400 and 500 mg groups.

Safety results

Adverse events

- Daily oral doses of 300 mg, 400 mg and 500 mg SAR302503 in consecutive 28-day cycles for the treatment of MF appeared to be tolerable. Treatment-emergent adverse events reported were those consistent with the known safety profile of SAR302503.
- The most common nonhematologic TEAEs of all grades irrespective of relation to study drug across all doses were diarrhea, nausea and vomiting (60 to 90% of patients in each group). Most cases of diarrhea, nausea, and vomiting were Grade 1 or 2, few required dose modification, and 1 patient discontinued due to nausea. The incidence of these events generally decreased over time.
- The most common all grade and Grade 3 or 4 hematologic TEAE irrespective of relationship to study drug was anemia (all grade and Grade 3, 4: 40% to 55%).
- Follow-up AEs were reported from the beginning of Thiamine Supplementation Period up to the end of the Thiamine Supplementation Period. One AE of special interest (AESI) was reported during this period (lipase increased).
- Serious adverse events (SAEs) were reported in 17 patients and the most common events were gastrointestinal.
- One patient in the 300 mg group had concurrent SAEs of hepatic failure and aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin elevations. These events met the criteria for Hy's Law and were considered related to study drug. After treatment discontinuation, the SAEs resolved. Following this event, the protocol was amended to add more frequent liver function tests and dose modifications related to abnormal test values. No other patients had events that met the criteria for Hy's Law.
- No subject died within 30 days of their last dose. Nine subjects died more than 30 days after their last dose of SAR302503 .Of these patients, 2 died during the Thiamine Supplementation Period, one due to complications from surgery and one due to unknown causes.
- Overall, 5 of 31 patients were prematurely discontinued from study treatment due to TEAEs including 1 patient with anemia and 1 patient with hepatic failure at 300 mg; 1 patient with leukocytosis and dyspnea and 1 patient with intermittent nausea at 400 mg; and 1 patient with anemia and thrombocytopenia at 500 mg. Two additional patients in the 400 mg group had at least 1 TEAE that lead to withdrawal of the study treatment. One patient had peripheral neuropathy and 1 patient had increased lipase.

Laboratory results

- Based on hematology laboratory tests, thrombocytopenia occurred in 50% to 63% of patients across treatment groups; few cases were Grade 3 or 4. Grades 1 to 3 anemia occurred in all patients; no patient had Grade 4 anemia. Lymphopenia occurred in 82% to 90% of patients across treatment groups and few cases were Grade 3 or 4.
- Of the 11 patients who had hematology tests from the end of the on-treatment period to the end of the Thiamine Supplementation Period, 8 (72.7%) patients had anemia, including 1 (9.1%) patient with Grade 3, 4 anemia. Four (36.4%) patients had thrombocytopenia, 3 (27.3%) had lymphopenia, and 1 (9.1%) had leukopenia, all of which were Grade 1 or 2.
- Liver enzyme elevations were common, and mostly Grade 1 or 2 and reversible. Two of the patients with elevations had Grade 3 or 4 liver enzymes. One of the patients as noted above met the criteria for Hy's Law and had a concurrent SAE of hepatic failure. The other patient had Grade 3 AST and ALT values concurrent with SAE of gastric ulcer perforation that were considered to be unrelated.
- Elevated creatinine values occurred in 50.0% to 73% of patients across treatment groups; all were Grade 1 or 2.
- Elevated amylase occurred in 30% to 46% of patients across treatment group and elevated lipase in 40% to 70% of patients. Few elevations were Grade 3 and none were Grade 4. Lipase and amylase elevations were asymptomatic and reversible to Grade ≤1.

Vital signs results

- There were no clinically meaningful changes in vital signs.
- Pharmacokinetics results
- Following once-daily oral doses of 300, 400, and 500 mg, SAR302503 was absorbed with a median t_{max} of 2 to 3 hours.
- For a 1.67- fold increase in dose from 300 to 500 mg, SAR302503 exposure increased 1.03- and 1.19-fold for C_{max} and AUC_{0-24}, respectively, after the first dose (Cycle 1 Day 1) and 1.57- and 1.76-fold for C_{max} and AUC_{0-24} , respectively, after repeated doses (Cycle 2 Day 1).
- Steady state appeared to have been achieved by Cycle 1 Day 15, with a 2.95- to 3.88-fold accumulation, after repeated once-daily oral doses of SAR302503.

Pharmacokinetics/pharmacodynamics

- The relationship between SAR302503 concentration and pSTAT3 inhibition was described by an inhibitory sigmoid E_{max} model with the mean (SE) concentration of 50% inhibition (EC_{50}) of 735 (1140) ng/mL. The steady state mean trough concentrations at 400 and 500 mg were above the EC_{50} by 1.3 and 2.0 fold, respectively, while mean trough concentration at 300 mg was slightly below the EC_{50}.

Issue date: 20-May-2015