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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Harrison CN, Schaap N, Vannucchi AM, et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study. *Lancet Haematol* 2017; published online June 8. http://dx.doi.org/10.1016/S2352-3026(17)30088-1.

Site Numbe	Site	Site Location	PI	of Patient
840010	The University of Michigan	Ann Arbor, United States	Talpaz, Moshe	7
840007	Mayo Clinic of Scottsdale	Scottsdale, United States	Mesa, Ruben	6
826001	Guy's & St. Thomas Hospital	London, United Kingdom	Harrison, Claire	6
528001	UMC St Radbound	Nijmegen, Netherlands	Schaap, Nicolaas	6
528002	VU Medisch Centrum	Amsterdam, Netherlands	Zweegman, Sonja	6
380004	Azienda Ospedaliera-Universitaria Careggi	Firenze, Italy	Vannucchi, Alessandro M.	5
250002	Hopital Saint-Louis	Paris, France	Kiladjian, Jean- Jacques	4
840005	Emory University	Atlanta, United Sattes	Winton, Elliott	4
56002	ZNA Stuivenberg	Antwerpen, Belgium	Wu, Ka Lung	4
250003	CHU De Nimes	Nimes, France	Jourdan, Eric	4
528003	Academisch Ziekenhuis Maastricht	Maastricht, Netherlands	Schouten, Hendricus	3
840022	Cleveland Clinic	Cleveland, United States	Tiu, Ramon	3
380003	Ospedale Di Circolo E Fondazione Macchi	Varese, Italy	Passamonti, Francesco	3
840009	NY Presbyterian-Weill Cornell Medical Center	New York, United States	Silver, Richard	3
840002	University of Texas - MD Anderson Cancer Center	Houston, United States	Cortes, Jorge	2
56003	UZ Leuven UZ Gasthuisberg	Leuven, Belgium	Devos, Timothy	2
276006	Universitatsklinikum Magdeburg	Magdeburg, Germany	Heidel, Florian	2
250001	Institut Paoli Calmettes	Marseille, France	Rey, Jerome	2
276001	Universitatsklinikum Mannheim gGmbH	Mannheim, Germany	Reiter, Andreas	2
276005	Universitatsklinikum Ulm	Ulm, Germany	Doehner, Konstanze	2
276007	Universitatsklinikum Leipzig AoR	Leipzig, Germany	Niederwieser, Dietger	2
724001	Hospital Clinic i Provincial	Barcelona, Spain	Cervantes, Francisco	2
724002	Hospital Universitario de Salamanca	Salamanca, Spain	Hemandez Rivas, Jesus Maria	2
840001	University of Kansas Medical Center	Kansas City, United States	Yacoub, Abdulraheem	2
840015	Huntsman Cancer Institute at the University of Utah	Salt Lake City, United States	Deininger, Michael	2
250004	Institut Universitaire du Cancer - Oncopole	Toulouse, France	Recher, Christian	1
724003	Hospital Universitario Puerta de Hierro	Madrid, Spain	Ojeda Gutierrez, Emilio	1
840004	Univeristy of California San Diego-Moores Cancer Center	Los Angeles, United States	Schiller, Gary	1
840019	Signal Point Clinical Research Center	Middletown, United States	Vrindavanam, Nandagopal	1
40001	AKH Wien	Wien, Austria	Gisslinger, Heinz	1
124001	Princess Margaret Hospital	Ontario, Canada	Gupta, Vikas	1

250006	Hopital Saint-Antoine	Paris, France	Casadevall, Nicole	1
380001	Ospedale Maggiore Policlinico	Milano, Italy	Iurlo, Alessandra	1
380002	Azienda Ospedaliera Universitaria Policlinico	Roma, Italy	Alimenta, Giuliana	1
840013	St Agnes Healthcare	Baltimore, United States	Miller, Carole	1
840014	University of Chicago	Chicago, United States	Odenike, Olatoyosi	1
				97

AMENDED CLINICAL TRIAL PROTOCOL 3

COMPOUND: SAR302503

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 NUMBER: ARD12181

STUDY NAME: JAKARTA2

VERSION DATE / STATUS: 28 November 2012 / Approved

CLINICAL STUDY DIRECTOR: Jenny Zhang

Protocol Amendment 3	Version number: 1	Date: 28-Nov-2012
Amended Clinical Trial Protocol 2	Version number: 1	Date: 29-Feb-2012
Protocol Amendment 2 – France Local Amendment 1	Version number: 1	Date: 29-Feb-2012
Amended Clinical Trial Protocol 1	Version number: 1	Date: 23-Feb-2012
Protocol Amendment 1	Version number: 1	Date: 23-Feb-2012
Clinical Trial Protocol	Version number: 1	Date: 20-Oct-2011

EudraCT: 2011-005226-21
IND number: 78,286

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	Dr Claire Harrison Guy's Hospital, Great Maze Pond, London, SE1 9RT 0207 188 2739 Claire.Harrison@gstt.nhs.uk
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	Dr Tun Tun Lin sanofi-aventis, CSU, One Onslow Street, Guildford, Surrey, GU1 4YS 01483 554307 01483 554825 tuntun.lin@sanofi-aventis.com
SPONSOR	Company: Address:	sanofi-aventis recherché & developpment, 1 avenue Pierre Brossolette 91385 Chilly Mazarin Cedex France
OTHER EMERGENCY TELEPHONE NUMBERS		01483 505515

CLINICAL TRIAL SUMMARY

COMPOUND: SAR302503	**STUDY No : ARD12181**
TITLE	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
INVESTIGATOR/TRIAL LOCATION	Global
STUDY OBJECTIVE(S)	**Primary Objective** • To evaluate the efficacy of once daily dose 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 (Post-PV MF), or post-essential thrombocythemia myelofibrosis (Post-ET MF) based on the reduction of spleen volume at the end of 6 treatment cycles **Secondary Objective(s)** • 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 6 • To evaluate the splenic response to SAR302503 at the end of Cycle 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 PK analysis, if warranted **Exploratory Objectives:** • To evaluate the Overall Survival (OS) • To evaluate efficacy based on the modified response criteria of the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) • To evaluate the splenic response defined as a ≥25% reduction from baseline • To evaluate durable splenic response, as measured by the number of cycles (out of 6) that subjects have a splenic response by palpation • To evaluate durable symptom response, as measured by the number of cycles (out of 6) that subjects have a symptom response using the modified MFSAF

	• To evaluate the effect of SAR302503 on bone marrow with regard to cytogenetics, cellularity, blast count, and the grade of reticulin fibrosis • To evaluate pharmacokinetic (PK)-pharmacodynamics of plasma SAR302503 exposure versus spleen volume • To evaluate the effect on health-related quality of life (QOL) using European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and Patient's Global Impression of Change (PGIC) scale • To evaluate the effect on additional Myeloproliferative Neoplasm (MPN)-associated symptoms, as measured by the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) and Brief Fatigue Inventory (BFI) • To evaluate the effects of SAR302503 on JAK-STAT and other signaling pathways • To identify tumor-specific gene mutations and other molecular changes that may correlate with response or resistance to JAK2-directed therapies
STUDY DESIGN	This is a phase II, multicenter, open label, single arm study of SAR302503 in subjects 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. This study consists of Screening, Treatment and Post-treatment observation visits. The screening period is up to 28 days. Following the screening period, eligible subjects will receive 400 mg/day of SAR302503 as starting dose on Day 1 of Cycle 1. A flexible dosing regimen may be employed to optimize efficacy and to minimize drug toxicity for individual subjects. If there is lack of adequate splenic response (≥ 50% splenic size reduction by palpation) and there is no unacceptable drug toxicity, the study drug dose can be titrated upwards in 100mg/day increments up to maximum of 600mg/day only after the end of Cycles 2 and 4 within the first 6 cycles of the treatment. If there is toxicity, the study drug dose will be titrated downwards in 100mg/day decrements to a minimum of 200 mg/day. The dose range is from 200mg to 600mg per day. Patients who don't tolerate 200 mg dose must discontinue after 2 cycles at 200 mg. SAR302503 will be self-administered orally on an outpatient basis once a day for at least 6 consecutive 28-day cycles. Subjects will continue to receive SAR302503 for as long as they are benefiting and have not experienced disease progression or unacceptable toxicity requiring discontinuation of SAR302503. For subjects who develop ≥Grade 3 alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin elevations at any time during the study, at least weekly monitoring of liver function tests (LFTs) must be performed until the adverse event has returned to Grade ≤1. Subjects may resume treatment after elevated LFTs have returned to Grade ≤1. If treatment is resumed, all subjects with the above mentioned elevations must have their dose reduced by 1 dose level. The monitoring of AST, ALT and bilirubin (total and direct) must be performed every 2 weeks for at least the 3 subsequent treatment cycles. Additional safety and other evaluations

	are presented in the Study Flow Chart in Section 1.2. Clinical safety and efficacy will be monitored during the study by internal sponsor committee. Committee consists the following members: Clinical Study Director, Medical monitor, Clinical Statistician, Global Safety Officer, Clinical Scientist, Clinical Lead, Pharmacokinetics representative, and Program Head. **Withdrawal Criteria:** Subjects will be withdrawn from treatment in the event of any one of the following: • Unacceptable toxicity (see Section 8.3). • Disease progression as defined by the modified IWG-MRT response criteria • Splenectomy • Relapse as defined by the modified IWG-MRT response criteria • Need for intervention or therapy determined by the Investigator to be medically necessary that is precluded by protocol. • Subject noncompliance with treatment or voluntary withdrawal of consent. Clinical safety will be evaluated during the entire study.
STUDY POPULATION **Main selection criteria:**	**Inclusion Criteria:** I 01. Diagnosis of PMF or Post-PV MF or Post-ET MF, according to the 2008 World Health Organization (Appendix B) and IWG-MRT criteria (Appendix C). I 02. Subjects who previously received Ruxolitinib treatment for PMF or Post-PV MF or Post-ET MF or PV or ET for at least 14 days (exposure of <14 days is allowed for subjects who discontinued Ruxolitinib due to intolerability or allergy) and discontinued the treatment for at least 14 days prior to the first dose of SAR302503. I 03. Myelofibrosis classified as intermediate -1 with symptoms, intermediate-2 or high-risk by Dynamic International Prognostic Scoring System (DIPSS) (Passamonti, et al, Blood 2010 [1]). I 04. Spleen ≥5 cm below costal margin as measured by palpation. I 05. Male and female subjects ≥18 years of age. I 06. Signed written informed consent. **Exclusion Criteria:** E 01. Eastern Cooperative Oncology Group (ECOG) performance status of >2 before the first dose of SAR302503 at Cycle 1 Day 1. E 02. 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 E 03. Subjects with known active (acute or chronic) Hepatitis A, B, or C; and hepatitis B and C carriers E 04. AST or ALT ≥2.5 x ULN E 05. Total Bilirubin: • Exclude if ≥3.0 x ULN • Subjects with total bilirubin between 1.5-3.0 x ULN must be excluded if the direct bilirubin fraction is ≥25% of the total E 06. Subjects with prior history of chronic liver disease (eg, chronic alcoholic liver disease, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemachromatosis, non-alcoholic steatohepatitis [NASH]]) E 07. Life expectancy <6 months. E 08. Subjects with any other prior malignancies are not eligible, except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which subject has been disease-free for at least 5 years E 09. Lack of willingness or ability to comply with scheduled visits, treatment plans, laboratory assessments and other study-related procedures E 10. Splenectomy E 11. Any chemotherapy, immunomodulatory drug therapy (eg, thalidomide, interferon-alpha), Anagrelide, immunosuppressive therapy, corticosteroids >10 mg/day prednisone or equivalent, or growth factor treatment (eg, erythropoietin), or hormones (eg, androgens, danazol) within 14 days prior to initiation of SAR302503; darbepoetin use within 28 days prior to initiation of SAR302503. The only chemotherapy allowed will be hydroxyurea within 1 day prior to initiation of SAR302503. E 12. Major surgery within past 28 days or radiation within 6 months prior to initiation of SAR302503 E 13. Concomitant treatment with or use of pharmaceutical or herbal agents known to be moderate or severe inhibitors or inducers of CYP3A4 E 14. Treatment with aspirin in doses >150 mg/day within a week E 15. Active acute infection requiring antibiotics E 16. 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 SAR302503 E 17. Participation in any study of an investigational agent (drug, biologic, device) within 30 days prior to initiation of SAR302503, unless during a non-treatment phase E 18. Pregnant or lactating female E 19. Women of childbearing potential, unless using effective contraception while on SAR302503

	E 20. Men who partner with a woman of childbearing potential, unless they agree to use effective contraception while on SAR302503 E 21. Known human immunodeficiency virus or acquired immunodeficiency syndrome-related illness E 22. Any severe acute or chronic medical, neurological, or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or SAR302503 administration, may interfere with the informed consent process and/or with compliance with the requirements of the study, or may interfere with interpretation of study results and, in the Investigator's opinion, would render the subject inappropriate for entry into this study E 23. Unable to swallow capsules E 24. Presence of any significant gastric or other disorder that would inhibit absorption of oral medication E 25. Subjects with a QTc prolongation > 450 ms at screening or prior to study drug administration Or subjects who need concomitant medicines that are known to prolong QTc (Applicable for France only)
Total expected number of subjects:	70 evaluable subjects
STUDY TREATMENT(s)	SAR302503 will be orally self-administered on an outpatient basis, once daily in consecutive 28-day cycles at a starting dose of 400 mg/day. SAR302503 will be dispensed to subjects at the beginning of each treatment cycle and will be taken on an empty stomach (1 hour before or 2 hours after meals) at approximately the same time each day. Especially for higher doses (eg, 500 and 600 mg/day), it is recommended that SAR302503 be taken 2 hours after meals at approximately the same time each day. Missed or vomited doses will not be replaced.
Investigational Medicinal Product(s) **Formulation**	SAR302503 will be supplied as hard capsules containing 100 mg of SAR302503 free base (equivalent to 117 mg dihydrochloride monohydrate). The drug product consists 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
Dose regimen:	SAR302503 will be orally self-administered on an outpatient basis, once daily in consecutive 28-day cycles. The starting dose is 400mg/day. A flexible dosing regimen may be employed to optimize efficacy and to minimize drug toxicity for individual subjects. The possible daily doses are 200mg, 300mg, 400mg, 500mg or 600mg. **Upwards titration details:** Within the first 6 cycles of the treatment, study drug dose upwards titration by 100mg/day is permitted only after the end of Cycles 2 and 4 if the splenic response does not achieve a ≥50% reduction in spleen size by palpation compared to baseline and there is no unacceptable drug toxicity as specified in the protocol. Of note, upwards titration decisions during the first 6 cycles of

	treatment will be based on the results of splenic size determinations by palpation, but, the splenic volume response will formally be determined by MRI or CT after 6 cycles. After Cycle 6, subjects will be allowed to have their dose titrated up (maximum dose 600mg/day) or down (minimum 200mg/day) in accordance with their individual responses and tolerability to study drug at the discretion of the Investigator or sub-Investigator based on their clinical assessment. **Downwards titration details:** If subjects experience drug toxicity as specified below, the dose will be downwards titrated by a 100 mg/day decrement**.** Definition of toxic events: • Grade 4 thrombocytopenia (platelet count <25 × 10^9/L) or neutropenia (ANC <0.5 × 10^9/L). In such cases, dosing may be suspended for up to 28 days and reinitiated if values return to the following levels (≤Grade 2, according to Common Terminology Criteria for Adverse Events [CTCAE], version 4.03): - Platelet count: ≥50 × 10^9/L - ANC: ≥1.0 × 10^9/L. • Grade ≥3 ALT, AST, or total bilirubin elevation. See additional LFT abnormality details below. • Grade 3 or higher nausea, vomiting, diarrhea, constipation, or fatigue which does not respond to therapeutic or supportive measures within 48 hours. In such cases, dosing may be suspended for up to 14 days and may be reinitiated if the toxicity resolves to Grade 1. • Any Grade ≥3 non-hematologic/non-gastrointestinal toxicity or Grade ≥2 peripheral neuropathy. In such cases, dosing may be suspended for up to 14 days, and may be reinitiated if the toxicity resolves to Grade 1. Except in the case of LFT abnormalities (see specific requirements below), subject dosing should be resumed at one dose level lower (a 100 mg/day decrement) than the dose at which the event was observed. Dose levels may be reduced a maximum of two times from starting dose. If a dose has been reduced for a given subject and the toxicity resolves as mentioned above for at least 1 cycle, the dose level may be re-escalated one dose level higher per cycle at the discretion of the Investigator. This can be repeated until the original dose level (defined as the dose level before receiving the downwards titration) is reached. Some subjects may experience Grade 4 non-hematological toxicity and require dose reduction. For these subjects, subsequent upward dose titration is not allowed. Treatment discontinuation may be considered based on the Investigator's judgment. If subjects experience an ECG abnormality (Grade 4, and confirmed by a cardiologist), the subjects must withdraw from the treatment. Some subjects may experience Grade 4 hematologic toxicity and require dose reduction. If the toxicity resolves as mentioned above for at least 1 cycle, the dose level may then be titrated upwards one

	dose level per cycle at the discretion of the Investigator. However, if these subjects experience recurrence of Grade 4 hematological toxicity, no subsequent upward dose titration will be permitted, even after the toxicity resolves. **Liver function test abnormalities** If a subject experiences LFT abnormalities, defined as ≥Grade 3 ALT, AST, or total bilirubin elevation, the following dose and monitoring modifications must occur: • Study treatment must be interrupted and subjects must have at least weekly monitoring of liver function tests until the adverse event has returned to Grade ≤1. Subjects may resume treatment after elevated LFTs have returned to Grade ≤1. If treatment is resumed, all subjects with the above mentioned elevations must have their dose reduced by 1 dose level. The monitoring of AST, ALT and bilirubin (total and direct) must be performed every 2 weeks for at least the 3 subsequent treatment cycles. • If study drug is interrupted for >14 days (ie, the AE has not returned to Grade ≤1), the subject must be withdrawn from study treatment. • No dose re-escalation will be permitted after dose reduction due to ≥Grade 3 ALT, AST, or total bilirubin elevation • If the above described ≥Grade 3 elevations occur again (second episode) despite dose reduction, the subject must be withdrawn from study treatment. Any subject experiencing Grade 4 ALT, AST, or total bilirubin elevations, in the absence of other demonstrable cause (non-drug related), must be withdrawn from study treatment. Dose reduction should also be considered for subjects who become transfusion-dependent and were previously considered not to be. In case of dose interruption, dosing may be held up to 28 days before reinitiation of the IMP. Transfusion dependence is defined as receiving an average of ≥2 units of red blood cell (RBC) transfusions/month over 3 months as per Gale RP et al (2). Subjects who do not tolerate therapy after 2 dose level reductions from starting dose must withdraw from the study. If toxicity does not resolve in the above mentioned time period subjects must withdraw from the study.
Non Investigational Medicinal Product(s) (if applicable) **Formulation**	NA
Route(s) of administration:	NA
Dose regimen:	NA
PRIMARY AND SECONDARY ENDPOINT(S)	**Primary Endpoint:** • Response Rate (RR), defined as the proportion of subjects who have a ≥35% reduction from baseline in volume of spleen at the end of Cycle 6 as measured by Magnetic Resonance Imaging (MRI) (or Computed Tomography

	(CT) scan in subjects with contraindications for MRI) **Secondary Endpoint(s):** • Symptom Response Rate (SRR): Proportion of subjects with a ≥50% reduction from baseline to the end of Cycle 6 in the total symptom score using the modified MFSAF • Duration of spleen response, measured by MRI (or CT scan in subjects with contraindications for MRI) • Proportion of subjects with a ≥50% reduction in length of spleen by palpation from baseline at the end of Cycle 6 • Response Rate (RR), at the end of Cycle 3 defined as the proportion of subjects who have a ≥35% reduction from baseline in volume of spleen at the end of Cycle 3 as measured by MRI (or CT scan in subjects with contraindications for MRI) • Percent change of spleen volume at the end of Cycles 3 and 6 from baseline as measured by MRI (or CT scan in subjects with contraindications for MRI) • The effect of SAR302503 on the $JAK2^{V617F}$ allele burden • Safety and tolerability, as assessed by clinical, laboratory, electrocardiogram (ECG), and vital sign events; graded by the CTCAE v4.03 • Plasma concentrations of SAR302503 **Exploratory endpoints:** • OS • Rates of complete remission (CR), partial remission (PR), clinical improvement (CI), stable disease (SD), progressive disease (PD), and relapse as measured by the modified IWG-MRT response criteria • Response Rate (RR), defined as the proportion of subjects who have a ≥25% reduction from baseline in volume of spleen at the end of Cycle 3 as measured by Magnetic Resonance Imaging (MRI) (or Computed Tomography (CT) scan in subjects with contraindications for MRI) • Proportion of subjects who have a ≥25% reduction in volume of spleen size at end of Cycle 6 as measured by MRI (or CT scan in subjects with contraindications for MRI) • The maximum months of continuous splenic response by palpation (a ≥50% reduction from baseline in spleen size) for each subject • The number of cycles (out of 6) that subjects have a splenic response by palpation (a ≥50% reduction from baseline in spleen size) • The maximum months of continuous symptom response (a ≥50% reduction from baseline in the total symptom score) for each subject using the modified MFSAF • The number of cycles (out of 6) that subjects have a symptom response using the modified MFSAF • To evaluate the effect of SAR302503 on bone marrow with regard to cytogenetics, cellularity, blast count, and degree

	of reticulin fibrosis • Change on health-related QOL using EORTC QLQ-C30 v3.0 and PGIC scale • Change from baseline in each of the individual symptoms of the MPN-SAF (MPN-SAF assessment) and BFI. • The effects of SAR302503 on JAK-STAT and other signaling pathways • Tumor-specific gene mutations and other molecular changes that may correlate with response or resistance to JAK2-directed therapies
ASSESSMENT SCHEDULE	A cycle is defined as 28 days of dosing SAR302503. Subjects will receive up to 6 cycles of SAR302503, after which subjects who continue to benefit clinically will be allowed to remain on study drug until the occurrence of disease progression (as defined by the modified IWG-MRT response criteria) or unacceptable toxicity requiring discontinuation of study drug (see Section 8.3). Subjects who remain on study drug past Cycle 6 will continue to be monitored by the Investigator as outlined within the protocol. Subjects will have study visits every 2 weeks (±3 days) during Cycle 1-3. For Cycles 4-5, subjects will be evaluated at the beginning of each cycle. At Cycle 6, subjects will be evaluated at the beginning and end of the cycle. An end of treatment (EOT) visit will occur in case of permanent treatment discontinuation, for whatever reason. EOT visit should be conducted within a week (allowable visit window) after treatment discontinuation. A follow-up visit should occur 30 days after the last dose of SAR302503. For subjects who continue the treatment, efficacy and safety evaluations will be continued as specified in the protocol. **Criteria for Evaluation:** **Safety:** • Evaluation based on the incidence of treatment-emergent adverse events (graded and reported using terminology from CTCAE v4.03); changes relative to baseline in clinical laboratory parameters, red blood cell and platelet transfusion requirements, vital signs and ECG. **Efficacy:** • Assessment of the primary endpoint is based on the response rate (RR), defined as the proportion of subjects who have a ≥35% reduction from baseline in volume of spleen size at the end of Cycle 6, measured by MRI (or CT scan in subjects with contraindications for MRI) by a central imaging laboratory. Detailed imaging instructions will be provided in an imaging manual provided to the sites. • Duration of spleen response, measured by MRI (or CT scan in subjects with contraindications for MRI) at Day 1 of Cycle 4, at the end of Cycle 6, at the end of every 6 cycles thereafter for two years, and at EOT. MRI (or CT scan) will be reviewed by a central imaging laboratory. • Proportion of subjects with a ≥50% reduction in length of

	spleen by palpation from baseline at the end of Cycle 6 • RR of a ≥35% reduction at the end of Cycle 3, defined as the proportion of subjects who have a ≥35% reduction from baseline in volume of spleen at the end of Cycle 3 as measured by MRI (or CT scan in subjects with contraindications for MRI) • Percent change of spleen volume at the end of Cycles 3 and 6 from baseline as measured by MRI (or CT scan in subjects with contraindications for MRI) • OS, defined as the time interval from the date of first dose to the date of death due to any cause. In the absence of confirmation of death before the analysis cut-off date, OS will be censored at the last date the subject was known to be alive or at the study cut-off date, whichever is earlier. • Rates of CR, PR, CI, SD, PD, and relapse based on modified IWG-MRT response criteria at Day 1 of Cycle 4, end of Cycle 6, at the end of each 6 cycles thereafter for two years and at EOT. Evaluation to be performed with MRI (or CT scan in subjects with contraindications for MRI) and bone marrow puncture when scheduled. • RR of a ≥25% reduction at the end of Cycle 3, defined as the proportion of subjects who have a ≥25% reduction from baseline in volume of spleen at the end of Cycle 3 as measured by MRI (or CT scan in subjects with contraindications for MRI) • Proportion of subjects who have ≥25% reduction in volume of spleen size at end of Cycle 6 as measured by MRI (or CT scan in subjects with contraindications for MRI). • The maximum months of continuous splenic response by palpation (a ≥50% reduction from baseline in spleen size) for each subject • The number of cycles (out of 6) that subjects have splenic response by palpation (a ≥50% reduction from baseline in spleen size). • Change in cytogenetics, cellularity, blast count, and degree of reticulin fibrosis in bone marrow for every subject at baseline (Cycle 1) and the end of Cycle 6, at the end of every 6 cycles thereafter for two years, and at EOT. Biopsies will be evaluated by central pathologists. If bone marrow is not available, cytogenetics can be performed from peripheral blood. **Quality of life:** • SRR: Proportion of subjects with ≥50% reduction in the total symptom score from baseline to the end of Cycle 6. This assessment will be conducted through the modified MFSAF diary. MF-associated symptoms will be recorded daily during the first 6 cycles. • Change from baseline in each individual item from the complete MPN-SAF assessment (18 MPN-specific symptoms from the MPN-SAF and 9 items assessing fatigue from the BFI questionnaire) and change from

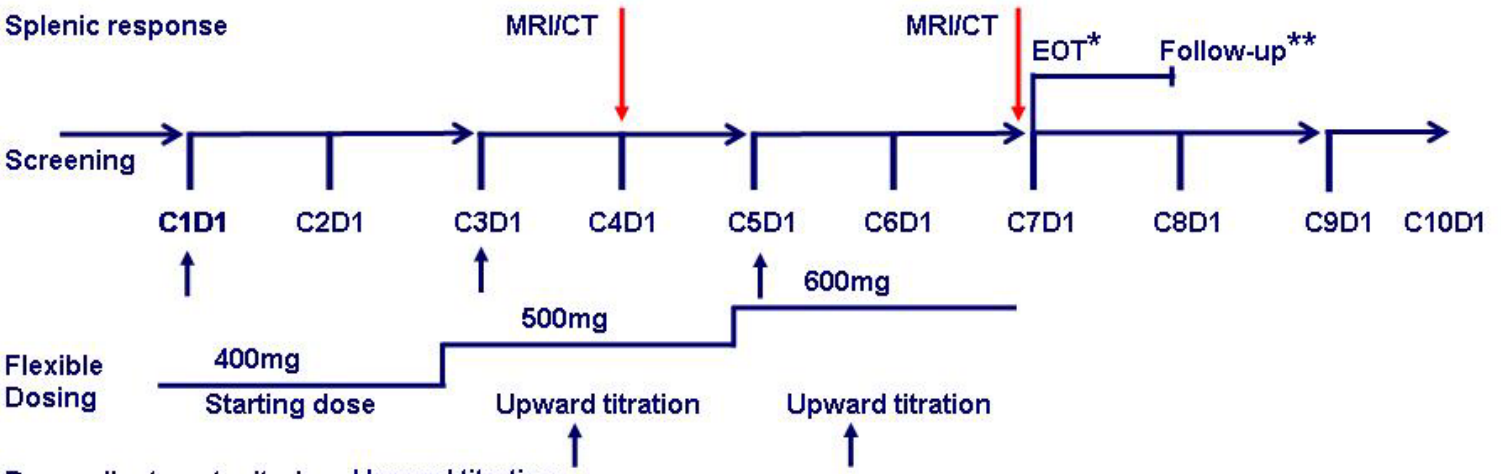
	baseline for the global Fatigue score from the BFI. These assessments will be conducted at baseline (predose, Day 1 of Cycle 1), at the end of Cycle 6, the Day 1 of Cycle 13, EOT, and the 30-day follow-up visit.. • Change on health-related QOL from baseline, measured by the EORTC QLQ C-30 and PGIC scales. The EORTC QLQ-C30 will be completed by subjects at baseline (predose, Day 1 of Cycle 1), day 1 of each treatment cycle up to Cycle 6, the end of Cycle 6, the Day 1of Cycle 13, EOT, and the 30-day follow-up visit. PGIC scale will be completed at the Day 1of Cycle 4, the Day 1 of Cycle 6, the end of Cycle 6, the Day 1 of Cycle 13, EOT, and the 30-day follow-up visit. Modified MFSAF diary will be completed using electronic diary system. All other QOL evaluations (MPN-SAF, BFI, EORTC QLQ C-30, and PGIC scale) will be performed using paper forms. **Pharmacokinetics:** • SAR302503 plasma concentrations for possible population PK analysis will be evaluated at 3 timepoints per visit from samples of blood taken on Day 1 of Cycles 1 and 2; pre-dose, between 0.5 and 2 hours and between 2.5 and 4 hours post-dose. In addition a predose blood sample will be obtained on Day 1 of Cycle 4. In case of Serious Adverse Event (SAE), a PK sample should be taken, when possible during the event. **Pharmacodynamics:** • $JAK2^{V617F}$ mutant allele in granulocytes will be measured predose at baseline for all subjects. In the subset of subjects who are positive for the mutation, $JAK2^{V617F}$ mutant allele will also be measured at Day 1 of Cycle 4 and at the end of cycle (EOC) of Cycles 6, 12, 18 and 24 and at EOT. Additional gene mutation/changes may also be analyzed for all subjects who develop disease progression. • JAK-STAT and other pathway signaling (including, but not limited to STAT3 phosphorylation) will be analyzed predose and 2.5 to 4 hours postdose on Day 1 of Cycle 1, predose on Day 1 of Cycle 2 and after disease progression (at the time of the EOT visit). **Pharmacogenomics:** • Tumor genomics analyses - Blood samples will be collected from subjects at predose on Day 1 of Cycle 1, Day 1 of Cycle 4, and at end of Cycle 6. Subtractive mutation analysis will be performed by comparing Deoxyribonucleic acid (DNA) from blood granulocytes and lymphocytes, and single cell mutation and gene expression analyses will be done in all samples, to elucidate potential mechanisms of response or resistance to JAK2-directed therapy. • Germ Line DNA

	• Saliva samples will be collected from consented subjects pre-dose on Day 1 of Cycle 1 for purposes of drug metabolizing enzyme genotyping. In addition, a second sample will be collected for possible future analysis of genes that are relevant to this disease.
STATISTICAL CONSIDERATIONS	**Sample size and power:** Primary RR: Assuming the response rate is 25%, 70 evaluable subjects will provide at least 90% power at a one-sided 2.5% alpha level to test the null hypothesis of ≤10% response rate. Based on the COMFORT1 results, approximately 60% subjects who received ruxolitinib were non responders, thus 60% of 70 evaluable subjects (42) will provide 80% power to test a response rate ≤10% for the subgroup of patients who did not reach the primary endpoint of splenic response during the ruxolitinib trials. **Analysis populations:** • Per-protocol population: This population consists of all enrolled and treated, with a baseline and first post-baseline MRI (CT in case of contraindications for MRI), and had no violation of inclusion/exclusion criteria and no other major protocol deviations. This population will be used for the primary analyses of efficacy endpoints. • All-Treated population: The all-treated population includes all subjects who were administered at least one dose (even if partial) of study medication and have at least one post-baseline safety evaluation. This population will be used for the safety analyses. This population will also be used for supportive analyses of efficacy endpoints when specified. **Analysis of the primary endpoint** • A Chi-squared test will be performed to compare the response rate to 10% at a 1-sided 2.5% alpha level. The response rates and 95% confidence intervals will be provided Analysis details related to endpoints other than the primary endpoint are included in the protocol. **Interim and final analyses:** An interim report will be prepared after approximately 1/3 of patients are enrolled and completed 3 cycles of the SAR302503 treatment; this interim report will be used for regulatory purposes. The sponsor will monitor the efficacy and safety of study drug; the trial will be stopped for futility if there is insufficient evidence of efficacy and/or unacceptable toxicity. The primary endpoint will be analyzed at the end of Cycle 6, while the study is ongoing to evaluate other efficacy endpoints (including OS) and safety.

DURATION OF STUDY PERIOD (per subject)	The expected duration of the treatment in this study is approximately 8 months, based on a maximum 28-day screening period, followed by a 6-month (6-cycle) treatment period, and an EOT visit for subjects who will not continue the treatment after completing the 6 cycles of SAR302503, or discontinue the treatment early for any reasons as well as a follow-up visit which should occur 30 days after the last administration of SAR302503. Subjects who continue to benefit clinically will be allowed to remain on SAR302503 beyond the 6-month treatment period until the occurrence of disease progression or unacceptable toxicity.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



Dose adjustment criteria •Upward titration

•< 50% reduction in spleen size by palpation, and

•No safety indication for study drug dose interruption/reduction/discontinuation

•Downward titration

•Safety indication for study drug dose interruption/reduction/discontinuation

Dose range (oral, once daily): 200mg, 300mg, 400mg, 500mg and 600mg

*Subjects who complete 6 cycles of the treatment and will not continue their treatment or discontinue the treatment early for any reasons will undergo EOT assessments within a week (allowable visit window) following the last dose of study drug.

**Follow-up visit should be conducted 30 days after the last dose of study drug.

1.2 STUDY FLOWCHART

Visit	Screening[a]	Treatment (All Visits may occur ±3 days)												Post Tx-Obs[b]
Day	-28 to -1	Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6		Cycle ≥7[c]	EOT	30 Day FU
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 1	Day1	End of cycle[d]	Day 1[d]		
Informed consent	X													
Medical history[e]	X													
IVRS[f]	X	X		X		X		X	X	X		X	X	
Prior medication history	X													
Inclusion/exclusion criteria	X													
Transfusion history[g]	X	X	X	X		X		X	X	X	X	X	X	X
Treatment:														
Study drug administration[h]		→	→	→		→		→	→	→	→	→		
Study drug dose adjustment[i]						X[i]			X[i]			X[i]		
Compliance		X	X	X		X		X	X	X	X	X	X	
Concomitant medications		X	X	X		X		X	X	X	X	X	X	X
Efficacy:														
Spleen size – palpation[j]	X	X	X	X		X		X	X	X	X	X	X	X
Spleen volume – MRI (or CT scan)[k]	X							X			X	X[k]	X	
Modified IWG-MRT response criteria[l]								X			X[l]	X	X	
Modified MFSAF diary[m]	X	X	X	X		X		X	X	X	X			
MPN-SAF and BFI[m]		X									X	X[m]	X	X
EORTC QLQ C-30[m]		X		X		X		X	X	X	X	X[m]	X	X
PGIC Scale[m]								X		X	X	X[m]	X	X

Visit	Screening[a]	Treatment (All Visits may occur ±3 days)											Post Tx-Obs[b]
Day	-28 to -1	Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6		Cycle ≥7[c]	EOT	30 Day FU
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 1	Day1	End of cycle[d]	Day 1[d]		
ECOG PS		X		X		X		X	X	X	X	X	X	X
Hospitalization data[n]	X	X[n]		X		X		X	X	X	X	X	X	X
Safety														
Body weight		X		X		X		X	X	X	X	X	X	X
Physical examination[o]	X[o]	X[o]	X	X		X		X	X	X	X	X	X[o]	X
Vital signs[p]	X	X	X	X		X		X	X	X	X	X	X	X
Clinical laboratory testing and smear[q]	X	X	X	X	X[q]	X	X[q]	X	X	X	X	X	X	X
Pregnancy test[r]	X[r]	X						X			X	X[r]	X[r]	
ECG[s]	X	X[s]		X[s]							X		X	
Adverse events		X	X	X		X		X	X	X	X	X	X	X
Biomarker														
JAK2^{V617F} allele burden[t]		X						X			X	X	X	
Bone marrow biopsy[u]	X							(X)			X	X	X	
JAK-STAT and other pathway signaling[v]		X[v]		X[v]									X[v]	
Tumor genomics analysis[w]		X												
Pharmacogenomics[x]		X												
PK[y]		X		X[y]				X[y]						

a The screening visit must occur between 1 to 28 days prior to Day 1 of Cycle 1.

b Subjects will also be followed by phone for survival every 3 months from date of treatment discontinuation up to 2 years and after 2 years, every 6 months until death. Every effort will be made to follow all enrolled subjects. If survival follow-up (SFU) is missed and is not obtained at the time of the scheduled interval, it should be obtained immediately. For subsequent SFU, the subject should be contacted at the original scheduled SFU intervals. If the subject is not reachable via phone from the Investigator or designee subject's caregiver or a family member may be contacted.

c For Cycle 7 and beyond (Cycle 10, 13, until Cycle x) at the Investigator's discretion, examinations may be performed every 3 cycles, unless otherwise specified.

d Assessments performed at the end of Cycle 6 visit do not need to be repeated at the Day 1 of Cycle 7 visit, if performed within 1 week.

e General and specific Medical history will be collected. Specific medical history will be related to the ruxolitinib prior treatment.

f IVRS will be used to allocate subject identification number, collect enrollment date, end of treatment date, and to collect the dose titration and IMP dispensing data (see IVRS user manual for details). Site staff should call IVRS at screening visit, each treatment visit, and EOT. For unscheduled visit, if dose adjustment is performed site staff should call IVRS.

g Obtain documentation of subject's prestudy transfusion requirements, including those from referring physicians/institutions, to determine pre-existing transfusion dependence. Collect at least 3 month prior transfusion history before start of the treatment. Record dates and volume (in units) of transfusions of red blood cells and platelets administered as a part of regular study visits, including documentation of transfusions obtained from subject's local institution if administered outside study physician's care. Specific values (ie, hemoglobin or platelet count) or symptoms resulting in transfusion should be recorded.

h Study drug must be taken at clinic after predose PK sampling on Day 1 of Cycles 1, 2 and 4.

i Study drug upward dose titration is permitted only after the end of Cycles 2 and 4 within the first 6 cycles of the treatment if the splenic response does not achieve a ≥50% reduction in spleen size by palpation compared to baseline and there is no unacceptable toxicity as specified in the protocol. The study drug dose can be titrated up in 100mg/day increment up to maximum dose 600mg/day. After Cycle 6, subjects will be allowed to have their dose titrated up (maximum 600mg/day) or down (minimum dose 200mg/day in accordance with their individual responses and tolerability to study drug at the discretion of the Investigator or sub-investigator based on their clinical assessment. If subjects experience drug toxicity as specified in the protocol, the dose will be downwards titrated by a 100 mg/day decrement during the study

j Every attempt should be made for all measurements to be performed by the same examiner within each subject. Spleen size should be measured by palpation at baseline (Cycle 1), Day 15 of Cycle 1, subsequently at the Day 1 of each treatment cycle, End of Cycle 6, after Cycle 6, every 3 cycles, EOT and 30 day FU.

k MRI (preferred) or CT scan (performed only in subjects with contraindications for MRI): the same method that is used at baseline (eg, MRI or CT scan) should be used consistently throughout the entire study. Every attempt should be made for all measurements to be performed by the same examiner within each subject. Evaluation must be performed within 14 days prior to initiation of dosing on Day 1 of Cycle 1 and ≥14 days following discontinuation of any prior MF drug therapy. Procedures should also be performed at Day 1 of Cycle 4, and end of Cycle 6, and at the end of every 6 cycles thereafter for up to 2 years.

l Assessment of clinical response to the treatment will be performed using the modified IWG-MRT response criteria with MRI (or CT scan in subjects with contraindications for MRI) and bone marrow puncture when scheduled. Assessment should also be performed at the end of every 6 cycles after Cycle 6 for up to 2 years

m The modified MFSAF diary will be assessed via an electronic diary. Diary must be dispensed to the eligible subject at the screening visit for use prior to Cycle 1. The eligible subjects will be also instructed to record their MF-associated symptoms daily for 7 days prior to Day 1 of Cycle 1, and daily during the first 6 cycles using MFSAF diary system. The completion of MFSAF diary will be monitored through the first 6 cycles. The MPN-SAF, BFI, EORTC QLQ C-30 and PGIC Scale are to be completed by the subjects using paper forms before any other assessments are performed by the Investigator or designee. The EORTC QLQ-C30 will be completed by subjects at baseline (predose, Day 1 of Cycle 1), day 1 of each treatment cycle up to Cycle 6, the end of Cycle 6, the Day 1 of Cycle 13, EOT, and the 30-day follow-up visit. MPN-SAF, and BFI will be completed at baseline (predose, Day 1 of Cycle 1), the end of Cycle 6, the Day 1 of Cycle 13, EOT, and the 30-day follow-up visit. PGIC Scale will be completed at the Day 1 of Cycle 4, Day 1 of Cycle 6, the end of Cycle 6, the Day 1 of Cycle 13, EOT, and the 30-day follow-up visit.

n Hospitalization data to be collected for health care consumption purposes. At baseline prior 3 months data will be collected.

o Complete physical examination will be performed at Screening, baseline and EOT. Symptom-directed examination will be performed at each visit.

p Body temperature, respiration, blood pressure, and heart rate. Height is measured only at the Day1 Cycle 1 visit.

q Hematology, coagulation, serum chemistry, and urinalysis will be performed. Note that a peripheral blood smear evaluation will also be performed at the same timepoints. On Day 15 at Cycles 2 and 3 only LFT monitoring (total bilirubin, direct bilirubin, ALT, and AST) will occur. For subjects who develop ≥Grade 3 ALT, AST, or total bilirubin elevations at any time during the study, at least weekly monitoring of LFTs must be performed until the adverse event has returned to Grade ≤1. Subjects may resume treatment after elevated LFTs have returned to Grade ≤1. If treatment is resumed, all subjects with the above mentioned elevations must have their dose reduced by 1 dose level. The monitoring of AST, ALT and bilirubin (total and direct) must be performed every 2 weeks for at least the 3 subsequent treatment cycles. If at any time during the study a subject develops ≥Grade 2 total bilirubin, the fractionated (direct and indirect) bilirubin must be recorded.
Hematology: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, platelet count, white blood cell count (absolute and percentage), differential cell count (percentage; neutrophils, lymphocytes, monocytes, eosinophils, and basophils), blasts (absolute and percentage), and reticulocyte count (absolute); peripheral blood smear: total cell count, blast cells, nucleated erythrocytes, myelocytes, metamyelocytes, and promyelocytes. Coagulation: prothrombin time and activated partial thromboplastin time. Blood chemistry: total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, amylase, lipase, total protein, albumin, globulin, sodium, potassium, chloride, calcium, phosphate, glucose, blood urea nitrogen or urea, creatinine, and uric acid. Urinalysis**:** pH, protein, and blood. In patients taking sensitive substrates for metabolism by CYP3A4 (but have a wider therapeutic range), close monitoring of laboratory parameters is recommended (see Section 8.10)

r Serum pregnancy test will be performed at screening and EOT. Urine or serum pregnancy test will be performed on Day 1 of Cycle1, Day 1 of Cycle 4, the end of Cycle 6 and every 6 cycles thereafter.

s ECG evaluation will be performed at screening, pre dose, and 2 hours post dose on Day 1 of Cycle 1 and Day 1 of Cycle 2. ECG evaluation will be also performed at the end of Cycle 6 and EOT. Additional tests should be performed if clinically indicated. Three ECGs, ~1-2 minutes apart, should be performed at each time point. Copies of all ECGs will be collected by the sponsor.

t On Day 1 of Cycle 1, predose whole blood samples will be collected from all subjects and $JAK2^{V617F}$ mutant allele burden in granulocytes will be measured. In the subset of subjects who are positive for the mutation, additional samples will be collected on Day 1 of Cycle 4 and at the end of Cycles 6, 12, 18 and 24, and EOT. A blood sample will be collected for all subjects who develop disease progression, and additional gene changes may also be analyzed.

u Bone marrow biopsy for baseline evaluation must be performed within 3 months prior to the first dose of SAR302503 and ≥14 days following discontinuation of any prior MF drug therapy. A 14 day restriction period is not applicable to patients treated with ruxolitinib or hydroxyurea. It is encouraged that biopsy is performed during the 28-day screening period. If subjects have their last bone marrow biopsy performed outside the study center, but within the specified period above and they can provide the biopsy specimens or slides to the selected central laboratory for central pathology evaluations, the evaluation results may be used as baseline. Biopsy on Day 1 of Cycle 4 is optional, but it is highly encouraged. Biopsy should also be performed at the end of cycle 6, and at the end of every 6 cycles thereafter for two years. The bone marrow evaluation includes assessment of cytogenetics, cellularity, reticulin fibrosis, and blasts. If biopsy is not feasible, cytogenetics can be obtained from peripheral blood.

v (Optional) Whole blood samples will be taken predose and 2.5 to 4 hours postdose on Day 1 of Cycle 1, predose on Day 1 of Cycle 2 and EOT (in case of disease progression). See Study Reference Manual for sample preparation and handling.

w Blood samples will be collected pre-dose on Day 1 of Cycle 1 (23 mL), Day1 of Cycle 4 (6 mL), and at the end of Cycle 6 (6 mL). Granulocyte-specific mutations will be identified by comparing gene sequences in granulocytes and in lymphocytes. Single cell gene mutation and MPN clonal evolution as well as gene expression changes will be analyzed.

x Pharmacogenomic saliva samples will be collected predose for all consenting subjects. A separate Informed Consent Form (ICF) will be provided.

y Blood samples (2 ml) will be collected for plasma drug concentration analyses at 3 time points per visit on Day 1 of Cycle 1 and Day 1 of Cycle 2. One blood sample needed to be taken predose and the second taken between 0.5 and 2 hours and the third sample taken between 2.5 and 4 hours postdose. One predose sample should be taken on Day 1 of Cycle 4.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse events of special interest
ALL	acute lymphocytic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	all treated
BFI	brief fatigue inventory
CI	clinical improvement
CR	complete remission
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
DR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EOC	end of cycle
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
ET	essential thrombocythemia
IB	Investigator's Brochure
ICF	informed consent form
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK2	Janus kinase 2
LFT	liver function test
MDS	myeloplastic syndrome
MF	myelofibrosis
MFSAF	myelofibrosis symptom assessment form
MPN	myeloproliferative neoplasm

MPN-SAF	myeloproliferative neoplasm symptom assessment form
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
OS	overall survival
PD	progressive disease
PCSA	potentially clinically significant abnormalities
PGIC	patient's global impression of change
PK	pharmacokinetic
PMF	primary myelofibrosis
Post ET-MF	post-essential thrombocythemia myelofibrosis
Post PV-MF	post-polycythemia vera myelofibrosis
PR	partial remission
PS	performance status
PV	polycythemia vera
QOL	quality of life
RBC	red blood cell
RR	response rate
SAE	serious adverse event
SD	stable disease
SFU	survival follow-up
SRR	symptom response rate
TEAE	Treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell

4 INTRODUCTION AND RATIONALE

Myelofibrosis (MF) presents as primary myelofibrosis (PMF), Post-polycythemia vera (PV) MF and Post-essential thrombocythemia (ET) MF. It is a BCR ABL1-negative myeloproliferative neoplasm (MPN).

PMF is a chronic myeloproliferative disorder characterized by a clonal proliferation involving pluripotent hematopoietic stem cells and clonal cell–derived cytokines. As a consequence, subjects typically present with cytopenias (anemia, thrombocytopenia, leucopenia) and/or variable degrees of thrombocytosis or leukocytosis, debilitating constitutional symptoms, such as weight loss, fatigue, night sweats, pruritus and cough as well as extramedullary hematopoiesis resulting in marked splenomegaly. Primary myelofibrosis usually affects subjects with advanced age but is occasionally seen in young subjects. Current approved drug therapy for PMF, such as erythropoiesis stimulating agents or hydroxyurea, have not been shown to influence survival and are often used for palliative purposes only. Allogeneic stem cell transplantation, which is so far the only curative option, carries high mortality and morbidity and is precluded by age, poor performance status (PS) and co-morbidities (3).

Janus kinase 2 (JAK2) mutations were described in approximately 50% of subjects with PMF. It is also expressed in 95% of the PV subjects and in 50% of essential thrombocythemia (ET) subjects. However, the contribution of these mutations is currently not yet understood. Still, certain mutations directly (eg, JAK2 or MPL mutations) or indirectly (eg, LNK or CBL mutations) induce JAK-STAT hyperactivation and lead to myeloproliferative syndrome associated features (4). It is therefore reasonable to target JAK2 as a treatment for this disease (5).

Several JAK inhibitors currently in development have been shown to relieve MF-related symptoms. The leading compound is ruxolitinib. Ruxolitinib (INCB018424), a selective JAK1 and JAK2 inhibitor, has been evaluated in subjects with PMF, Post PV-MF or Post ET-MF. Ruxolitinib-treated subjects experienced significant reductions in splenomegaly and improvement in symptoms and in measures of overall quality of life (QOL) compared to subjects treated with placebo or best available therapy (BAT) (6,7). Although no survival benefit has been proven, JAK appears to be a valid target to manage disease symptoms. In Comfort I, a placebo controlled Phase 3 study, 41.9% of ruxolitinib-treated subjects achieved a 35% or greater reduction in spleen volume at 24 weeks, which was defined as the study primary endpoint (6). In Comfort II, a BAT controlled Phase 3 study, 28.5% of ruxolitinib-treated subjects achieved a 35% or greater reduction in spleen volume at Week 48, which was defined as the study primary endpoint. At Week 24, 31.9% of ruxolitinib-treated subjects achieved the criterion splenic response (7). Overall, ruxolitinib had an acceptable safety profile as compared with placebo and BAT. The most common adverse events (AEs) were anemia (Grade 3/4: ~45%) and thrombocytopenia (Grade 3/4: ~10%). The discontinuation rate was 14% to 18% overall, and the AE rate was 8% to 11% (6,7). Ruxolitinib treatment has been restricted to a subject population with platelet counts at least above 100 x 10^9/L. Ruxolitinib dosing has been also limited to thrombocytopenia. If platelet counts fall below 100 x 10^9/L during the treatment, a dose reduction is required. If platelet counts

fall below <50 x 10^9/L, dosing has to be stopped. This indicates some subjects need other options to manage their disease-related symptoms or to improve their response to treatment.

Risk stratification in PMF has been described by Cervantes et al. (8). Causes of death in subjects with MF include leukemic transformation, disease progression without leukemic transformation, thrombosis, cardiovascular complications and infection. The International Prognostic Scoring System uses variables obtained at time of diagnosis. The same prognostic variables are used to stratify subjects seen at any time during the course of their disease. Variables include age >65, constitutional symptoms, hemoglobin <10 g/dl, a white blood cell (WBC) count >25 x 10^9/L or blood blasts ≥1%. On the basis of the presence of zero (low risk), one (intermediate risk-1), two (intermediate risk-2), or three (high risk) of these variables, four risk groups have been defined. These risk factors were subsequently validated showing a median overall survival (OS) of 2.3 years in the high risk group and 4 years in the intermediate-2 risk group. Subjects in the intermediate-1 and low risk groups showed a longer OS of 7.4 years and 14.6 years, respectively. Post ET-MF and post-Post PV-MF are both clinically indistinguishable entities from PMF but develop due to the fact that subjects are experiencing fibrotic transformation from prior PV and ET (9).

4.1 SAR302503

SAR302503 (previously referred to as TG101348) is a protein kinase inhibitor and a selective JAK2 inhibitor. Unlike ruxolitinib, which is a selective JAK1 and JAK2 inhibitor, SAR302503 inhibited enzyme activity of four kinases by 50% (IC50) at concentrations of <25 nM. These kinases included three variants of JAK2 (JAK2 JH1 JH2 V617F, JAK2 JH1 JH2 and JAK2 JH1) and MFS-like tyrosine kinase (FLT3). In the kinase screen focused solely on Janus family kinases, SAR302503 was 36-, 76-, and 136-fold more potent against JAK2 than JAK1, JAK3, and TYK2 (ie, tyrosine kinase 2), respectively. Taken together, the kinase screens with SAR302503 revealed that it potently and selectively inhibits JAK2 and FLT3, which are important targets in the treatment of hematological malignancies. SAR302503 is being developed as an orally available treatment for MF.

In vitro, SAR302503 shows dose-dependent inhibition of JAK2-induced proliferation and induction of apoptosis in human erythroid leukemia cells at concentrations associated with inhibition of phosphorylation of the JAK2 substrate, STAT5(10) . SAR302503 demonstrated dose dependent inhibition of stem cell colony formation selectively for subject-derived stem cells expressing a mutation in the tyrosine kinase, JAK2, that results in a substitution of valine for phenylalanine at codon 617 of JAK2 ($JAK2^{V617F}$) (<300 nM), with no effect on JAK2wild type (300 nM). In vivo models show dose-dependent efficacy with increased survival in a mouse Ba/F3: $JAK2^{V617F}$ circulating tumor cell model (11,12). SAR302503 treatment resulted in dose dependent inhibition of tumor growth in a mouse human erythroid leukemia xenograft model (13). However, in vivo Phase 1 data has shown a clinical effect of SAR302503 independent of the JAK2 mutational status (14).

Refer to the Investigator's Brochure (IB) for a complete summary of nonclinical experience with SAR302503.

4.2 RATIONALE

4.2.1 Study rationale

Two studies with SAR302503 have targeted the population of combined primary and secondary MF subjects. The clinical presentation and the involvement of exaggerated JAK2 function are common to primary and secondary forms of the disease and thus subjects with both types were included.

The first study (MF-TG101348-001, completed on October 22, 2009) was a Phase 1, multicenter, open-label, non-randomized, dose-escalation study of SAR302503 in subjects with primary and secondary MF. SAR302503 (at doses of 30, 60, 120, 240, 360, 520, 680, and 800 mg/day) was administered orally on a daily basis, in consecutive 28-day cycle, for a maximum of 24 weeks (6 cycles of therapy).

The second study (MF-TG101348-002, currently ongoing) is an open-label extension of Study MF-TG101348-001 in subjects with primary or secondary MF who completed 6 cycles of treatment in the primary study. The primary objective of this study is to determine the long-term effects of continued treatment with SAR302503 on safety, clinical activity, and pharmacodynamics in subjects with primary or secondary MF who have stable disease (SD), clinical improvement (CI), partial remission (PR) or complete remission (CR) per the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) response criteria in the group of subjects who tolerated SAR302503 treatment in the MF-TG101348-001 study.

The completed dose-escalation study MF-TG101348-001 also contained an expanded cohort at the maximum tolerated dose (MTD). In the dose-confirmation phase, SAR302503 was administered orally once daily in consecutive 28-day cycles. A total of 59 subjects were enrolled into the MF-TG101348-001 study. These were subjects with either Mayo PSS high-risk MF or intermediate risk type-2 MF that was accompanied by either symptomatic splenomegaly or was unresponsive to available therapy. In total, 28 subjects were studied in the dose-escalation phase and 31 subjects were studied in the dose-confirmation phase. A total of 44 subjects completed the study. In both portions of the study, a maximum of 6 cycles of SAR302503 was administered. Subjects who completed 6 cycles without progression or unacceptable toxicity were allowed to continue on to the ongoing extension study (MF-TG101348-002). In the dose-escalation phase, escalation to the highest tolerated dose was permitted after completion of at least 3 cycles of treatment at the starting dose, in the absence of disease progression or unacceptable toxicity. SAR302503 doses ranging from 30 mg/day to 800 mg/day were evaluated in the dose-escalation phase and dose-limiting toxicity was observed at 800 mg/day. The MTD of SAR302503 was identified as 680 mg/day, and the dose-confirmation phase of the study was performed at this dose.

Pharmacokinetic findings:

Following oral administration on Day 1, SAR302503 plasma concentrations were quantifiable at the first sampling time (0.5 hours). Plasma levels increased and reached peak values within 2 to 4 hours after administration; then decreased in an apparently multi-exponential manner. On Day 28 sampling, the predose concentrations signified the accumulation of repeated doses of SAR302503. (Ratios of Day 28 and Day 1 pharmacokinetic (PK) parameters were 1.25 – 4.06 and 2.49 – 5.29 for C_{max} and AUC0-tau, respectively, based on the mean values.) The concentration reached peak levels approximately around the same interval as Day 1, and eliminated in an apparent multi-exponential fashion. Mean Cmax and $AUC_{0\text{-}tau}$ for SAR302503 on both Day 1 and Day 28 increased with increasing SAR302503 dose. SAR302503 exposure increased in a greater than dose proportional manner over the entire 27-fold dose range of 30 to 800 mg (ie, 53.5-fold increase in C_{max} and 87.8-fold increase in $AUC_{0\text{-}tau}$) on Day 28. The variability in plasma concentrations was high, possibly due in part to the small groups of subjects that made up most of the cohorts.

Clinical experience and clinical safety profile

Please refer to the current version of the IB for additional details of the clinical experience with SAR302503.

The first study (TED12037) was a Phase 1, multicenter, open-label, non-randomized, dose-escalation study of SAR302503 in subjects with primary and secondary MF. SAR302503 (at doses of 30, 60, 120, 240, 360, 520, 680, and 800 mg/day) was administered orally on a daily basis, in consecutive 28-day cycle, for a maximum of 24 weeks (6 cycles of therapy). The completed dose-escalation study also contained an expanded cohort at the maximum tolerated dose (MTD). In the dose-confirmation phase, SAR302503 was administered orally once daily in consecutive 28-day cycles. A total of 59 subjects were enrolled into this study. In total, 28 subjects were studied in the dose-escalation phase and 31 subjects were studied in the dose-confirmation phase. A total of 44 subjects completed the study. The dose-limiting toxicity in 2 of 6 subjects treated at 800 mg/day was asymptomatic, reversible Grade 3 or 4 hyperamylasemia (with or without hyperlipasemia). The MTD of SAR302503 was identified as 680 mg/day, and the dose-confirmation phase of the study was performed at this dose.

The second study (TED12015, currently ongoing) is an open-label extension of Study MF-TG101348-001 in subjects with primary or secondary MF who completed 6 cycles of treatment in the primary study. 43 of the 44 eligible subjects rolled over into this study. As of October 31, 2012, 12 subjects are still ongoing with a median of 3.5 years.

The most common adverse events (AEs), regardless of causality, reported in $\geq$ 10 % of subjects have been anemia, thrombocytopenia and platelet count decreased, neutropenia, fatigue, diarrhea, nausea, vomiting, constipation, abdominal pain, flatulence, peripheral edema, increased ALT, increased AST, increased creatinine, increased alkaline phosphatase, increased lipase and hyperlipasemia, hypocalcemia, anorexia, hyperkalemia, muscle spasms, headache, dyspnea, dry sin, pruritis, rash, contusion, and skin exfoliation.

The most frequent AEs assessed by investigators as related to SAR302503 were anemia, thrombocytopenia, abdominal pain, diarrhea, nausea, vomiting, peripheral edema, incease AST, increased ALT, increased alkaline phosphatase, increased blood creatinine, elevated lipase, hyperlipasemia, anorexia, hypocalcemia, and dry skin. Grade 3 or 4 events assessed by investigators as related to SAR302503 were anemia, thrombocytopenia, diarrhea, nausea, vomiting, increased ALT, increased AST, increased lipase, hyperlipasemia, and hypocalcemia.

A total of 96 SAEs have been reported, of these 34 were assessed as related to SAR302503 by investigator/company. The most frequent SAE's considered related to SAR302503 were anemia, thrombocytopenia, diarrhea, nausea, vomiting, dehydration, and hyperlipasemia.

Of note, one subject experienced an SAE of Grade 4 AST, ALT and bilirubin elevation and went into hepatic failure. SAR302503 was discontinued and the subject was treated with steroids and has recovered from this event. Despite thorough evaluation, no other (non-drug) cause could found for this event and was considered a Hy's law event.

There have been two fatal SAEs reported that were considered related by the investigators. One was an elderly female with history of hypertension and stroke who was found by paramedics unresponsive in a slow moving car in cardiac arrest, with hypoxemia with cyanosis. She was seen in clinic on the same day before the event occurred and was clinically stable with normal sinus rhythm, and no prolonged QT interval on three ECGs. She was given 2 units of packed red blood cells before being discharged home. In the ICU following admission, she had bilateral pulmonary edema, right pneumothorax, ejection fraction about 20%, elevated troponin values, and died of respiratory failure two days after the event. The second subject was an elderly male who was discontinued from study due to depression. Twelve weeks later, the subject died as a result of suicide.

In ad-hoc analysis, using the common terminology criteria for adverse events (CTCAE) grading system, baseline hemoglobin levels were characterized as Grades 1, 2 or 3. There were no subjects with Grade 4 at study entry. Over 6 cycles of treatment, there were no marked changes in median hemoglobin for each grade category as compared with baseline median hemoglobin levels. These observations were consistent for both overall and MTD cohorts. The median or mean dose levels in both groups over 6 cycles were stable. This suggests that the most subjects, including those with low hemoglobin at baseline, tolerated the treatment well.

Thirty-seven subjects did not meet the definition of transfusion dependence at baseline (IWG-MRT definition). After receiving SAR302503 treatment, 18 of these 37 subjects were considered to be transfusion dependent (defined as ≥2 transfusions over 6 consecutive cycles). Of these 18 subjects, 83% (15/18) had any grade anemia at baseline and 72% (13/18) had Grade 2 or 3 anemia at baseline (2 with Grade 1, 9 with Grade 2 and 4 with Grade 3). Only 3 subjects with normal hemoglobin required red cell transfusion: one was treated with 520mg of SAR302503 and 2 were in the MTD cohort. Although the subjects required transfusion, 72% (13/18) had completed their 6 cycles of the treatment, including 11 subjects who were in MTD cohort.

Using a similar approach for grouping subjects, baseline platelet counts were characterized as $\geq 100 \times 10^9$/L or $\geq 50 \times 10^9$/L and $<100 \times 10^9$/L. There were no subjects with platelet counts $<50 \times 10^9$/L at the study entry. Over 6 cycles of treatment, there were no marked changes in

median platelet count for either category, as compared with baseline median platelet counts for both overall and for the MTD cohort. The median or mean dose levels in both groups over 6 cycles were stable. This suggests that the most of the subjects, including those with platelet counts <100 x 10^9/L at baseline, tolerated the treatment well. This feature will give a treatment option for subjects with platelet counts ≥50 x 10^9/L and <100 x 10^9/L and not eligible for receiving ruxolitinib treatment.

Using the CTCAE grading system, baseline platelet levels were characterized as Grades 1, 2 or 3. There were no subjects with Grade 4 at study entry. Six subjects in the MTD cohort experienced Grade 3 thrombocytopenia, 2 had Grade 2 thrombocytopenia, 3 had Grade 1 thrombocytopenia and 1 had normal platelet counts at baseline. Three subjects developed Grade 4 thrombocytopenia during the treatment; at baseline, 1 had Grade 1 thrombocytopenia and 2 had Grade 2 thrombocytopenia. No subject who had a normal platelet count in the MTD cohort experienced Grade 4 thrombocytopenia.

Responses

The following efficacy findings refer to studies MF-TG101348-001 and MF-TG101348-002.

Splenomegaly: The onset of spleen response was rapid and generally seen within the first 2 cycles. By Cycle 6, 36 subjects (61%) experienced a ≥25% decrease in palpable spleen size, including 65% in the MTD cohort (intent-to-treat analysis). By this time point, a >50% decrease in palpable spleen size persisting for at least 8 weeks (ie, CI per IWG-MRT response criteria) had been observed in 39% and 45% of subjects overall and in the MTD cohort, respectively. Three (75%) of 4 subjects with $JAK2^{V617F}$–negative MF who completed 6 cycles of treatment achieved CI. The lowest starting dose at which CI was observed was 240 mg/day. The median time to CI across doses was 141 days (range: 41 to 171 days) and was 113 days (range, 41 to 170 days) for the MTD cohort. By Cycle 12, spleen responses (CI) were observed in 47% and 50% of subjects for the overall and MTD cohorts, respectively. The mean duration of spleen response per IWG-MRT response criteria was 315 days (standard deviation, 129 days) and 288 days (76 days) for the overall and MTD cohorts, respectively.

Reduction of splenomegaly was very durable. The data from the Phase 1 (MF-TG101348-001) and extension studies (MF-TG101348-002) indicate that a majority (68%) of subjects continued on study for at least 12 treatment cycles. At data cutoff, the number of treatment cycles completed ranged from 7 to 29; 39 (66%) subjects, including 27 (68%) from the MTD cohort, completed 12 treatment cycles. At data cutoff, 28%, and 14% of subjects who entered the extension study had completed 18 and 24 treatment cycles, respectively.

In ad-hoc analysis, in MTD cohort, eighty percent of subjects (4 out of 5) with platelet counts ranging between 50 x 10^9/L and <100 x 10^9/L achieved the splenic response. Sixty-two percent of subjects (18 out of 21) who had platelet counts >100 x 10^9/L achieved the splenic response. The new data for SAR302503 suggests that subjects with platelet counts ≥50 x 10^9/L and <100 x 10^9/L, who are not eligible for treatment with ruxolitinib, would benefit from treatment with SAR302503.

Constitutional symptoms: Thirty-five subjects in the MTD cohort rated the presence and severity of early satiety, fatigue, night sweats, cough, and pruritus on an 11-point scale (0 = absence of symptoms to 10 = worst imaginable symptoms) at baseline and at the end of at least one cycle. Symptoms were categorized as absent (score = 0), mild (score = 1 to 3), moderate (score = 4 to 7), or severe (score = 8 to 10). Early satiety was reported by 29 (85%) subjects at baseline. After 2 cycles of treatment (n = 27), 56% reported complete resolution of this symptom. Fatigue was reported at baseline by 26 (76%) subjects. After 6 cycles (n = 16), 63% reported improvement, and 25% reported complete resolution of this symptom. Night sweats were reported at baseline by 14 (40%) subjects. After 1 cycle, 64% of subjects had complete resolution of this symptom; after 6 cycles, this proportion had increased to 89% (n = 9). Cough was reported at baseline by 13 subjects (37%). After 1 cycle (n = 12), 75% reported improvement and 67% reported complete resolution of this symptom. Pruritus was reported by 8 (23%) subjects at baseline. After 1 cycle, 75% had improvement and 50% reported complete resolution. Responses in constitutional symptoms were durable in most instances.

In MTD cohort, all the subjects (4/4) with platelet counts ranging between 50 x 10^9/L and <100 x 10^9/L achieved a ≥50% reduction in total symptom score. Sixty-seven percent of subjects (10 out of 15) who had platelet counts >100 x 10^9/L achieved the symptom response.

Body weight: At the end of 6 and 12 cycles, the median body weight was stable relative to baseline for the overall and MTD cohorts.

Leukocytosis and thrombocytosis: Leukocytosis (WBC >11 X 10^9/L) was present at baseline in 33 (56%) subjects, 28 of whom completed six cycles of treatment; of these, 18 were in the MTD cohort. After 6 cycles, 16 (57%) subjects across doses and 13 (72%) subjects in the MTD cohort achieved a normal WBC; after 12 cycles, 14 (56%) of 25 subjects across doses and 10 (59%) of 17 in the MTD cohort had normal WBC levels.

Thrombocytosis (platelet count >450 X 10^9/L) was noted at baseline for 10 (17%) subjects across doses and for 7 (19%) subjects in the MTD cohort (n = 37), all of whom completed 6 cycles of therapy. At this time point, 90% and 100% of subjects across doses and in the MTD cohort, respectively, achieved a normal platelet count; after 12 cycles, 7 (88%) of 8 subjects across doses and all 6 subjects in the MTD cohort had a normal platelet count.

$JAK2^{V617F}$ allele burden: Fifty-one subjects (86%) were $JAK2^{V617F}$ positive and had a median allele burden of 20% (range, 3% to 100%). Of these, 23 (45%) had a significant allele burden (defined as 20% at baseline) with a median of 60% (range, 23% to 100%). For the overall mutation-positive subjects, there was a significant decrease in the $JAK2^{V617F}$ allele burden after both six cycles (P = .04) and 12 cycles of treatment (P=.01). After six and 12 cycles of treatment, the median allele burdens were 17% (range, 0% to 100%) and 19% (range, 0% to 100%), respectively. Similarly, for the 23 subjects with baseline $JAK2^{V617F}$ allele burden of greater than 20%, there was a significant and even more pronounced decrease in the $JAK2^{V617F}$ allele burden after six cycles (P =.002) and 12 cycles of treatment (P = .002). After six and 12 cycles of treatment, the median allele burdens were 31% (range, 4% to 100%) and 32% (range, 7% to 100%), respectively. After six cycles, 16 out of 20 (80%) subjects with baseline allele burden greater than 20% and who reached this time point exhibited a median 61% (range, 6% to 96%) decrease, and nine subjects (45%) had a 50% decrease. In contrast, four subjects (20%) exhibited an increase (one each with increase of 18%, 21%, 30%, and 58%). Eighteen subjects (78%) of the group with allele burden greater than 20% completed 12 cycles of treatment with a median 50% (range, 29% to 82%) decrease, and seven (39%) subjects had a 50% decrease in $JAK2^{V617F}$. Three subjects (17%) exhibited an increase in allele burden (one each with increase of 7%, 18%, and 22%), and two others with 100% allele burden at baseline exhibited no change (14).

No $JAK2^{V617F}$ allele burden reduction has been observed in other JAK2 inhibitors. The effects of SAR302503 on $JAK2^{V617F}$ allele burden suggests that it may provide unique and additional benefits to MF subjects.

Design Rationale

The proposed trial is a Phase 2, multicenter, open label, single arm study of SAR302503 in subjects 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. The objectives of the study include the following

Primary Endpoint is response rate (RR), defined as the proportion of subjects who have a ≥35% reduction from baseline in volume of spleen size at the end of Cycle 6 as measured by magnetic resonance imaging (MRI) (or computed tomography [CT] scan in subjects with contraindications for MRI).This was chosen based on the feedbacks from regulatory agencies. One of secondary efficacy endpoint is symptom RR (SRR), defined as proportion of subjects with a ≥50% reduction in the total symptom score from baseline to the end of Cycle 6 using the modified myelofibrosis symptom assessment form (MFSAF) diary. This endpoint has been used as a key secondary endpoint for ruxolitinib Phase 3 studies.

SAR302503 potently and selectively inhibits JAK2 and FLT3, important targets in the treatment of hematological malignancies. In contrast, Ruxolitinib is not markedly active against FLT3. $JAK2^{V617F}$ allele-burden was decreased significantly after either 6 or 12 cycles of SAR302503 treatment in mutation-positive subjects. Forty-five percent of subjects in the MTD cohort who completed at least 6 cycles of therapy and who had baseline allele-burden values >20% had a ≥50% reduction in JAK2V617F allele-burden at the end of Cycle 6. Subjects tolerated SAR302503 treatment well: over 6 cycles of treatment, the median platelet counts or hemoglobin levels for the CTCAE categories remained stable. Subjects with platelet counts ranging between

50 x 109/L and 100 x 109/L had similar splenic and SRRs as subjects who had platelet counts >100 x 109/L. This indicates that SAR302503 was well-tolerated and effective in reducing spleen size and improving MF symptoms. MF is a devastating disease with limited therapy options, representing a significant unmet medical need. For patients who cannot tolerate, or respond poorly to ruxolitinib or have disease progression after receiving ruxolitinib treatment, SAR302503 may represent a useful treatment option.

Based on the efficacy, safety, and PK data of the Phase 1/2 studies, SAR302503 will be orally self-administered on an outpatient basis, once daily in consecutive 28 day cycles. A flexible dosing regimen may be employed to optimize efficacy and to minimize drug toxicity for individual subjects. The starting dose is 400mg/day. This dose falls within the clinically effective dose range (240 mg to 520 mg) observed in the Phase 1/ 2 study. The dose range is 200 mg to 600mg/day (100 mg increments). This range is within the range that was tested in the Phase 1/2 study. The study drug dose can be titrated up in 100 mg/day increments to a maximum 600 mg/day based on the splenic response. Within the first 6 cycles of the treatment, study drug dose titration is permitted only after the end of cycles (EOCs) 2 and 4 if the splenic response does not achieve a ≥50% reduction in spleen size by and there is no unacceptable drug toxicity as specified in the protocol. The 2 cycle interval was chosen because the median time to a 50% reduction in spleen size was found to be 2 cycles in the Phase 1/2 study. If subjects experience drug toxicity as specified below, the dose can be down titrated by a 100 mg/day to a minimum of 200mg/day.

As of September 2012, approximately 290 subjects have been treated with SAR302503 as a single agent.

Amendment rationale

The trial sample size is being increased in an attempt to provide sufficient statistical power (at least 90%) for testing response rate beyond a clinically important threshold: 10% response rate; for this other JAK2 treatment - refractory population; in addition, the increased sample size allows sufficient evaluations for subgroups. Seventy evaluable subjects will provide at least 90% power at a one-sided 2.5% alpha level to test the null hypothesis of ≤10% response rate; and approximately 70*0.6= 42 evaluable subjects will provide 80% power to test a response rate ≤10% for the subgroup of patients who did not reach the primary endpoint of splenic response during the JAKAFI trials.

The inclusion of subjects who are intolerant to or allergic to ruxolitinib, or who are categorized as intermediate – 1 with symptoms, will expand the population to be studied for this protocol.

The risk classification algorithm for MF is being changed from the original International Prognostic Scoring System to the newer Dynamic International Prognostic Scoring System (Passamonti et al., Blood 2010 (1). The former is a point-in-time assessment that is validated for use at the time of initial MF diagnosis, while the latter is usable during the disease course. Since the current trial enrolls subjects who have been previously diagnosed with MF and have already undergone treatment, the dynamic risk classification scoring system is the most appropriate for use in the Inclusion Criteria.

The wash-out period of ruxolitinib before taking the first dose of SAR302503 is reduced from 30 days to 14 days and wash-out period of hydroxyurea before taking the first dose of SAR302503 is reduced from 14 days to 1 day due to short half-life period of each drug.

During the screening period, assessment of bone marrow in <14 days after discontinuing ruxolitinib or hydroxyurea is allowed. It is unlikely that ruxolitinib and hydroxyurea affect bone marrow architecture in MF patients in such a short duration; therefore patients may undergo bone marrow biopsy during the screening period while taking ruxolitinib and/or hydroxyurea.

Based on the recent information, SAR302503 is likely a moderate-to-potent inhibitor of CYP3A4. Thus, the concomitant medication section is amended.

Tumor genomics: An additional whole blood sample (6 mL) will be collected pre-dose at baseline (Cycle 1/Day 1), at Cycle 4 Day1 and at the end of Cycle 6 to analyze potential molecular pathways associated with response/resistance to JAK2 treatment. Mutation analysis will be performed on MPN-related genes in progenitor cells at single cell level to determine clonal architecture of PMN and its evolution during SAR302503 treatment. Changes in gene expression will also be analyzed using nucleic acids extracted from the sample.

5 STUDY OBJECTIVES

5.1 PRIMARY

- To evaluate the efficacy of once daily dose of SAR302503 in subjects 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 based on the reduction of spleen volume at the end of 6 treatment cycles.

5.2 SECONDARY

- To evaluate the effect of SAR302503 on MF associated symptoms as measured by the MFSAF diary.
- To evaluate the durability of splenic response
- To evaluate the splenic response to SAR302503 by palpation at the end of Cycle 6
- To evaluate the splenic response to SAR302503 at the end of Cycle 3
- To evaluate the effect of SAR302503 on the $JAK2^{V617F}$ allele burden
- To evaluate the safety and tolerability of SAR302503 in this population
- To evaluate plasma concentrations of SAR302503 for population PK analysis, if warranted

5.3 EXPLORATORY OBJECTIVES:

- To evaluate the Overall Survival
- To evaluate efficacy, as measured by the rates of CR, PR, CI, SD, progressive disease (PD), and relapse, based on the modified response criteria of the IWG-MRT (Appendix A).
- To evaluate the splenic response defined as a ≥25% reduction from baseline
- To evaluate durable splenic response, as measured by the number of cycles (out of 6) that subjects have a splenic response by palpation
- To evaluate durable symptom response, as measured by the number of cycles (out of 6) that subjects have a symptom response using the modified MFSAF
- To evaluate the effect of SAR302503 on bone marrow with regard to cytogenetics, cellularity, blast count, and the grade of reticulin fibrosis
- To evaluate PK-pharmacodynamics of plasma SAR302503 exposure versus spleen volume
- To evaluate the effect on health-related QOL using European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and patient's global impression of change (PGIC) scale

- To evaluate the effect on additional MPN-associated symptoms, as measured by the MPN-symptom assessment form (SAF) and brief fatigue inventory (BFI)
- To evaluate the effects of SAR302503 on JAK-STAT and other signaling pathways
- To identify tumor-specific gene mutations and other molecular changes that may correlate with response or resistance to JAK2-directed therapy by subtractive mutation analysis.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is a phase 2, multicenter, open label, single arm study of SAR302503 in subjects 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 (Appendix B, Appendix C).

This study consists of Screening, Treatment and Post-treatment observation visits. The screening period is up to 28 days. Following the screening period, eligible subjects will receive 400 mg/day of SAR302503 as starting dose on Day 1 of Cycle 1. A flexible dosing regimen may be employed to optimize efficacy and to minimize drug toxicity for individual subjects. If there is lack of adequate splenic response (≥50% splenic size reduction by palpation compared to baseline) and there is no unacceptable drug toxicity, the study drug dose can be titrated upwards in 100 mg/day increments up to maximum of 600 mg/day only after the EOCs 2 and 4 within the first 6 cycles of the treatment. If there is toxicity, the study drug dose will be titrated downwards in 100 mg/day decrements to a minimum of 200 mg/day. The dose range is from 200 mg to 600 mg per day. Patients who don't tolerate 200 mg dose must discontinue after 2 cycles at 200 mg.

SAR302503 will be self-administered orally on an outpatient basis once a day for at least 6 consecutive 28-day cycles. Subjects will continue to receive SAR302503 for as long as they are benefiting and have not experienced disease progression or unacceptable toxicity requiring discontinuation of SAR302503.

Withdrawal Criteria: Subjects will be withdrawn from treatment in the event of any one of the following:

- Unacceptable toxicity (see Section 8.3)
- Disease progression as defined by the modified IWG-MRT response criteria
- Splenectomy
- Relapse as defined by the modified IWG-MRT response criteria
- Need for intervention or therapy determined by the Investigator to be medically necessary that is precluded by protocol.
- Subject noncompliance with treatment or voluntary withdrawal of consent.

Clinical safety will be evaluated during the entire study. Laboratory safety testing (hematology, coagulation, serum chemistry, and urinalysis) will be performed on Day 1 and 15 at Cycle 1, then on Day 1 of each subsequent treatment cycle, at the end of study dosing or early discontinuation, and at follow-up. In addition to these timepoints, LFT monitoring (total bilirubin, direct bilirubin, ALT, and AST) will occur on Day 15 at Cycles 2 and 3.

For subjects who develop ≥Grade 3 ALT, AST or total bilirubin elevations at any time during the study, at least weekly monitoring of LFTs must be performed until the adverse event has returned

to Grade ≤1. Subjects may resume treatment after elevated LFTs have returned to Grade ≤1. If treatment is resumed, all subjects with the above mentioned elevations must have their dose reduced by 1 dose level. The monitoring of AST, ALT and bilirubin (total and direct) must be performed every 2 weeks for at least the 3 subsequent treatment cycles.

For subjects progressing via imaging (MRI or CT scan), confirmation of progression by central imaging review is not required for study withdrawal. Central imaging review will be performed for reporting purposes. In case of PD due to either bone marrow or blood criteria, an MRI (CT scan) is not necessary for confirmation of progression.

Imaging scans must be sent to a designated central imaging review laboratory within 5 business days of progression. The imaging laboratory will be given 5 days to report results to the Sponsor. Further details on providing imaging scans and receipt of scan results from the third-party imaging laboratory will be provided in an Imaging Instruction Manual.

For upward dose titration at the end of Cycle 2 or 4, if dose adjustment criteria (<50% reduction in spleen size by palpation compared to baseline and no safety indication for study drug dose interruption/reduction/ discontinuation) are met, the dose can be increased in the increments of 100 mg/day at each titration step and recorded via Interactive Voice Response System (IVRS). The maximum dose is 600mg per day.

For downward dose titration, the dose can be decreased in the decrements of 100 mg/day at each titration step and recorded via IVRS based on safety criteria described in Section 8.3. Dose levels may be reduced a maximum of two times from starting dose. The minimum dose is 200 mg per day. If subjects do not tolerate a minimum dose of 200mg/day, they must withdraw from the study.

If toxicity does not resolve within the specified time period defined in Section 8.3 subjects must withdraw from the study.

Also see Section 8.3 for detailed instructions for LFT abnormalities (≥Grade 3 ALT, AST, or total bilirubin elevations).

Subjects who have progressed after receiving 600 mg/day of investigational medicinal product (IMP) for at least 2 cycles of SAR302503 may be discontinued from treatment at the discretion of the Investigator or sub-Investigator based on their clinical assessment.

Detailed descriptions of study assessments and their timing are located in Section 9.

Clinical safety and efficacy will be monitored during the study by internal sponsor committee. Committee consists the following members: Clinical Study Director, Medical monitor, Clinical Statistician, Global Safety Officer, Clinical Scientist, Clinical Lead, Pharmacokinetics representative, and Program Head.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each subject

The expected duration of a subject's treatment in this study is approximately 8 months, based on a 1 to 28-day screening period, followed by a 6-month (6-cycle of 28 days) treatment period, and a follow-up visit, which should be performed approximately 30 days following the last administration of IMP.

Subjects who continue to benefit clinically will be allowed to remain on IMP beyond the 6-month treatment period until the occurrence of disease progression or unacceptable toxicity.

6.2.2 Determination of end of clinical trial (all subjects)

The study duration will be approximately 55 months, which includes 10-month enrollment period. The cut-off date for the analysis of the primary endpoint of response will be (at the maximum) at the end of 6 cycles after the date of first dose of IMP of the last treated subject.

6.2.3 Survival follow up

Subjects will be followed by phone for survival every 3 months from the date of treatment discontinuation up to 2 years and after 2 years, every 6 months until death. Every effort will be made to follow all enrolled subjects. If survival follow-up (SFU) is missed and is not obtained at the time of the scheduled interval, it should be obtained immediately thereafter. For subsequent SFU, the subject should be contacted at the original scheduled SFU intervals. If the subject is not reachable via phone from the Investigator or designee, subject's caregiver or a family member may be contacted. The OS analysis will be performed after 4 years following the enrollment of last patient in the study.

7 SELECTION OF SUBJECTS

7.1 NUMBER OF SUBJECTS PLANNED

Seventy (70) evaluable subjects will be enrolled in this study.

7.2 INCLUSION CRITERIA

I 01. Diagnosis of PMF or Post-PV MF or Post-ET MF, according to the 2008 World Health Organization (Appendix B) and IWG-MRT criteria (Appendix C).

I 02. Subjects who previously received Ruxolitinib treatment for PMF or Post-PV MF or Post-ET MF or PV or ET for at least 14 days (exposure of <14 days is allowed for subjects who discontinued ruxolitinib due to intolerability or allergy) and discontinued the treatment for at least 14 days prior to the first dose of SAR302503.

I 03. Myelofibrosis classified as intermediate-1 with symptoms, intermediate-2 or high-risk (DIPSS) (Passamonti et al., Blood 2010 [1]).

I 04. Spleen ≥5 cm below costal margin as measured by palpation.

I 05. Male and female subjects ≥18 years of age.

I 06. Signed written informed consent.

7.3 EXCLUSION CRITERIA

Subjects who have met all the above inclusion criteria listed in Section 7.2 will be screened for the following exclusion criteria:

7.3.1 Exclusion criteria related to study methodology

E 01. Eastern Cooperative Oncology Group (ECOG) PS of >2 before the first dose of SAR302503 at Cycle 1 Day 1 (Appendix E).

E 02. 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

E 03. Subjects with known active (acute or chronic) Hepatitis A, B, or C; and hepatitis B and C carriers

E 04. AST or ALT ≥2.5 x ULN

E 05. Total Bilirubin:

- Exclude if ≥3.0 x ULN
- Subjects with total bilirubin between 1.5-3.0 x ULN must be excluded if the direct bilirubin fraction is ≥25% of the total

E 06. Subjects with prior history of chronic liver disease (eg, chronic alcoholic liver disease, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemachromatosis, non-alcoholic steatohepatitis [NASH])

E 07. Life expectancy <6 months.

E 08. Subjects with any other prior malignancies are not eligible, except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which subject has been disease-free for at least 5 years

E 09. Lack of willingness or ability to comply with scheduled visits, treatment plans, laboratory assessments and other study-related procedures

E 10. Splenectomy

E 11. Any chemotherapy, immunomodulatory drug therapy (eg, thalidomide, interferon-alpha), Anagrelide, immunosuppressive therapy, corticosteroids >10 mg/day prednisone or equivalent, or growth factor treatment (eg, erythropoietin), or hormones (eg, androgens, danazol) within 14 days prior to initiation of SAR302503; darbepoetin use within 28 days prior to initiation of SAR302503. The only chemotherapy allowed will be hydroxyurea within 1 day prior to initiation of SAR302503.

E 12. Major surgery within past 28 days or radiation within 6 months prior to initiation of SAR302503

E 13. Concomitant treatment with or use of pharmaceutical or herbal agents known to be moderate or severe inhibitors or inducers of CYP3A4 (Appendix D)

E 14. Treatment with aspirin in doses >150 mg/day within a week

E 15. Active acute infection requiring antibiotics

E 16. 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 SAR302503(Appendix F)

E 17. Participation in any study of an investigational agent (drug, biologic, device) within 30 days prior to initiation of SAR302503, unless during a non-treatment phase

E 18. Pregnant or lactating female

E 19. Women of childbearing potential, unless using effective contraception while on SAR302503

E 20. Men who partner with a woman of childbearing potential, unless they agree to use effective contraception while on SAR302503

E 21. Known human immunodeficiency virus or acquired immunodeficiency syndrome-related illness

E 22. Any severe acute or chronic medical, neurological, or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or SAR302503 administration, may interfere with the informed consent process and/or with compliance with the requirements of the study, or may interfere with interpretation of study results and, in the Investigator's opinion, would render the subject inappropriate for entry into this study

E 23. Unable to swallow capsules

E 24. Presence of any significant gastric or other disorder that would inhibit absorption of oral medication

E 25. Subjects with a QTc prolongation > 450 ms at screening or prior to study drug administration Or subjects who need concomitant medicines that are known to prolong QTc (Applicable for France only)

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

IMP will be supplied in bottles as hard capsules containing 100 mg of IMP free base (equivalent to 117 mg dihydrochloride monohydrate). The drug product consists of a blend of IMP drug substance and microcrystalline cellulose, with a small quantity of sodium stearyl fumarate added as a lubricant to facilitate manufacturing.

IMP will be orally self-administered on an outpatient basis, once daily in consecutive 28-day cycles at the assigned dose level. IMP will be dispensed to subjects at the beginning of each treatment cycle and will be taken on an empty stomach (1 hour before or 2 hours after meals) at approximately the same time each day. Especially for higher doses (eg, 500 and 600 mg/day), it is recommended that SAR302503 be taken 2 hours after meals at approximately the same time each day. Missed or vomited doses will not be replaced.

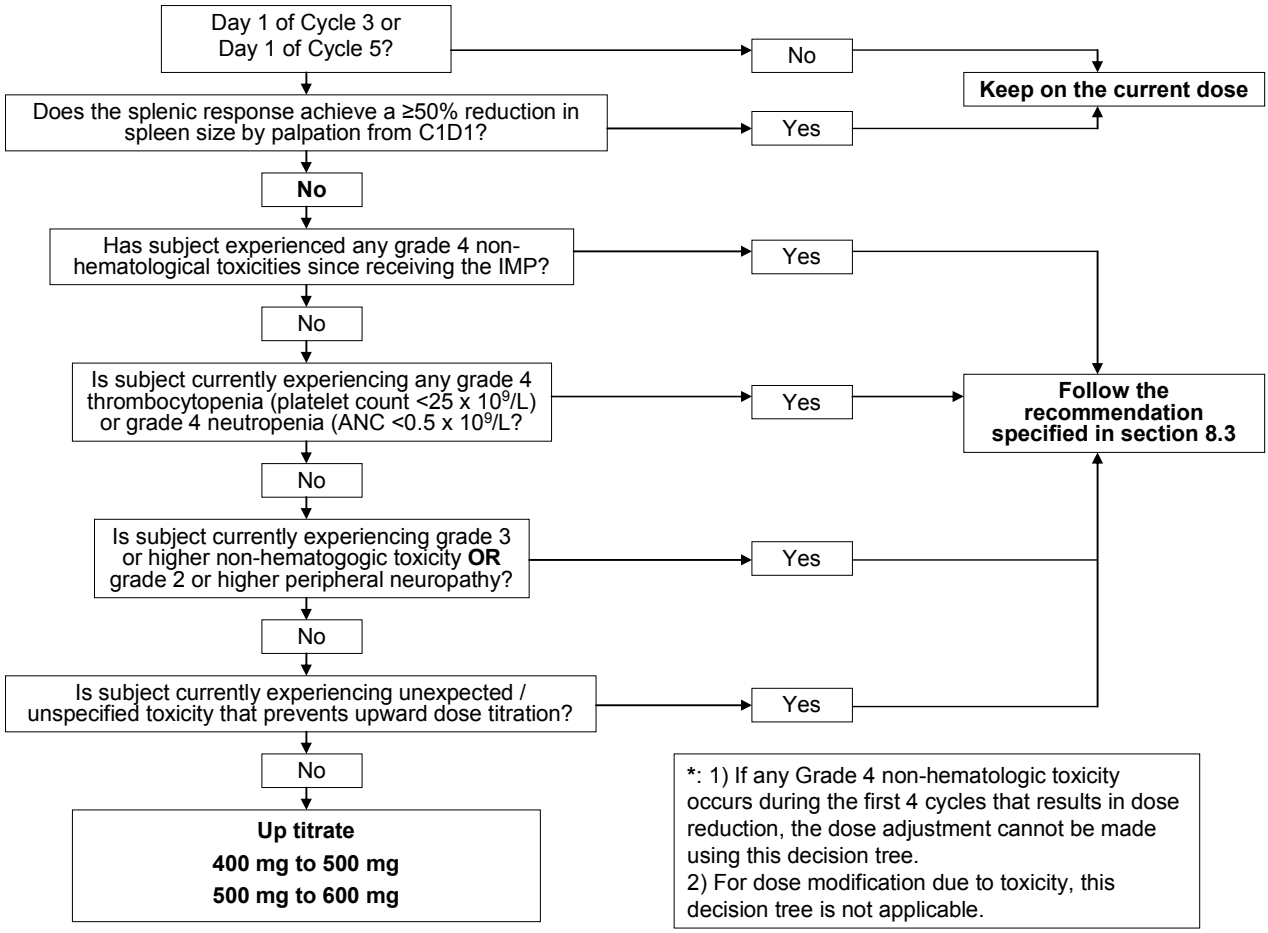
8.2 DOSE MODIFICATION: UPWARDS TITRATION FOR EFFICACY

Within the first 6 cycles of the treatment, if the splenic response does not achieve a ≥50% reduction in spleen size by palpation and there is no unacceptable drug toxicity (ie, Grade4 thrombocytopenia/anemia, Grade ≥3 non-hematologic toxicity or Grade ≥2 peripheral neuropathy (Section 8.3), an upwards titration of the study drug dose is strongly recommended (unless a significant, unexpected and/or unspecified safety issue occur at the time, which prevents investigators from increasing the dose). During the first 6 cycles of the study period, the upwards titration is only permitted at the end of Cycles 2 and 4, as most subjects take approximately 2 cycles of the treatment to demonstrate a full effect of SAR302503 on spleen size. Each titration step size is 100mg/day. The maximum dose is 600mg per day. Upwards titration decisions during the first 6 cycles of treatment will be made based on the results of splenic size measured by palpation (Figure 1).

IVRS will be used to manage the dose titration and IMP dispensing (see IVRS user manual for details). Investigators or study site staff members need to go through IVRS for the dose titration and IMP dispensing/drug accountability.

For the primary endpoint analysis, the splenic volume responses will be determined by MRI or CT Scan at the end of Cycle 6.

Figure 1 - Decision Tree for Upwards Dose Titration During the First 6 Cycles*



After Cycle 6, subjects will be allowed to have their dose titrated up (maximum dose 600 mg/day) or down (minimum 200 mg/day) in accordance with their individual responses and tolerability to the study drug at the discretion of the investigator or sub-investigator based on their clinical assessment. Each titration step size is 100 mg/day. For the upwards dose titration, an interval of at least 2 cycles of treatment should be considered. The same upwards titration criteria are recommended to optimizing efficacy for individual subjects. IVRS will be used to manage IMP dispensing/drug accountability (see IVRS user manual for details).

If the dose level needed be re-escalated after toxicity resolves during the study, dose modification criteria for toxicity in Section 8.3 below are recommended to optimize safety for individual subjects.

8.3 DOSE MODIFICATION: DOWNWARD TITRATION FOR TOXICITY

If subjects experience drug toxicity as specified below, the dosing must be interrupted and in some cases (ie, when it is not an LFT abnormality) may be titrated by a 100 mg/day decrement during the study, depending upon Investigator judgment. In the case of LFT abnormality, see requirements below.

Definition of toxic events:

- Grade 4 thrombocytopenia (platelet count $<25 \times 10^9$/L) or neutropenia (ANC $<0.5 \times 10^9$/L). In such cases, dosing may be suspended for up to 28 days and resumed at one dose level lower if values return to the following levels (≤Grade 2, according to CTCAE, version 4.03):
  - Platelet count: $\geq 50 \times 10^9$/L
  - ANC: $\geq 1.0 \times 10^9$/L.
- Grade ≥3 ALT, AST, or total bilirubin elevation. See additional LFT abnormality details below.
- Grade 3 or higher nausea, vomiting, diarrhea, constipation, or fatigue which does not respond to therapeutic or supportive measures within 48 hours. In such cases, dosing may be suspended for up to 14 days and may be resumed at one dose level lower if the toxicity resolves to Grade 1.
- Any Grade ≥3 non-hematologic/non-gastrointestinal toxicity or Grade ≥2 peripheral neuropathy. In such cases, dosing may be suspended for up to 14 days, and may be resumed at one dose level lower if the toxicity resolves to Grade 1.

Except in the case of LFT abnormalities (see specific requirements below), subject dosing should be resumed at one dose level lower (a 100 mg/day decrement) than the dose at which the event was observed. Dose levels may be reduced a maximum of two times from starting dose. If a dose has been reduced for a given subject and the toxicity resolves for at least 1 cycle, the dose level may be re-escalated one dose level higher per cycle at the discretion of the Investigator. This can be repeated until the original dose level (defined as the dose level before receiving the downwards titration) is reached.

Some subjects may experience Grade 4 non-hematological toxicity and require dose reduction. For these subjects, subsequent upward dose titration is not allowed. Treatment discontinuation may be considered based on the Investigator's judgment. If subjects experience an ECG abnormality (Grade 4, and confirmed by a cardiologist), the subjects must withdraw from the treatment.

Some subjects may experience Grade 4 hematologic toxicity and require dose reduction. If the toxicity resolves for at least 1 cycle, the dose level may then be titrated upwards one dose level per cycle at the discretion of the Investigator. However, if these subjects experience recurrence of Grade 4 hematological toxicity, no subsequent upward dose titration will be permitted, even after the toxicity resolves.

Liver function test abnormalities

If a subject experiences an LFT abnormality, defined as ≥Grade 3 ALT, AST, or total bilirubin elevation, the following dose and monitoring modifications must occur:

- Study treatment must be interrupted and subjects must have at least weekly monitoring of liver function tests until the adverse event has returned to Grade ≤1. Subjects may resume treatment after elevated LFTs have returned to Grade ≤1. If treatment is resumed, all subjects with the above mentioned elevations must have their dose reduced by 1 dose level. The monitoring of AST, ALT and bilirubin (total and direct) must be performed every 2 weeks for at least the 3 subsequent treatment cycles.
- If study drug is interrupted for >14 days (ie, the AE has not returned to Grade ≤1), the subject must be withdrawn from study treatment.
- No dose re-escalation will be permitted after dose reduction due to ≥Grade 3 ALT, AST, or total bilirubin elevation.
- If the above described ≥Grade 3 elevations occur again (second episode) despite dose reduction, the subject must be withdrawn from study treatment.
- Any subject experiencing Grade 4 ALT, AST, or total bilirubin elevations, in the absence of other demonstrable cause (non-drug related), must be withdrawn from study treatment.

Dose reduction should also be considered for subjects who become transfusion-dependent and were previously considered not to be. In case of dose interruption, dosing may be held up to 28 days before reinitiation of the IMP. Transfusion dependence is defined as receiving an average of ≥2 units of RBC transfusions/month over 3 months per Gale RP, et. al (2).

Subjects who do not tolerate therapy after 2 dose level reductions from starting dose must withdraw from the study. If toxicity does not resolve in the above mentioned time period subjects must withdraw from the study.

8.4 DOSE SUSPENSION DUE TO PLANNED MEDICAL PROCEDURES

After the subject has completed 6 cycles of treatment, with the approval of the Medical Monitor and at the Investigator's discretion, study medication may be suspended for up to 4 weeks and then resumed in the event of an elective surgical procedure or other intervening medical condition unrelated to the study or IMP. Subjects unable to resume treatment after this time period must be withdrawn from study.

8.5 COMPENSATION FOR LACK OF BLINDING

In this open label study, the dose adjustment criteria are pre-specified. The splenic response will be evaluated as the primary efficacy endpoint. It will be based on MRI images (or CT scan in subjects with contraindications for MRI) and evaluated by independent central readers. For independent central readers, the treatment levels will be blinded to reduce the potential bias in this evaluation process.

8.6 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUP

- This is an open label and single arm study. The starting dose is 400 mg/day. A flexible dosing regimen may be employed to optimize efficacy and to minimize drug toxicity for individual subjects.
- For upward dose titration at the end of Cycle 2 or 4, if dose adjustment criteria (<50% reduction in spleen size by palpation and no safety indication for study drug dose interruption/reduction/ discontinuation) are met, the dose will be changed to either 500 mg/day or 600 mg/day dose level. For downward dose titration, the dose will be adjusted based on safety criteria described in Section 8.3 . The dose level modifications will be recorded in IVRS.

8.7 PACKAGING AND LABELING

IMP will be primarily packaged in high-density polyethylene, white, opaque, round, child- and tamper-resistant bottles. Each bottle will contain 35 capsules and will be labeled with its contents, packaging /lot number, recommended storage conditions, Sponsor's name and the content of the labeling is in accordance with the local regulatory specifications and requirements.

Each subject will have adequate IMP to last for one cycle or until the next dispensing visit.

In the case of dose reduction, the subject should still be instructed to take the appropriate number of capsules from the dose bottle.

Subject will always be instructed to bring back the previously dispensed bottles at the next visit.

8.8 STORAGE CONDITIONS AND SHELF LIFE

IMP should be stored according to the label information in a secure area in accordance with the manufacturer's instructions.

8.9 RESPONSIBILITIES

The Investigator, the Hospital Pharmacist, or other personnel who are allowed to store and dispense IMP will be responsible for ensuring that the IMP used in the clinical trial are securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All IMP shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this Clinical Trial Protocol, or dispose of IMP in any other manner.

8.10 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the subject concomitantly to the IMP.

All treatments taken by the subject 30 days prior to enroll into the study and at any time during the study are regarded as concomitant treatments and the type, dose, and route of administration must be documented on the appropriate pages of the electronic case report form (eCRF).

Concomitant medication usage should be kept to a minimum during the study. However, if the concomitant medications are considered necessary for the subject's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the Investigator and recorded in the eCRF.

Based on in vitro evaluations, IMP is extensively metabolized by human CYP3A4. Agents that may increase IMP plasma concentrations (ie, CYP3A4 inhibitors) or decrease IMP plasma concentrations (ie, CYP3A4 inducers), including herbal agents and foods (eg, grapefruit/grapefruit juice), are not permitted while receiving IMP. In addition, since IMP is a substrate of CYP2C19, strong inhibitors of CYP2C19 (such as omeprazol) should be used with caution.

Based on in vitro evaluations and preliminary data from a clinical drug interaction study, the IMP is likely a moderate-to-potent inhibitor of CYP3A4. Thus, administration of drugs which are substrates with narrow therapeutic range is contraindicated in patients receiving the IMP. In addition agents that are sensitive substrates for metabolism by CYP3A4 (but have a wider

therapeutic range) should be used with caution since co-administration with the IMP may result in higher plasma concentrations of the co-administered agent.

Substrates with narrow therapeutic range	Sensitive substrates
Alfentanil, astemizole*, cisapride*, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine* * Withdrawn from the United States market because of safety reasons	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil

This is not an exhaustive list of sensitive and narrow therapeutic index CYP3A substrates. It is periodically updated at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Additionally, oral contraceptive and hormonal replacement therapies that include estrogen (ie, ethinyl estradiol) and progesterone (ie, levonorgestrel) are substrates of CYP3A4 and are not recommended for use during this study.

In patients taking CYP 3A4 sensitive substrates (but have a wider therapeutic range), close monitoring of laboratory parameters is recommended.

A list of clinically relevant inducers and inhibitors as well as a selection of substrates of CYP3A4 can be found in Appendix D.

SAR302503 may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medication, or herbal products.

Subjects may not receive any other drug treatment for MF while on study. Treatment with cytotoxic or immunosuppressive therapy, including hydroxyurea or systemic corticosteroids (ie, >10 mg/day prednisone or equivalent for >5 days), is prohibited. Use of any other investigational agents during the study is prohibited.

Transfusions are allowed, as clinically indicated. Erythropoietin and darbepoetin may not be used while on study. Granulocyte growth factors (eg, granulocyte colony stimulating factor or granulocyte-monocyte colony stimulating factor) are not permitted.

8.11 TREATMENT ACCOUNTABILITY AND COMPLIANCE

Administration of IMP will be supervised by the Investigator or sub-Investigator. Any delegation of this responsibility must follow the standard procedures.

The person responsible for drug dispensing is required to maintain adequate records of the IMP. These records (eg, drug movement form) include the date the study medication is received from the Sponsor, dispensed for subject and destroyed or returned to the Sponsor. The packaging number on the vial must be recorded on the drug accountability form.

At the time of PK sampling, the person responsible for drug administration to the subject will record precisely the date and the time of the drug administration.

The Investigator will not destroy any unused study medication unless the Sponsor or designee provides written authorization. If written authorization is received from the Sponsor, the study medication will be destroyed as per Institution policy.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY

9.1.1 Primary endpoint

9.1.1.1 Response rate

The primary endpoint is the subject RR, defined as the proportion of subjects who have a ≥35% reduction in volume of spleen size at the end of Cycle 6, will be measured by MRI (or CT scan in subjects with contraindications for MRI) and will be compared to the baseline value by a central imaging laboratory (reviewers will be blinded to the IMP doses). MRIs (or CT scan in patients with contraindications for MRI) performed within 14 days prior to Cycle 1 Day 1 is considered baseline for the primary efficacy evaluation. Detailed imaging instructions will be described in an imaging manual provided to the sites.

The same method that is used at baseline (MRI or CT scan) should be used consistently throughout the entire study. Every attempt should be made for all measurements to be performed by the same examiner within each subject.

Spleen size will also be assessed by palpation at baseline and every study visit, ie, on Day 1 of each cycle for the first 6 cycles, Day 15 of Cycle 1, end of Cycle 6; after Cycle 6, every 3 cycles, the end of treatment (EOT) visit, and at the 30-day follow-up visit. The eligibility for study entry will be determined by palpation.

9.1.2 Secondary endpoints

9.1.2.1 Symptom response rate

The SRR will be measured as proportion of subjects with a ≥50% reduction from baseline to the end of Cycle 6 in the total symptom score using the modified MFSAF diary.

9.1.2.2 Duration of spleen response

The duration response (DR) of spleen will be measured by MRI (or CT scan in subjects with contraindications for MRI) beginning within 14 days prior to initiation of dosing on Day 1 of Cycle 1 and at Day 1 of Cycle 4, at end of Cycle 6, at the end of every 6 cycles thereafter for two years, and at EOT. Measurement and assessment of the reduction in spleen volume on MRI or CT scan will be determined by a central imaging laboratory; reviewers will be blinded to the IMP doses.

9.1.2.3 Proportion of subjects with a ≥50% reduction in length of spleen by palpation from baseline at the end of Cycle 6

Spleen size will also be assessed by palpation at baseline and every study visit, ie, on Day 1 of each cycle for the first 6 cycles, Day 15 of Cycle 1, end of Cycle 6; after Cycle 6, every 3 cycles, the EOT visit, and at the 30-day follow-up visit. The eligibility for study entry will be determined by palpation.

9.1.2.4 Response Rate at the end of Cycle 3

Response Rate at the end of Cycle 3 is defined as the proportion of subjects who have a ≥35% reduction from baseline in volume of spleen to the end of Cycle 3 as measured by MRI (or CT scan in subjects with contraindications for MRI).

9.1.2.5 Percent Change of Spleen Volume

Percent change of spleen volume at the end of Cycles 3 and 6 from baseline will be measured by MRI (or CT scan in subjects with contraindications for MRI).

9.1.2.6 $JAK2^{V617F}$ mutant allele burden

Whole blood sample (5ml) will be collected and granulocytes will be isolated for nucleic acid extraction. $JAK2^{V617F}$ mutant allele burden in granulocytes will be measured in all subjects at predose baseline (Cycle 1/Day1). In the subset of subjects who are positive for the mutation, allele burden will also be measured on Day 1 of Cycle 4, the end of Cycles 6, 12, 18 and 24 and at EOT.

A blood sample will also be collected from all subjects who develop disease progression regardless of the JAK2 mutation status. Besides JAK2, additional gene changes may also be analyzed, including potentially by whole genome/whole exome sequencing to elucidate potential resistance mechanisms to SAR302503. The primary analysis will be the comparison of on-treatment granulocyte genotype/sequence to pretreatment granulocyte genotype/sequence to discover acquired mutations in the somatic genome. The analysis is not designed to elucidate genotypes or sequence variants in the germline (hertiable) genome that modulate risk of disease, response to therapy, or metabolism of drug. The analysis of somatic (granulocyte) sequence to discover acquired resistance mutations to SAR302503 is mandatory. This analysis can be also considered as specific tumor mutation analysis.

9.1.3 Exploratory endpoints

9.1.3.1 Overall survival

Overall survival is defined as the time interval from the date of first dose to the date of death due to any cause. In the absence of confirmation of death before the analysis cut-off date, OS will be censored at the last date the subject was known to be alive, or at the study cut-off date, whichever is earlier.

9.1.3.2 Assessment of clinical activity (modified international working group for myelofibrosis research and treatment criteria)

Assessment of the rates of CR, PR, CI, SD, and PD following treatment with IMP will be performed at Day 1 of Cycle 4, end of Cycle 6, at the end of each 6 cycles thereafter for two years, and at the EOT visit. The assessment will use IWG-MRT response criteria with MRI (or CT scan in subjects with contraindications for MRI) and bone marrow puncture when scheduled. See Appendix A for the modified IWG-MRT response criteria.

9.1.3.3 Proportion of subjects with a ≥25% reduction from baseline in volume of spleen at the end of Cycle 3

The RR is defined as the proportion of subjects who have a ≥25% reduction from baseline in volume of spleen at the end of Cycle 3 as measured by MRI (or CT scan in subjects with contraindications for MRI).

9.1.3.4 Proportion of subjects with a ≥25% reduction from baseline in volume of spleen at the end of Cycle 6

The RR at the end of Cycle 6 is defined as the proportion of subjects who have a ≥25% reduction from baseline in volume of spleen at the end of Cycle 6 as measured by MRI (or CT scan in subjects with contraindications for MRI).

9.1.3.5 Maximum months of continuous splenic response (≥50% reduction from baseline in spleen size)

The maximum number of months that a subject has a continuous splenic response as measured by palpation (defined as a ≥50% reduction from baseline in spleen size).

9.1.3.6 Number of cycles (out of 6) with splenic response (≥50% reduction from baseline in spleen size)

The number of cycles (out of 6) that a subject has a splenic response as measured by palpation (defined as a ≥50% reduction from baseline in spleen size).

9.1.3.7 Bone marrow assessments

Bone marrow analyses, including cytogenetics, cellularity, blast count, and the degree of reticulin fibrosis will be performed for every subject at screening, optional at Day 1 of Cycle 4, at end of Cycle 6, at the end of every 6 cycles thereafter for two years, and at EOT. Biopsies will be evaluated by central pathologists. If bone marrow is not available, cytogenetics may be performed from peripheral blood.

Bone marrow biopsy for baseline evaluation must be performed within 3 months prior to the first dose of SAR302503 and ≥14 days following discontinuation of any prior MF drug therapy. A 14 day restriction period is not applicable to patients treated with ruxolitinib or hydroxyurea. It is

encouraged that biopsy is performed during the 28-day screening period. If subjects have their last bone marrow biopsy performed outside the study center, but within the specified period above and they can provide the biopsy specimens or slides to the selected central laboratory for central pathology evaluations, the evaluation results may be used as baseline.

Bone marrow cellularity will be reported in percentages.

Reticulin fibrosis will be graded using the European consensus on grading bone marrow fibrosis provided below.

Fibrosis Grade	Description
0	Scattered linear reticulin with no intersections corresponding to normal bone marrow
1	Loose network of reticulin with many intersections, especially in perivascular areas
2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis.
3	Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

Cytogenetics will be reported as follows:

1 Not done

2 Done but no metaphases obtained

3 Normal

4 Abnormal

For cytogenetic assessments, the number of metaphases examined will be determined. If the bone marrow cytogenetics is reported as abnormal, the report will indicate if all metaphases are abnormal or if it is a mosaic or mixture of normal and abnormal metaphases. Description of chromosomal abnormalities must also be included. In case bone marrow is not available cytogenetics can be performed from peripheral blood.

9.1.3.8 Pharmacodynamic and signaling pathway analysis

JAK-STAT and other pathway signaling (Optional): JAK-STAT and other pathway signal profiling is strongly recommended if study sites have capability to prepare and ship the samples. Blood samples (10ml) will be collected to assess the effects of SAR302503 treatment on pharmacodynamic biomarker(s) of JAK2 pathway activation (including, but not limited to STAT3) on Cycle 1/Day 1 (predose and 2.5 to 4 hours postdose), Cycle 2/Day 1 predose and EOT (for subjects disease progression). Additional signaling pathways that may potentially be

associated with the disease may also be analyzed. Instruction for preparation, handling, and shipping of the samples will be provided in the study reference manual.

9.1.3.9 Tumor genomics

Whole blood sample (17 mL) will be collected from all subjects on Cycle 1/Day1 predose. Lymphocytes will be isolated for nucleic acid extraction as the source of normal deoxyribonucleic acid (DNA). This DNA, as well as the matching granulocyte DNA (tumor DNA) extracted in 9.1.2.5 ($JAK2^{V617F}$ mutant allele burden), may be subjected to genomic studies, including targeted gene resequencing and also potentially whole genome/whole exome sequencing. Subtractive mutation analysis will be performed to identify mutations existing only in the granulocyte (tumor cell) genome to elucidate potential mechanisms of response or resistance to JAK2-directed therapy. The primary analysis is not designed to elucidate genotypes or sequence variants in the germline (hertiable) genome that modulate risk of disease, response to therapy, or metabolism of drug. Specimens will not be retained beyond the end of the study and any data generated will be decoupled from subject clinical data at the conclusion of the study.

An additional whole blood sample (6 mL) will be collected pre-dose at baseline (Cycle 1/Day 1), at Cycle 4 Day1 and at the end of Cycle 6 to analyze potential molecular pathways associated with response/resistance to JAK2 treatment. Mutation analysis will be performed on MPN-related genes in progenitor cells at single cell level to determine clonal architecture of PMN and its evolution during SAR302503 treatment. Changes in gene expression will also be analyzed using nucleic acids extracted from the sample.

9.2 SAFETY

9.2.1 Physical examination

A complete physical examination will be performed at screening, baseline, and at the EOT visit. Physical examinations performed at all other visits will be symptom-directed (see Section 1.2). Whenever possible, the same examiner will perform examinations. If clinically significant worsening from baseline is noted at any study visit, the changes will be documented as AEs on the AE page of the eCRF. Clinical significance is defined as any variation in physical findings that has medical relevance resulting in an alteration in medical care. The Investigator will continue to monitor the subject until the condition returns to baseline or until the Investigator determines that follow-up is no longer medically necessary.

9.2.2 Vital signs

Vital signs, including sitting systolic and diastolic blood pressure (after 5 min resting, measured in mm Hg), heart rate (beats/minute), respiration, body temperature, and body weight, will be obtained and recorded at each study visit, including the EOT and the 30-day follow-up visits. Height will be obtained from Cycle 1 Day 1 visit only. All vital signs, except weight and height, should be obtained with the subject sitting or supine, but position must be consistent for each subject throughout the study.

If clinically significant changes from baseline in vital signs are noted, the changes will be documented as AEs on the AE page of the eCRF. Clinical significance will be defined as any variation in vital signs that has medical relevance resulting in an alteration in medical care. The Investigator will continue to monitor the subject until the parameter returns to baseline or until the Investigator determines that follow-up is no longer medically necessary.

9.2.3 Clinical laboratory evaluation and peripheral blood smear

Hematology, coagulation, serum chemistry, and urinalysis will be performed at each study visit, including the EOT and the 30-day follow-up visits. However, on Day 15 of Cycles 2 and 3, only LFT monitoring (total bilirubin, direct bilirubin, ALT, and AST) is required for the clinical laboratory evaluation.

Note that a peripheral blood smear evaluation also will be performed at the same time points. Specific parameters to be measured are listed below.

Hematology: RBC, hemoglobin, hematocrit, mean corpuscular volume, platelet count, WBC count (absolute), differential cell count (percentage; neutrophils, band cells, segmented granulocytes, lymphocytes, monocytes, eosinophils, and basophils), blasts (absolute and percentage), and reticulocyte count (absolute).

Peripheral Blood Smear: Total cell count, blast cells, nucleated erythrocytes, myelocytes, metamyelocytes, and promyelocytes, band cells.

Coagulation: Prothrombin time and activated partial thromboplastin time.

Blood Chemistry: Total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, amylase, lipase, total protein, albumin, globulin, sodium, potassium, chloride, calcium, phosphate, glucose, blood urea nitrogen or urea, creatinine, and uric acid.

If a subject develops ≥Grade 3 ALT, AST or total bilirubin elevations at any time, treatment must be interrupted and at least weekly monitoring of LFTs must be performed until the adverse event has returned to Grade ≤1. Subjects may resume treatment after elevated LFTs have returned to Grade ≤1. If treatment is resumed, all subjects with the above mentioned elevations must have their dose reduced by 1 dose level. The monitoring of AST, ALT and bilirubin (total and direct) must be performed every 2 weeks for at least the 3 subsequent treatment cycles. See Section 8.3 for additional details.

If at any time during the study a subject develops ≥Grade 2 total bilirubin, the fractionated (direct and indirect) bilirubin must be recorded.

Urinalysis: pH, protein, and blood.

In addition to the above, serum pregnancy tests are required at baseline and at the end of study dosing or early discontinuation for women of childbearing potential. During the study, urine or serum pregnancy tests are performed.

Standard laboratory documents (certification and/or license and normal reference ranges) will be obtained prior to study initiation. Specimens must be appropriately processed by the designated laboratory.

Investigators should use their clinical judgment when considering clinical significance. If clinically significant laboratory changes from baseline are noted, the changes will be documented as AEs on the AE page of the eCRF only if they lead to discontinuation, dose delay, dose reduction, dose interruption and/or fulfill a seriousness criterion. Clinical significance will be defined as any variation in laboratory parameters that has medical relevance resulting in an alteration in medical care. The Investigator will continue to monitor the subject with additional laboratory assessments until follow-up is no longer medically necessary.

Safety will be assessed by standard clinical and laboratory tests (hematology, serum chemistry). Toxicity grade is defined by the CTCAE v4.03.

General safety assessments/evaluations are detailed in Section 10.

9.2.4 Electrocardiogram

Electrocardiograms (ECGs) (12 lead) will be performed at screening, pre dose and 2 hours post dose on Day 1 Cycle 1 and Day 1 Cycle 2. ECG evaluation will also be performed at the end of Cycle 6 and EOT. Additional measurements should be performed if clinically indicated. The subject should be relaxed and must be in a supine position at least for 5 minutes prior to assessment. Three ECGs, ~1-2 minutes apart, should be performed at each time point. The ECG will be reviewed by the investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs. If abnormal ECG (grade 3 or above by CTCAEv4.03) is reported, the ECG needs to be reviewed and confirmed by a cardiologist.

Copies of all ECGs will be collected by the sponsor.

9.3 QUALITY OF LIFE

The QOL/symptoms evaluation will be performed using the following:

- Modified MFSAF Diary
- MPN-SAF and BFI questionnaire
- EORTC-QLQ C30 V3.0 questionnaire
- PGIC scale

Modified MFSAF diary evaluations will be performed using electronic diary system. All other QOL evaluations will be performed using paper forms at the time of study visits.

9.3.1 Modified myelofibrosis symptom assessment form diary

The key MF-associated symptoms will be assessed using the modified MFSAF Diary: night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain. The subjects will be strongly encouraged and instructed to record their symptoms at the same time of each day during the evaluation period. These will be measured on a scale from 0 (absent) to 10 (worst imaginable). An example is provided in (Appendix G).

MF-associated symptoms will be recorded daily for 7 days prior to Day 1 of Cycle 1, and daily during the first 6 cycles using MFSAF diary system. The completion of MFSAF diary will be monitored through the first 6 cycles. Diary device will be provided to the subject and site will provide training on how to complete Diary at screening.

A Total Symptom Score is defined as the sum of the scores for each of the 6 symptoms. For each day a Total Symptom Score will be calculated.

For each individual symptom score and for the Total Symptom Score a weekly score (weekly mean) will be calculated only if 5 of the 7 days daily assessment were actually available in the subject diary. All analyses will be performed on these weekly scores.

It is mandatory that a key person (eg, research nurse) at each center be responsible for the collection of this assessment in order to optimize compliance of the subject and to ensure completeness of the data. Additionally, the Investigator/study staff must not influence the subject's assessment. Every effort should be made to maintain an unbiased assessment. If a subject cannot complete the assessment because of illiteracy or other documented reason, it should be omitted. Reasons for missing data must be documented and will be incorporated into the analysis as necessary.

9.3.2 Myeloproliferative neoplasm symptom assessment form

As exploratory objective, the MPN-associated symptoms, will be assessed using the complete MPN-SAF, which includes fatigue assessment (via the BFI – Cancer 1999), and additional MPN-associated symptoms for presence and severity during the week prior to the assessment on a scale from 0 (absent) to 10 (worst imaginable) (via the MPN-SAF). A last item in the MPN-SAF questionnaire assesses the overall QOL of the subject. An example of the BFI and MPN-SAF are respectively provided in (Appendix H, Appendix I).

The complete MPN-SAF is to be completed by the subject at the study visit before any other assessments are performed by the Investigator/study staff at baseline (predose, Day 1 of Cycle 1), at the end of Cycle 6, at the Day 1 of Cycle 13, EOT and the 30-day follow-up visit.

It is mandatory that a key person (eg, research nurse) at each center be responsible for the collection of this assessment in order to optimize compliance of the subject and to ensure completeness of the data. Additionally, the Investigator/study staff must not influence the subject's assessment. Every effort should be made to maintain an unbiased assessment. If a subject cannot complete the assessment because of illiteracy or other documented reason, it

should be omitted. Reasons for missing data must be documented and will be incorporated into the analysis as necessary.

9.3.3 EORTC-QLQ-C30

The EORTC-QLQ-C30 is a questionnaire that is developed to assess the QOL of cancer patients. It is self-administered and takes about 5 to 10 minutes to complete. The validity and reliability of the EORTC-QLQ-C30 has been established in various types of cancers.

The EORTC-QLQ-C30 was chosen as cancer-specific instrument to provide a comprehensive assessment of the principal patient reporting outcome dimensions identified as relevant by cancer subjects (physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, global QOL, impact of symptoms and of toxicities). EORTC-QLQ-C30 is one of the standard instruments used in oncology for the evaluation of new chemotherapies. An example is provided in Appendix J.

The first 28 questions of the EORTC-QLQ-C30 V3.0 questionnaire use a 4-category response system (not at all / a little / quite a bit / very much) that correspond to numeric values 1, 2, 3, 4, respectively. Then for each item a high score represents a high level of symptomatology/problems.

The last 2 questions represent subject assessment of overall health and QOL. These items are coded on a 7-point response category scale, 1 being very poor and 7 excellent, with no label between.

The EORTC-QLQ-C30 is to be completed by the subject at the study visit before any other assessments are performed by the Investigator/study staff at baseline, Day 1 of each treatment cycle up to cycle 6, the end of Cycle 6, the Day 1 of Cycle 13, the EOT and the 30-day follow-up visit.

9.3.4 Patient's global impression of change

The PGIC questionnaire is a single-item response evaluating the global impression of change or improvement on a 7-point Likert scale (from 1 "Very much improved" to 7 "Very much worse"). An example is provided in Appendix K.

The PGIC scale is to be completed by the subject at the study visit before any other assessments are performed by the Investigator/study staff at the Day 1 of Cycle 4, Day 1 of Cycle 6, the end of Cycle 6, the Day 1 of Cycle 13, the EOT and the 30-day follow-up visit.

9.4 PHARMACOKINETICS

9.4.1 Sampling time

The sampling times for blood collection are as follows:

Table 1 - Blood sampling schedule for pharmacokinetic samples

Cycle	Day	Relative Time (h)	SAR302503 sample code
1	1	Predose	P00
		0.5h – 2h	P01
		2.5h – 4h	P02
2	1	Predose	P00
		0.5h – 2h	P01
		2.5h – 4h	P02
4	1	Predose	P00

Actual times of blood collection should be recorded on the eCRF. The days of sampling and the times of drug administration should also be precisely recorded. Missed or lost samples, for any reason, should be recorded. In case of serious adverse event (SAE), a PK sample should be taken when possible during the event.

9.4.2 Pharmacokinetic handling procedure

Additional details for the preparation, handling, and shipping instructions for PK samples will be provided in the study reference manual. A summary is provided below (Table 2).

Table 2 - Pharmacokinetic handling for SAR302503

Sample Type	SAR302503
Blood sample volume	2 mL
Anticoagulant	EDTA
Blood handling procedures	Keep blood on ice until plasma harvest (must be within 60 min of sampling time) by centrifugation at approx. 1500g for approximately 10 min. Separate the plasma into a storage tube.
Storage conditions	at -20^{0}C or below.

9.4.3 Bioanalytical method

Analyses of the PK samples for SAR302503 will be performed using validated LC-MS/MS methods.

Table 3 - Summary of bioanalytical method

Analyte	SAR302503
Matrix	Plasma
Analytical Technique	LC-MS/MS
Lower limit of Quantification	1.0 ng/mL
Assay volume	0.100 mL
Site of Bioanalysis	Covance
Method Reference	SARHPP

9.4.4 Pharmacokinetic parameters

SAR302503 plasma concentrations will be summarized by category (ie. predose to study, predose after start of study, 0.5 to 2.0 h samples and 2.5 – 4.0 h samples). In addition plasma concentrations at predose for Cycle 2 Day 1 and Cycle 4 Day 1 will be correlated with spleen size reduction.

Population PK parameters, clearance and volume, of SAR302503 will be determined if warranted using nonlinear mixed effects modeling. Population PK analysis plans and subsequent report will be presented in a separate documents from the Statistical Analysis Plan and the Clinical Study Report.

9.4.5 Pharmacogenetic samples

Saliva samples will be collected for pharmacogenomic purposes. A portion of the DNA from these samples will be immediately analyzed, while the remainder will be stored (see below for explanation of the storage sample). The data from the immediate analysis of the germ line genetic material can be used to determine a possible relationship between genes and responses to treatment with Drug SAR302503, how the body processes Drug SAR302503 and possible side effects to Drug SAR302503. DNA from this aliquot, left over after these testing will be destroyed at the completion of the Clinical study.

Special procedures for storage and shipping of pharmacogenetic samples are summarized below (Table 4) and will be described in detail in the laboratory manual.

Table 4 - Summary of handling procedures for DNA storage samples

Sample Type(s)	Pharmacogenetics
Sample Volume	2 x 2 mL Saliva
Tube Type	“Oragene container
Saliva Handling Procedures	See laboratory reference manual
Storage Conditions	Room temperature

The Sponsor has included safeguards for protecting subject confidentiality for the other DNA obtained from saliva, the DNA storage sample. The saliva sample and DNA that is extracted for DNA storage will be assigned a second number, a Genetic ID (de-identification code) that is different from the Subject ID. This "double coding" is performed to separate a subject's medical information and DNA data. The clinical study data (coded by Subject ID) will be stored in a distinct database at a different location from the database containing the pharmacogenetic data (coded by Genetic ID). The key linking Subject ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality. DNA will be stored for up to 15 years in the USA from the completion of the Clinical Study Report.

10 SUBJECT SAFETY

10.1 SAFETY ENDPOINTS ASSESSED IN THIS TRIAL

The safety and tolerability of IMP will be evaluated and characterized based on incidence, severity, chronicity and cumulative nature of treatment-emergent adverse events (TEAE) to establish its safety profile. TEAEs are defined as AEs that develop while on-treatment or for pre-existing conditions that worsen in grade or become serious during the on-treatment period. Safety will be assessed based on changes in clinical laboratory parameters, RBC and platelet transfusion requirements, ECG, and vital signs relative to baseline.

TEAEs will be summarized with respect to the frequency, duration, relatedness, seriousness, and type as assessed by the Medical Dictionary for Regulatory Activities (MedDRA current version or immediate previous version). The CTCAE v4.03 will be used to grade the severity of clinical and laboratory AEs. Please see Study Reference Manual for copy.

Note: Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of IMP for the concerned subject. Abnormal ECG (grade 3 or above by CTCAE v4.03) will be reviewed and confirmed by a cardiologist.

Also refer to Section 11 for details on temporary and permanent treatment discontinuation or study discontinuation.

10.2 SAFETY INSTRUCTIONS

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

10.3 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

10.4 DEFINITIONS OF ADVERSE EVENTS

10.4.1 Adverse event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.2 Serious adverse event

A SAE is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event:
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

  Note: The following medically important events intend to serve as a guideline for determining which condition has to be considered as a medically important event. It is not intended to be exhaustive:

  - Intensive treatment in an emergency room or at home for:
    - allergic bronchospasm,
    - blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia…),
    - convulsions (seizures, epilepsy, epileptic fit, absence…)
  - Development of drug dependency or drug abuse,
  - ALT >3 ULN + total bilirubin >2 ULN or asymptomatic ALT increase >10 ULN ,
  - Suicide attempt or any event suggestive of suicidality,
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
  - Bullous cutaneous eruptions,
  - Cancers diagnosed during the study or aggravated during the study (only if judged as unusual/significant by the Investigators in oncology studies),
  - Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged as unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.4.3 Adverse event of special interest

An Adverse Event of Special Interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. AESIs may be added or removed during a study by Protocol Amendment.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 General guidelines for reporting adverse events

- All AEs regardless of seriousness or relationship to IMP/non-IMP, spanning from the signature of the informed consent form, until the end of the study as defined by the protocol for that subject, are to be recorded on the corresponding page(s) or screen(s) included in the CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP.
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal or until progression has been stabilized or death in order to ensure the safety of the subjects.. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the Monitoring Team up to as noticed by the sponsor.
- When treatment is prematurely discontinued, the subject's observations will continue until the end of the study as defined by the protocol for that subject.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if they are medically relevant (including but not exclusive to):
  - Symptomatic and/or change from baseline
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI.
- See Table 5 for a summary of AE reporting guidelines.

10.5.2 Instructions for reporting serious adverse events

In the case of occurrence of a SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send the notification to the Monitoring Team after approval of the Investigator within the eCRF or after a standard delay.
- SEND (preferably by fax or e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the Monitoring Team whose name, fax number and email address appear on the Clinical Trial Protocol. Care should be taken to ensure that the subject's identity is protected and the subject's identifiers in the Clinical Trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for Lab data, concomitant Medication, subject status ...) should be sent (by fax or e-mail) to the Monitoring Team within 24 hours of knowledge. In addition, any effort should be made to further document each Serious AE that is fatal or life threatening within the week (7 days) following initial notification.
- A back-up plan is available and should be used (using paper CRF process) when the eCRF system does not work.
- Any SAE occurring within 30 days after last study treatment administration, regardless of relationship to the study treatment must be reported within 24 hours.
- All SAEs related to the study drug occurring beyond 30 days must also be reported within 24 hours.
- All deaths regardless of cause, including progression of disease, that occur within 30 days of study drug need to be reported as SAE, regardless of relationship to the study drug.
- All SAEs related to study treatment must be followed until resolution, stabilization or death.
- In case of any SAE brought to the attention of the Investigator at any time after the end of the study for the subject and considered by him/her to be caused by the IMP with a reasonable possibility, this should be reported to the Monitoring team.

10.5.3 Guidelines for reporting adverse events of special interest

AESIs (ie, that require pre-specified monitoring) are AEs (serious or non-serious) that need to be monitored, documented, and managed in a pre-specified manner described in the protocol.

For these AEs, the Sponsor will be informed immediately (ie, within 24 hours), even if not fulfilling a seriousness criterion, using the corresponding screens in the eCRF, following the same process as described for the SAEs. The following AEs will be considered AESI in this study:

- Pregnancy
  - Pregnancy will be recorded as an SAE in all cases.
  - In the event of pregnancy (documented by serum or urine tests), study treatments should be discontinued and the Sponsor should be informed immediately (within 24 hours), even if the event does not fulfill a seriousness criterion, using the AE form together with the SAE complementary form to be entered in the eCRF.
  - Follow-up of the pregnancy will be mandatory until the outcome has been determined.
- Second malignancies
  - All cases of second primary malignancy arising at any time in the subject's life, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphocytic leukemia (ALL), must be recorded as SAE. Copy of the pathology report confirming AML/MDS/ALL and cytogenetics report (if available) must be provided.
- Overdose
  - An overdose with the study treatment is an event suspected by the Investigator or spontaneously notified by the subject and defined as an overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as anything more than the intended dose in one day Symptomatic overdose must be reported in the e-CRF.
  - Symptomatic overdose must be reported in the eCRF. In case of accidental or intentional overdose with the study treatment that is symptomatic, even not fulfilling a seriousness criterion, is to be notified to the Sponsor immediately (within 24 hours) using the corresponding screens in the eCRF(AE and safety complementary forms), following the same process as described for the SAEs.
- Grade 3 and 4 thrombocytopenia (platelet count $<25 \times 10^9$/L) according to CTCAE criteria, v4.03)
- Grade 3 and 4 anemia according to CTCAE criteria, v4.03
- Grade 3 and 4 hyperlipasemia according to CTCAE criteria, v4.03
- Grade 3 and 4 hyperamylesemia according to CTCAE criteria, v4.03
- Grade 3 and 4 ALT, AST, or total bilirubin elevations according to CTCAE criteria, v4.03
- Development of transfusion dependency (transfusion dependence is defined as receiving an average of ≥2 units of RBC transfusions/month over 3 months (2).

10.5.4 Guidelines for management of specific laboratory abnormalities

The following laboratory abnormalities should be monitored, documented, and managed according to the standard of care.

- Neutropenia
- Thrombocytopenia
- LFT elevations

Table 5 - Summary of adverse event reporting instructions

EVENT CATEGORY	REPORTING TIMEFRAME	SPECIFIC EVENTS IN THIS CATEGORY	CASE REPORT FORM COMPLETION		
			AE form	Safety Comple-mentary Form	Other specific forms
AE (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
SAE (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.2	Yes	Yes	No
AESI WITHOUT immediate notification (non-SAE)	Routine	Asymptomatic overdose with IMP/NIMP	Yes	No	No
AESI WITH immediate notification (non-SAE)	Expedited (within 24 hours)	Pregnancy of female subject/subject	Yes	Yes	Yes
		Symptomatic overdose with IMP/NIMP	Yes	Yes	Yes
		Thrombocytopenia (Grade 3,4) Anemia (Grade 3,4) Hyperamylasemia (Grade 3,4), Hyperlipasemia (Grade 3,4) Development of Transfusion dependency	Yes	Yes	No
		ALT, AST, or total bilirubin elevations (Grade 3,4)	Yes	Yes	No
Laboratory, vital sign, or ECG abnormality (non-SAE, non-AESI) that is: - change from baseline - requiring corrective treatment or consultation - leading to IMP discontinuation or dose modification	Routine		Yes	No	No

10.6 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- all SAEs that are both unexpected and at least reasonably related to the IMP (Suspected Unexpected Serious Adverse Reaction), to the Health Authorities, Independent Ethics Committees (IECs)/ Independent Review Boards (IRBs) as appropriate and to the Investigators.
- all SAEs that are expected and at least reasonably related to the IMPs to the Health Authorities, according to local regulations.

Only those listed in the IB will be considered expected and not any others. Sponsor will update the IB as needed.

Any other AE not listed as an expected event in the IB or in this protocol will be considered as unexpected.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report (CSR).

11 HANDLING OF SUBJECT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF SUBJECT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined if the stop can be made temporarily; permanent IMP discontinuation should be a last resort (see Section 8.3 for dose modification requirements). Any IMP discontinuation should be fully documented in the eCRF. In any case, the subject should remain in the study as long as possible.

11.1 TEMPORARY TREATMENT DISCONTINUATION WITH INVESTIGATIONAL MEDICINAL PRODUCT(S)

After the subject has completed 6 cycles of treatment, with the approval of the Medical Monitor and at the Investigator's discretion, study medication may be held for up to 4 weeks and then resumed in the event of an elective surgical procedure or other intervening medical condition unrelated to the study or IMP.

All temporary treatment interruption, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

11.2 PERMANENT TREATMENT DISCONTINUATION WITH INVESTIGATIONAL MEDICINAL PRODUCT(S)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the subject not to re-expose the subject to the IMP at any time.

11.2.1 List of criteria for definitive treatment discontinuation

The subjects may withdraw from treatment with IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the eCRF.

Subjects will be withdrawn from treatment in the event of any one of the following:

- Unacceptable toxicity (see Section 8.3)
- Disease progression. Disease progression is defined as:
  - Progressive splenomegaly, defined as enlargement of spleen volume confirmed by MRI (or CT scan in subjects with contraindications for MRI) of ≥25% compared to baseline value.
  - Leukemic transformation, confirmed by a bone marrow blast count of ≥20% or the occurrence of a granulocytic sarcoma (chloroma).

- An increase in peripheral blood blast percentage of ≥20% that persists for at least 1 week.

- Subjects undergoing splenectomy.
- Relapse according to modified IWG-MRT response criteria.
- Need for intervention or therapy (determined by the Investigator to be medically necessary) that is precluded by protocol.
- Subject noncompliance with treatment or voluntary withdrawal of consent.

In addition, the Sponsor may decide to discontinue the trial prematurely for any reason.

In all cases, the Sponsor must be notified of all study terminations as soon as possible; the reason for and date of withdrawal must be recorded in the eCRF and in the subject's medical record. Whenever possible, all tests and evaluations listed for the EOT visit should be performed. Radiologic scans should be collected through the end of the subject's study participation. If a subject fails to return for the necessary visits, every effort must be made to contact the subject and determine the reason(s); this should be recorded on the eCRF.

11.2.2 Handling of subjects after permanent treatment discontinuation

Subjects will be followed up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the subjects will be assessed using the procedure normally planned for the last dosing day with the IMP.

All permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

11.3 PROCEDURE AND CONSEQUENCE FOR SUBJECT WITHDRAWAL FROM STUDY

The subjects may withdraw from the study, before study completion if they decide to do so, at any time and irrespective of the reason:

If possible, the subjects are assessed using the procedure normally planned for the end-of-trial visit.

For subjects who fail to return to the site, the Investigator should make the best effort to re-contact the subject (eg, contacting subject's family or private physician, review available registries or health care database), and to determine his/her health status, including at least his/her vital status. Attempts to contact such subjects must be documented in the subject's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter)

The statistical analysis plan will specify how these subjects lost to follow-up for their primary endpoints will be considered.

- All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the subject's medical records when considered as confirmed (at least date of and reason for withdrawal should be included);
- If possible, the subjects are assessed using the procedure normally planned for the EOT (or according to other procedures to be specified here such as follow-up phase);

Subjects who have withdrawn from study treatment cannot be re-entered in the study. Such subjects may be replaced if considered to be appropriate.

12 STUDY PROCEDURES

A tabular presentation of all study assessments is provided in Section 1.2 (study flow chart); refer to the footnotes for additional details on assessments and timing. Assessments may be completed ±3 days of the indicated time point, unless otherwise specified. Results of all assessments will be recorded in the subject's chart until the subject completes the follow-up period.

The modified MFSAF diary will be completed by the subject daily for 7 days prior to Day 1 of Cycle 1, and daily during the first 6 cycles.

12.1 VISIT SCHEDULE

12.1.1 Screening assessments (within 28 days of first dose of study medication)

Informed consent must be obtained prior to the performance of any study-specific tests or evaluations, including the screening assessments. The following screening assessments must be performed within 1 to 28 days prior to the first dose of study medication (on Day 1/Cycle 1), except as noted.

- Informed consent
- IVRS call
- Medical History - General and specific Medical history will be collected. Specific medical history will be related to the ruxolitinib prior treatment.
- Prior Medication History (including previous ruxolitinib intake and the use of other medications/therapies for MF))/Concomitant medications
- Inclusion/exclusion criteria
- Transfusion History
- ECG
- Modified MFSAF diary (provide subjects with training and electronic device)
- Spleen size (palpation)
- Spleen Volume (MRI or CT scan in subjects with contraindications for MRI, to occur within 14 days prior to the first dose of study medication)
- Complete physical examination
- Vital signs (body temperature, heart rate, respiration, and blood pressure)
- Clinical laboratory testing and Peripheral blood smear
- Pregnancy test (serum)
- Bone marrow biopsy**
- Hospitalization data

** Bone marrow biopsy for baseline evaluation must be performed within 3 months prior to the first dose of SAR302503 and ≥14 days following discontinuation of any prior MF drug therapy. A 14 day restriction period is not applicable to patients treated with ruxolitinib or hydroxyurea. It is encouraged that biopsy is performed during the 28-day screening period. If subjects have their last bone marrow biopsy performed outside the study center, but within the specified period above and they can provide the biopsy specimens or slides to the selected central laboratory for central pathology evaluations, the evaluation results may be used as baseline.

12.1.2 Cycle 1/Day 1

- IMP administration
- IVRS call
- Transfusion history
- ECG (predose and 2 hours postdose)
- Study compliance
- Concomitant medications
- Spleen size (palpation)
- Modified MFSAF diary
- EORTC QLQ C-30 questionnaire
- MPN-SAF and BFI questionnaire
- ECOG PS
- Body weight
- Complete physical examination
- Vital signs (body temperature, heart rate, height, respiration, and blood pressure)
- Clinical laboratory testing and peripheral blood smear‡
- Pregnancy test (urine or serum)
- AEs
- Blood sample prior to dosing for $JAK2^{V617F}$ allele burden assay and for additional gene changes in patients who have disease progression.
- Blood samples prior to dosing and 2.5 - 4 hours post-dose for JAK-STAT and other pathway signaling (optional)
- Blood sample prior to dosing for tumor genomics analysis
- Blood samples for PK (predose, [0.5 - 2] hours postdose and [2.5 – 4] hours postdose)
- Pharmacogenetics / Pharmacogenomics (predose for all consenting subjects)
- Hospitalization data

‡ At any time during the study, if a subject develops ≥Grade 3 ALT, AST, or total bilirubin elevations, study treatment must be interrupted and at least weekly monitoring of LFTs must

be performed until the adverse event has returned to Grade ≤1. Subjects may resume treatment after elevated LFTs have returned to Grade ≤1. If treatment is resumed, all subjects with the above mentioned elevations must have their dose reduced by 1 dose level. The monitoring of AST, ALT and bilirubin (total and direct) must be performed every 2 weeks for at least the 3 subsequent treatment cycles.

If at any time during the study a subject develops ≥Grade 2 total bilirubin, the fractionated (direct and indirect) bilirubin must be recorded.

12.1.3 Cycle 1/Day 15

- IMP administration
- Transfusion history
- Study compliance
- Concomitant medications
- Spleen size (palpation)
- Modified MFSAF diary
- Physical examination (symptom-directed)
- Vital signs (body temperature, heart rate, respiration, and blood pressure)
- Clinical laboratory testing and peripheral blood smear
- AEs

12.1.4 Cycle 2/Day 1

- IMP administration
- IVRS call
- Transfusion history
- Study compliance
- Concomitant medications
- Spleen size (palpation)
- Modified MFSAF diary
- EORTC QLQ C-30 questionnaire
- ECOG PS
- Hospitalization data
- Body weight
- Physical examination (symptom-directed)
- Vital signs (body temperature, heart rate, respiration, and blood pressure)
- Clinical laboratory testing and peripheral blood smear

- ECGs (predose and 2 hours postdose)
- AEs
- Blood sample prior to dosing for JAK-STAT and other pathway signaling (optional)
- PK (predose, [0.5 - 2] hours postdose and [2.5 – 4] hours postdose)

12.1.5 Cycle 2/Day 15

- Clinical laboratory testing: LFT monitoring (total bilirubin, direct bilirubin, ALT, and AST)

12.1.6 Cycle 3/Day 1

- IMP administration
- IVRS call
- IMP dose adjustment
- Transfusion history
- Study compliance
- Concomitant medications
- Spleen size (palpation)
- Modified MFSAF diary
- EORTC QLQ C-30 questionnaire
- ECOG PS
- Hospitalization data
- Body weight
- Physical examination (symptom-directed)
- Vital signs (body temperature, heart rate, respiration, and blood pressure)
- Clinical laboratory testing and peripheral blood smear
- AEs

12.1.7 Cycle 3/Day 15

- Clinical laboratory testing: LFT monitoring (total bilirubin, direct bilirubin, ALT, and AST)

12.1.8 Cycle 4/Day 1

- IMP administration
- IVRS call
- Transfusion history

- Study compliance
- Concomitant medications
- Spleen size (palpation)
- Spleen volume (by MRI or CT scan)
- Modified IWG-MRT response criteria
- Modified MFSAF diary
- EORTC QLQ C-30 questionnaire
- PGIC Scale
- ECOG PS
- Hospitalization data
- Body weight
- Physical examination (symptom-directed)
- Vital signs (body temperature, heart rate, respiration, and blood pressure)
- Clinical laboratory testing and peripheral blood smear
- Pregnancy test (urine or serum)
- AEs
- Blood sample prior to dosing for $JAK2^{V617F}$ allele burden assay
- Blood sample prior to dosing for tumor genomics analysis
- Bone marrow biopsy*
- Blood sample for PK (predose)

*If biopsy is not feasible, cytogenetics can be obtained from peripheral blood.

12.1.9 Cycles 5-6 /Day 1

- IMP administration
- IVRS call
- IMP dose adjustment (Day 1 Cycle 5 only)
- Transfusion history
- Study compliance
- Concomitant medications
- Spleen size (palpation)
- Modified MFSAF diary
- EORTC QLQ C-30 questionnaire

- PGIC Scale (Day 1 Cycle 6 only)
- ECOG PS
- Hospitalization data
- Body weight
- Physical examination (symptom-directed)
- Vital signs (body temperature, heart rate, respiration, and blood pressure)
- Clinical laboratory testing and peripheral blood smear
- AEs

12.1.10 Cycle 6 – End of Cycle

- IMP administration
- IVRS call
- Transfusion history
- Study compliance
- Concomitant medication
- Spleen size (palpation)
- Spleen volume (by MRI or CT scan)
- Modified IWG-MRT response criteria
- Modified MFSAF diary
- MPN-SAF and BFI questionnaire
- EORTC QLQ C-30 questionnaire
- PGIC Scale
- ECOG PS
- Hospitalization data
- Body weight
- Physical examination (symptom-directed)
- Vital signs (body temperature, heart rate, respiration, and blood pressure)
- Clinical laboratory testing and peripheral blood smear
- Pregnancy test (urine or serum)
- ECG
- AEs
- Blood sample prior to dosing for $JAK2^{V617F}$ allele burden assay
- Blood sample prior to dosing for tumor genomics analysis

- Bone marrow biopsy*

* Bone marrow biopsy is strongly recommended. If biopsy is not feasible, cytogenetics can be obtained from peripheral blood.

12.1.11 Cycle 13, 19 and 25/Day 1

- Spleen volume (by MRI or CT scan)

12.1.12 Cycle 7 and Cycle 10, 13, until cycle x /Day 1

- IMP administration
- IVRS call
- IMP dose adjustment
- Transfusion history
- Study compliance
- Concomitant medications
- Spleen size (palpation)
- Modified IWG-MRT response criteria*
- MPN-SAF and BFI questionnaire**
- EORTC QLQ C-30 questionnaire**
- PGIC Scale**
- ECOG PS
- Hospitalization data
- Body weight
- Physical examination (symptom-directed)
- Vital signs (body temperature, heart rate, respiration, and blood pressure)
- Clinical laboratory testing and peripheral blood smear
- Pregnancy test (End of Cycles 12, 18, and 24; urine or serum)
- AEs
- Blood samples prior to dosing for $JAK2^{V617F}$ allele burden assay (End of Cycles 12, 18 and 24)
- Bone marrow biopsy (End of Cycles 12, 18 and 24)***
- For Cycle 7 and beyond, at the Investigator's discretion, examinations may be performed every 3 cycles, unless otherwise specified.

* Modified IWG-MRT response criteria evaluation is performed at the end of every 6 months up to 2 years.

** MPN-SAF, EORTC QLQ C-30 and PGIC scale questionnaires will be performed at the Day 1 of Cycle 13.

*** Bone marrow biopsy is strongly recommended. If biopsy is not feasible, cytogenetics can be obtained from peripheral blood.

12.1.13 End of treatment or early discontinuation

- Transfusion history
- Study compliance
- Concomitant medications
- Spleen size (palpation)
- Spleen volume (by MRI or CT scan)
- Modified IWG-MRT response criteria
- EORTC QLQ C-30 questionnaire
- MPN-SAF and BFI questionnaire
- PGIC Scale
- ECOG PS
- Hospitalization data
- Body weight
- Complete Physical examination
- Vital signs (body temperature, heart rate, respiration, and blood pressure)
- Clinical laboratory testing and peripheral blood smear
- Pregnancy test (serum)
- ECG
- AEs
- Blood samples for $JAK2^{V617F}$ allele burden assay and additional gene changes in patients who have disease progression
- Bone marrow biopsy*
- Blood samples for JAK-STAT and other pathway profiling (optional and disease progression only)

* Bone marrow biopsy is strongly recommended. If biopsy is not feasible, cytogenetics can be obtained from peripheral blood.

12.1.13.1 Follow-up (30 +/- 3 days after the last dose of investigational medicinal product)

- Transfusion history
- Concomitant medications
- Spleen size (palpation)
- EORTC QLQ C-30 questionnaire
- MPN-SAF and BFI questionnaire
- PGIC Scale
- ECOG PS
- Hospitalization data
- Body weight
- Physical examination (symptom-directed)
- Vital signs (body temperature, heart rate, respiration, and blood pressure)
- Clinical laboratory testing and peripheral blood smear
- AEs

12.1.13.2 Survival follow up

At post treatment long term follow up, subjects will be followed by phone for survival every 3 months from date of treatment discontinuation up to 2 years, and after 2 years, every 6 months until death. Every effort will be made to follow all enrolled subjects. If SFU is missed and is not obtained at the time of the scheduled interval, it should be obtained immediately. For subsequent SFU, the subject should be contacted at the original scheduled SFU intervals. If the subject is not reachable via phone from the Investigator or designee, subject's caregiver or a family member may be contacted

12.2 DEFINITION OF SOURCE DATA

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents and data records include hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, MRI/CT images, subject files, and records kept at the pharmacy, the laboratories, and other departments involved in the clinical study. For local laboratory values, local standards will be collected.

All protocol-required information collected during the study must be recorded by the Investigator or other study personnel in the source documentation for the study. The source documentation

will be used to enter the protocol-required information into the eCRF. No data should therefore be directly entered into the eCRF.

13 STATISTICAL CONSIDERATIONS

13.1 DETERMINATION OF SAMPLE SIZE

Assuming the RR (primary endpoint) is 25%, 70 evaluable subjects will provide at least 90% power at a one-sided 2.5% alpha level to test the null hypothesis of ≤10% RR. Based on the COMFORT1 results, approximately 60% subjects who received ruxolitinib were non responders, thus 60% of 70 evaluable subjects (42) will provide 80% power to test a response rate ≤10% for the subgroup of patients who did not reach the primary endpoint of splenic response during the ruxolitinib trials.

13.2 ANALYSIS ENDPOINTS

13.2.1 Efficacy endpoints

13.2.1.1 Primary efficacy endpoint(s)

The primary endpoint is the subject RR, defined as the proportion of subjects who have a ≥35% reduction in volume of spleen size at the end of Cycle 6, will be measured by MRI (or CT scan in subjects with contraindications for MRI) and will be compared to the baseline value. The review of MRI or CT will be performed by a central imaging laboratory (blinded to the IMP doses).

13.2.1.2 Secondary efficacy endpoint(s)

- SRR: defined as the proportion of subjects with ≥50% reduction from baseline to the end of Cycle 6 in the Total Symptom Score
- DR, measured by MRI (or CT scan in subjects with contraindications for MRI): defined as the time from the date of the first response to the date of subsequent PD or death, whichever is earlier:
  - DR (months) = [Earlier of (Date of subsequent documented disease progression, date of death) - Date of first documented response +1] x (12/365.25)
  - DR is determined only for subjects who have a response; this value will be missing for other subjects.

In the absence of disease progression or death before the analysis cut-off date, the DR will be censored at the date of the last valid assessment performed before the analysis cut-off date.

- Proportion of subjects with a ≥50% reduction in length of spleen by palpation from baseline at the end of Cycle 6
- RR at the end of Cycle 3, defined as the proportion of subjects who have a ≥35% reduction from baseline in volume of spleen at the end of Cycle 3 as measured by MRI (or CT scan in subjects with contraindications for MRI)

- Percent change of spleen volume at the end of Cycles 3 and 6 from baseline as measured by MRI (or CT scan in subjects with contraindications for MRI)

13.2.1.3 Exploratory efficacy endpoints

- OS: defined as the time interval from the date of first dose to the date of death due to any cause. In the absence of the confirmation of death before the analysis cut-off date, OS will be censored at the last date the subject was known to be alive or at the study cut-off date, whichever is earlier.
- Rates of CR, PR, CI, SD, PD, and relapse as measured by the modified IWG-MRT response criteria
- RR, defined as the proportion of subjects who have a ≥25% reduction from baseline in volume of spleen at the end of Cycle 3 as measured by MRI (or CT scan in subjects with contraindications for MRI)
- Proportion of subjects who have a ≥25% reduction in volume of spleen size at end of Cycle 6 as measured by MRI (or CT scan in subjects with contraindications for MRI)
- The maximum months of continuous splenic response by palpation (a ≥50% reduction from baseline in spleen size) for each subject
- The number of cycles (out of the first 6 cycles) that subjects have a splenic response by palpation (a ≥50% reduction from baseline in spleen size)
- The maximum months of continuous symptom response (a ≥50% reduction from baseline at the end of Cycle 6 in the total symptom score) for each subject using the modified MFSAF
- The number of cycles (out of the first 6 cycles) that subjects have a symptom response using the modified MFSAF
- Change on health-related QOL using EORTC QLQ-C30 v3.0 and Subjects' Global Impression of Change (PGIC) scale on Day 1 of Cycle 4, the Day 1 of Cycle 6, the end of Cycle 6, the Day 1 of Cycle 13, EOT, and 30-day follow-up visit
- Change from baseline to end of Cycle 6 in each of the individual symptoms of both the BFI and MPN-SAF (complete MPN-SAF assessment). In addition, Fatigue score will be evaluated as the average of the 9 BFI scores.

13.2.2 Safety endpoints

The characterization of the safety profile of IMP will be based on incidence, severity, chronicity and cumulative nature of TEAEs. Treatment-emergent adverse events are defined as AEs that develop on-treatment or are pre-existing conditions that worsen in grade or become serious during the on-treatment period. Safety will be assessed based on changes in clinical laboratory parameters, RBC and platelet transfusion requirements, and vital signs relative to baseline.

Pretreatment AEs and TEAEs will be summarized with respect to the frequency, duration, relatedness, seriousness, and type as assessed by the Medical Dictionary for Regulatory Activities

current version or immediate previous version). The CTCAE v4.03 will be used to grade the severity of clinical and laboratory AEs. Please see Study Reference Manual for copy.

Observation period

- Treatment period: defined from the date of the first dose of any IMP up to 30 days after the last dose of any IMP.
- Baseline observation: Safety endpoints that are present prior to the first dose of IMP on Day 1 of Cycle 1 will be considered the sign and symptoms at baseline.
- TEAE: defined as any AE that is new, a worsening condition compared to baseline, or an event that becomes serious during the treatment period.

13.2.2.1 Adverse events

Adverse event observation period:

The AE observations are per the observation periods defined above.

AE observations will include TEAEs, SAEs, AEs leading to death, AEs that causes dose reduction and/or delay or treatment interruption, AEs that cause treatment discontinuation, and AE related to study treatment.

13.2.2.2 Deaths

Death observation period:

The death observations are per the observation periods defined above.

Deaths occurring within 30 days of last dose of IMP will be included in safety analysis. For efficacy analysis of OS, deaths from enrollment to the study cut-off date will be taken into consideration.

13.2.2.3 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including hematology, clinical chemistry and urinalysis). Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

13.2.2.4 Vital signs

Vital Signs include sitting systolic and diastolic blood pressure, heart rate, respiration, body temperature, height, and body weight.

13.2.2.5 Electrocardiogram variables

ECG evaluation will be performed at screening, pre dose, and 2 hours post dose on Day 1 of Cycle 1 and Day 1 of Cycle 2. ECG evaluation will be also performed at the end of Cycle 6 and EOT. Additional tests should be performed if clinically indicated.

13.2.2.6 Other safety endpoints

Other safety variables such as body weight, physical exams, and pregnancy tests will be collected according to the study flow chart in Section 1.2.

13.2.3 Pharmacokinetic variables

SAR302503 plasma concentrations for possible population PK analysis will be evaluated at 3 timepoints per visit on Day 1 of Cycles 1 and 2, and a single predose time point on Day 1 of Cycle 4. One blood sample needed to be taken predose and the second taken between 0.5 and 2 hours and the third sample taken between 2.5 and 4 hours postdose. In case of SAE, a PK sample should be taken, when possible during the event.

13.2.4 Pharmacodynamic/tumor genomics variables

- $JAK2^{V617F}$ mutant allele burden in granulocytes will be measured predose at baseline for all subjects. In the subset of subjects who are positive for the mutation, $JAK2^{V617F}$ mutant allele will also be measured predose, Cycle 4 Day1 and at EOC of Cycles 6, 12, 18 and 24 and at EOT.
- JAK-STAT and other pathway signaling (including, but not limited to STAT3 phosphorylation) will be analyzed predose and 2.5 to 4 hours postdose on Day 1 of Cycle 1, predose on Day 1 of Cycle 2, and at EOT (in case of disease progression).
- Subtractive mutation analysis may be performed by comparing DNA from blood granulocytes and lymphocytes to identify mutations existing only in granulocyte DNA to elucidate potential mechanisms of response or resistance to JAK2-directed therapy.
- Clonal architecture at single cell level and gene expression at Cycle 1 Day1, Cycle 4 Day 1 and Cycle 6 EOC.
- Pharmacogenomic analysis related to drug metabolizing enzymes. Saliva samples will be collected predose on Day 1 of Cycle 1 for all subjects who have given their consent.

13.2.5 Pharmacogenomics variables

- Pharmacogenomic analysis related to drug metabolizing enzymes: Saliva samples will be collected predose on Day 1 of Cycle 1 for all subjects who have given their consent to document the patient's genotype for drug metabolizing enzymes.

13.2.6 Health economic variables

Health Care Consumption: Hospitalization data will be recorded at each visit (except Day 15 of Cycle 1) throughout the study.

13.2.7 Further therapy after stop of investigational medicinal product administration during the study

At the discretion of the Investigator or sub-Investigator based on their clinical assessment, further anti-MF treatment may be given to the subjects after study discontinuation.

13.3 DISPOSITION OF SUBJECTS

Screen failures and other analysis populations will be summarized. Treatment discontinuation will be summarized by reason.

Screened subjects are defined as any subject who met the inclusion criteria and signed the informed consent.

13.4 ANALYSIS POPULATIONS

13.4.1 Efficacy populations

- Per-protocol population: This population consists of all enrolled and treated, with a baseline and first post-baseline MRI (CT Scan in case of contraindications for MRI), and had no violation of inclusion/exclusion criteria and no other important protocol deviations. This population will be used for the primary analyses of efficacy endpoints.
- All-Treated (AT) population: The AT population includes all subjects who were administered at least one dose (even if partial) of study medication. This population will also be used for supportive analyses of efficacy endpoints when specified.

13.4.2 Safety population

The AT population defined above will be used for the safety analyses.

13.4.3 Pharmacokinetic population

The PK population will be comprised of subjects who received at least 1 full cycle of study treatment and have evaluable drug concentration data.

13.4.4 Pharmacodynamic population

The PD population will be comprised of subjects who received at least 1 full cycle of study treatment and have evaluable pharmacodynamic marker drug concentration data.

13.5 STATISTICAL METHODS

13.5.1 Demographic and baseline characteristics

Standard demographic and baseline characteristics (including age and race), medical history, cancer diagnosis and prior anti-cancer therapy will be collected at baseline (Cycle 1). Baseline efficacy variables (eg, MRI) and other prognostic variables will be assessed as well. Baseline value is defined as the last value or measurement taken prior to the first dose in the study. Baseline spleen size by palpation is defined as the spleen size by palpation on Cycle 1 Day 1. Baseline spleen volume is defined as the screening spleen volume measurement by MRI (or CT scan in case of contraindications for MRI).

Parameters will be summarized for all enrolled subjects. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the primary analysis population.

13.5.2 Prior or concomitant medications (other than anti-cancer therapies)

The prior and concomitant medications will be presented for all enrolled subjects.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the ATC class (anatomic category) and the first three digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, subjects will be counted once in each ATC categories (anatomic or therapeutic) linked to the medication, therefore subjects may be counted several time for the same medication.

13.5.3 Extent of study treatment exposure and compliance

Extent of exposure will be assessed within the safety population.

Dose information will be assessed by the following variables:

- Duration of IMP exposure is defined as: last dose date – first dose date regardless of unplanned intermittent discontinuations.
- The cumulative dose at Cycle k is the sum of all doses from Cycle 1 to, and including, Cycle k, where k is based on the Investigator's report.
- The actual dose intensity is defined as the cumulative dose divided by the duration of IMP exposure in terms of the number of weeks on study.
- The relative dose intensity is defined as the ratio of the actual dose intensity to the planned dose intensity. Relative dose intensity is an indicator of the feasibility of the chosen schedule of administration. The planned dose intensity is defined as the planned dose for each cycle divided by planned cycle length in weeks.
- Dose reduction and reason for dose reduction: Dose reduction will be derived using the definition provided in the protocol compared to the previous dose. For the second and

subsequent cycles, a dose is deemed to have been reduced if the dose level a subject receives is lower than the previous actual dose level.

- Dose delays: A cycle is deemed to have been delayed if start date of the current cycle – end date of previous Cycle >4 days.
- Dose interruption: if dose is interrupted for IMP at a given cycle, multiple start and end dates will be reported in the eCRF.

The number of subjects treated, number of cycles administered, duration of dosing (weeks), cumulative dose (mg), dose intensity (mg/week), and relative dose intensity (%) will be summarized by treatment group.

Dose delays and dose reductions will also be analyzed.

13.5.3.1 Extent of investigational medicinal product exposure

Extent of exposure will be assessed within the safety population.

Dose information will be assessed by the following variables:

- Duration of IMP exposure is defined as: last dose date – first dose date regardless of unplanned intermittent discontinuations.
- The cumulative dose at Cycle k is the sum of all doses from Cycle 1 to, and including, Cycle k.
- The actual dose intensity is defined as the cumulative dose divided by the duration of IMP exposure in terms of the number of weeks on study.
- The relative dose intensity is defined as the ratio of the actual dose intensity to the planned dose intensity. Relative dose intensity is an indicator of the feasibility of the chosen schedule of administration. The planned dose intensity is defined as the planned dose for each cycle divided by planned cycle length in weeks.
- Dose reduction and reason for dose reduction: Dose reduction will be derived using the definition provided in the protocol compared to the previous dose. For the second and subsequent cycles, a dose is deemed to have been reduced if the dose level a subject receives is lower than the previous actual dose level.
- Dose delays: A cycle is deemed to have been delayed if start date of the current cycle – end date of previous Cycle >4 days.
- Dose interruption: if dose is interrupted for IMP at a given cycle, multiple start and end dates will be reported in the eCRF.

The number of subjects treated, number of cycles administered, duration of dosing (weeks), cumulative dose (mg), dose intensity (mg/week), and relative dose intensity (%) will be summarized.

Dose delays and dose reductions will also be analyzed.

13.5.4 Analyses of efficacy endpoints

13.5.4.1 Analysis of primary efficacy endpoint(s)

The data cut-off for the primary efficacy endpoint (RR) will occur when the last enrolled subject has completed 6 cycles of IMP. A Chi-squared test will be performed to compare the RR with 10% at a 1-sided 2.5% alpha level. The RRs and 95% confidence intervals will be provided. Last observation carried forward method will be used to impute the missing end of Cycle 6 spleen volume measurement with the Cycle 4 Day 1 spleen volume measurement.

13.5.4.2 Analyses of secondary efficacy endpoints

- DR: for spleen responders only: Kaplan-Meier estimates of the 25th, 50th, and 75th percentiles and the 95% confidence intervals of median will be provided. Kaplan-Meier curve will be plotted.
- Proportion of subjects with a ≥50% reduction by palpation from baseline to the end of Cycle 6: to be analyzed in the same manner as RR.
- RR at the end of Cycle 3: summary statistics will be provided.
- Percent change of spleen volume at the end of Cycles 3 and 6 from baseline: summary statistics and 95% confidence interval will be reported.

13.5.4.3 Analysis of exploratory efficacy endpoints

- OS: Kaplan-Meier estimates of the 25th, 50th, and 75th percentiles and the 95% confidence intervals of median will be provided. Kaplan-Meier curve will be plotted.
- RR25: to be analyzed in the same manner as RR.
- Rates of CR, PR, CI, SD, PD, and relapse as measured by the modified IWG-MRT response criteria: summary statistics will be provided when appropriate.
- The maximum months of continuous splenic response by palpation (a ≥50% reduction from baseline in spleen size) for each subject: summary statistics will be provided.
- The number of cycles (out of the first 6 cycles) that subjects have a splenic response by palpation (a ≥50% reduction from baseline in spleen size): summary statistics will be provided.
- The maximum months of continuous symptom response (a ≥50% reduction from baseline in any of the 6 symptoms present at baseline) for each subject using the modified MFSAF: summary statistics will be provided.
- The number of cycles (out of the first 6 cycles) that subjects have a symptom response using the modified MFSAF: summary statistics will be provided.

13.5.4.4 Multiplicity considerations

Multiplicity will not be adjusted.

13.5.5 Analyses of safety data

The summary of safety results will be provided. Analysis of AEs and laboratory data will be descriptive and conducted on the safety population. Summary of safety data will also be performed by subject and by cycle. For each of the safety parameters, a baseline value will be defined as the last value or measurement taken up to the first dose of IMP in the study. Similar analyses will be presented for SAEs and AEs that cause dose reduction, dose delay and treatment discontinuation. The denominator will be the total subject-cycles.

AE incidence tables will present by system organ class (sorted by an internationally agreed upon order) high level group level terms, high level terms, and preferred terms sorted in alphabetical order, the number (n) and percentage (%) of subjects experiencing an AE. Multiple occurrences of the same event in the same subject will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population.

The grade and cycle will be taken into account in the summary. For subjects with multiple occurrences of the same event, the maximum grade will be used. The denominator will be the total subject-cycles. For a given event, a subject contributes 1 to the numerator for each cycle in which an episode occurred (ie, if the date of onset is on or after the first day of the cycle, but prior to the first day of the next cycle).

For deaths, the following summaries will be generated:

- Number (%) of subjects who died by study period (TEAE, on-study) and reasons for death summarized on the safety population.
- TEAEs leading to death (death as an outcome on the AE eCRF page as reported by the Investigator) and related TEAEs leading to death by primary system organ class, alphabetic order of high level group level terms, high level terms, and preferred terms showing number (%) of subjects.

Hematological toxicities will be assessed from laboratory parameters. Worst CTCAE grades of leukopenia, neutropenia, thrombocytopenia, and anemia will be calculated according to the common terminology criteria.

Qualitative and quantitative results will be summarized for hematological toxicities. Qualitative data (worst CTCAE grade) will be summarized by cycle and by subject.

Biochemistry will be analyzed using the worst CTCAE grade, whenever applicable (laboratory normal ranges, otherwise) calculated from laboratory values.

13.5.6 Analyses of pharmacokinetic and pharmacodynamic variables

Plasma concentrations of IMP will be used for evaluation of the PK of IMP by non-linear mixed effects modeling (population PK), if warranted. Additional details of the analysis plan and the results will be provided in separate documents.

13.5.7 Analyses of pharmacodynamic and pharmacogenomic variables

- In the subset of subjects who are positive for the $JAK2^{V617F}$ mutation in granulocytes, changes of the mutant allele burden at baseline predose to that at EOC of Cycles 3, 6, 12, 18 and 24 and at EOT will be summarized.
- JAK-STAT and other signaling pathway status (including, but not limited to STAT3 phosphorylation) in samples collected at predose and 2.5 to 4 hours postdose on Day 1 of Cycle 1, predose on Day 1 of Cycle 2 and at EOT (in case of disease progression) will be compared and summarized.
- Subtractive mutation analysis may be performed by comparing DNA from blood granulocytes and lymphocytes to identify mutations existing only in granulocyte DNA to elucidate potential mechanisms of response or resistance to JAK2-directed therapy.
- Clonal architecture and gene expression at Cycle 4 Day 1 and Cycle 6 EOC, as compared to Cycle 1 Day1 will be summarized.

13.5.8 Analyses of pharmacokinetic/pharmacodynamic correlation

The relationship of spleen size reduction and plasma IMP concentration will be explored, if warranted.

13.5.9 Analyses of quality of life/health economics variables

The compliance profile over time will be summarized (number and percentage of forms received versus expected, and number and percentage of forms evaluable versus expected) for each questionnaire.

- Modified MFSAF diary: A descriptive summary of each of the individual symptoms and for the Total Symptom Score at each visit and change from baseline will be provided.
  - Primary analysis (SRR): The proportion of subjects and its 95% Confidence Interval will be provided.
  - Secondary analyses:
    - The maximum months of continuous symptom response (a ≥50% reduction from baseline in the total symptom score) and the number of cycles (out of the first 6 cycles) that subjects have a symptom response will be described.
    - The proportion of patients with ≥50% reduction from baseline in the total symptom score will be displayed graphically over time.
    - For Total Symptom Score and for each individual symptom, the Cumulative Distribution Function of the percent change (continuous plot of the percent change from baseline on the X-axis and the percent of subjects experiencing that change on the Y-axis) will be displayed at Week 24 (end of Cycle 6).

- Complete MPN-SAF questionnaire: Change from baseline to end of Cycle 6 for each of the symptoms assessed in the MPN-SAF, each of the fatigue items assessed in the BFI and global fatigue score from the BFI.
- EORTC QLQ C-30 questionnaire: The change from baseline to each visit for the Global health status (scoring of items 29 & 30), the five functional scales (Physical, Role, Emotional, Cognitive and Social), the three symptom scales (Fatigue, Nausea/vomiting and Pain) and the last 6 single items will be described.
- PGIC scale: The PGIC at C4D1, C6D1, end of Cycle 6, C13D1, EOT, 30 days follow-up will be graphically described.
- Health economic variables: a separate Statistical Analysis Plan (SAP) will describe the analyses of the hospitalization data.

13.6 DATA HANDLING CONVENTIONS

This section describes general rules for data handling conventions, especially for subjects with missing data.

Missing dates will be handled using conservative approaches, and no imputation will be applied at the data level:

- If the date of the last dose of investigational drug is missing, the exposition duration should be kept as missing.
- If a medication date or time is missing or partially missing, it will be considered as a prior, concomitant, and a follow-up medication, when no reasonable conclusion can be reached in this situation.
- If onset dates and times are missing or partially missing, the AE will be classified as treatment-emergent. If the date and time of the first investigational drug is missing, all AEs that occurred after or on the day of randomization will be considered as treatment emergent AEs.
- Handling of potentially clinically significant abnormalities (PCSAs): If a subject has a missing baseline he will be grouped in the category “normal /missing at baseline”. For PCSA with two conditions, one based on a change from baseline value or a normal range and the other one on a threshold value, the first condition being missing, the PCSA will be based only on the second condition. For PCSA defined on a threshold and / or a normal range, this PCSA will be derived using this threshold only if the normal range is missing. eg, for eosinophils the PCSA is > 0.5 GIGA/L or > ULN if ULN ≥ 0.5 GIGA /L. When ULN is missing the value 0.5 should be used.
- Last observation carried forward method will be used to impute missing end of Cycle 6 spleen volume measurement data for the primary efficacy endpoint.

13.7 INTERIM ANALYSIS

A formal interim report will be prepared after approximately 1/3 of patients are enrolled and completed 3 cycles of the SAR302503 treatment; this interim report will be used for regulatory purposes. The sponsor will monitor the efficacy and safety of study drug; the trial will be stopped for futility if there is insufficient evidence of efficacy and/or unacceptable toxicity. This monitoring will start after 15% of the enrollment is complete or 3 months after first patient is enrolled. After the first meeting, subsequent meetings will be conducted on every 3- month rolling basis. The primary endpoint will be analyzed at the end of Cycle 6, while the study is ongoing to evaluate other efficacy endpoints (including OS) and safety. The OS analysis will be performed after 4 years following the enrollment of last patient in the study.

13.8 DATABASE LOCK

Database is planned to be locked approximately 4 weeks after Last Subject Last Visit.

13.9 ETHICAL PRINCIPLES

This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice.

In compliance with sanofi-aventis public disclosure commitments, this clinical trial will be recorded in the public registry website clinicaltrials.gov before the enrollment of the first subject. The registry will contain basic information about the trial sufficient to inform interested subjects (and their healthcare practitioners) how to enroll in the trial.

13.10 LAWS AND REGULATIONS

This Clinical Trial will be conducted in compliance with all international guidelines, and national laws and regulations of the country(ies) in which the Clinical Trial is performed, as well as any applicable guidelines (Section 14.1).

13.11 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the Subject of all pertinent aspects of the Clinical Trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a subject’s participation in the Clinical Trial, the written Informed Consent Form (ICF) should be signed, name filled in and personally dated by the subject or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written ICF will be provided to the subject.

The ICF used by the Investigator for obtaining the subject's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

For pharmacogenomics optional studies, separate ICF will be used.

13.12 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this Clinical Trial Protocol to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, ICF, IB, Investigator's curriculum vitae, etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the Clinical Trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the subjects, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of subjects or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the IB will be sent to the Ethics Committee (IRB/IEC).

A progress report is sent to the Ethics Committee (IRB/IEC) at least annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

14 STUDY MONITORING

14.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) and delegated Investigator staff undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol (with the help of the eCRF, Discrepancy Resolution Form or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the subject's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the Clinical Trial in accordance with the Clinical Trial Protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the Clinical Trial Protocol and all necessary information.

14.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the eCRFs. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and subject compliance with Clinical Trial Protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: subject informed consent, subject recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, subject compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

14.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the eCRF entries against the source documents, except for the pre-identified source data directly recorded in the eCRF. The ICF will include a statement by which the subject allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the eCRFs (eg,, subject's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

14.4 USE AND COMPLETION OF ELECTRONIC CASE REPORT FORMS AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All eCRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the Sponsor after receipt of the eCRFs may generate additional requests (Discrepancy Resolution Form) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be appended to the eCRFs held by the Investigator and the Sponsor.

14.5 USE OF COMPUTERIZED SYSTEMS

Computerized systems used during the different steps of the study are:

- For data management activities, Oracle Clinical with RDC system
- For statistical activities, SAS
- For pharmacovigilance activities, AWARE
- For monitoring activities, IMPACT POLARIS
- For medical writing activities, DOMASYS.

15 ADMINISTRATIVE RULES

15.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Sub-Investigator will be signed, dated and provided to the Sponsor prior to the beginning of the Clinical Trial.

15.2 RECORD RETENTION IN STUDY SITES(S)

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least fifteen (15) years after the completion or discontinuation of the Clinical Trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the Clinical Trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

16 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the eCRFs, the IB and the results obtained during the course of the Clinical Trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this Clinical Trial Protocol and other necessary documentation to the Ethics Committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Clinical Trial.

The Investigator and the Sub-Investigators shall use the information solely for the purposes of the Clinical Trial, to the exclusion of any use for their own or for a third party's account.

Furthermore, the Investigator and the Sponsor agree to adhere to the principles of personal data confidentiality in relation to the subjects, Investigator and its collaborators involved in the study.

17 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the Clinical Trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the Clinical Trial.

As the case may be, the Investigator and/or the Sub-Investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

18 DATA PROTECTION

- The subject's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the subjects, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

19 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from maintaining their own liability insurance policy. An insurance certificate will be provided to the Ethics committees/IRB or Health Authorities in countries requiring this document.

20 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the subjects should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

21 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

21.1 DECIDED BY THE SPONSOR IN THE FOLLOWING CASES:

- If the information on the product leads to doubt as to the benefit/risk ratio;
- If the Investigator has received from the Sponsor all IMP, means and information necessary to perform the Clinical Trial and has not included any subject after a reasonable period of time mutually agreed upon;
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the Clinical Trial Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for Good Clinical Practice;
- If the total number of subjects are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

21.2 DECIDED BY THE INVESTIGATOR

The Investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed according to applicable regulatory requirements.

22 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a Clinical Study Report and to provide a summary of study results to the Investigator.

23 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the Study and/or results of the Study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the Study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, first presentation or publication of the results of the Study shall be made only as part of a publication of the results obtained by all sites performing the Protocol. However, if no multicenter publication has occurred within twelve (12) months of the completion of this Study at all sites, the Investigator shall have the right to publish or present independently the results of this Study to the review procedure set forth herein. The Investigator shall provide the Sponsor with a copy of any such presentation or publication derived from the Study for review and comment at least thirty (30) days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed ninety (90) days, to allow for filing of a patent application or such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The sponsor has the right at any time to publish the results of the study.

24 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this Clinical Trial Protocol.

The Investigator should not implement any deviation from, or changes of the Clinical Trial Protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to Clinical Trial Subjects, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this Clinical Trial Protocol.

Any amendment to the Clinical Trial Protocol requires written approval/favorable opinion by the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the Informed Consent Form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised Informed Consent Form prior to implementation of the change and subject signature should be re-collected if necessary.

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11. TargeGen, Inc. Document Number PH-07-101348-081. Effects of orally administered TG101348 on hematopoietic stem cells expressing JAK2V617F. September 2007.

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26 APPENDICES

Appendix A Modified International Working Group for Myelofibrosis Research and Treatment Response Criteria

Complete remission (CR)

- Complete resolution of disease-related symptoms and signs including normalization of spleen volume in MRI (or CT scan in subjects with contraindications for MRI).
- Peripheral blood count remission defined as hemoglobin level at least 110 g/L, platelet count at least 100 x 10^9/L, and absolute neutrophil count at least 1.0 x 10^9/L. In addition, all 3 blood counts should be no higher than the upper normal limit.
- Normal leukocyte differential including disappearance of nucleated RBCs, blasts, and immature myeloid cells in the peripheral smear, in the absence of splenectomy (Because of subjectivity in peripheral blood smear interpretation, CR does not require absence of morphologic abnormalities of red cells, platelets, and neutrophils)
- Bone marrow histologic remission defined as the presence of age-adjusted normocellularity, no more than 5% myeloblasts, and an osteomyelofibrosis grade no higher than 1.
- In subjects with CR, a complete cytogenetic response is defined as failure to detect a cytogenetic abnormality in cases with a pre-existing abnormality. Apartial cytogenetic response is defined as 50% or greater reduction in abnormal metaphases. In both cases, at least 20 bone marrow- or peripheral blood-derived metaphases should be analyzed. A major molecular response is defined as the absence of a specific disease-associated mutation in peripheral blood granulocytes of previously positive cases. In the absence of a cytogenetic/molecular marker, monitoring for treatment-induced inhibition of endogenous myeloid colony formation is encouraged. Finally, baseline and post-treatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process.

Partial remission (PR)

Requires all of the criteria for CR except for bone marrow histologic remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill criteria for CR.

Clinical improvement (CI)

Requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment (CI response is validated only if it lasts for no fewer than 8 weeks)

- A minimum 20 g/L increase in hemoglobin level or becoming transfusion independent (applicable only for subjects with baseline hemoglobin level of less than 100 g/L. Transfusion dependency is defined as receiving an average of ≥2 units of RBC transfusions/month over 3 months per Gale RP, et. al (2). and is discouraged unless it is clinically indicated.
- A reduction of ≥35% in spleen volume as measured by MRI (or CT scan in subjects with contraindications for MRI).
- A minimum 100% increase in platelet count and an absolute platelet count of at least 50 x 10^9/L (applicable only for subjects with baseline platelet count below 50 x 10^9/L).
- A minimum 100% increase in ANC and an ANC of at least 0.5 x 10^9/L (applicable only for subjects with baseline absolute neutrophil count below 1 x 10^9/L).

Progressive disease

Requires one of the following:

- Progressive splenomegaly that is defined by >25% increase of spleen volume as assessed by MRI (or CT scan in subjects with contraindications for MRI) compared to the baseline value.
- Leukemic transformation confirmed by a bone marrow blast count of ≥20% or occurrence of a histologically documented granulocyticsarcoma (chloroma).
- An increase in peripheral blood blast percentage of ≥20% that lasts for at least 1 week.

Stable disease

Stable disease will be characterized by ≤35% decrease to ≤25% increase in spleen volume.

Relapse

Relapse is defined as a loss of CR, PR, or CI. In other words, a subject with CR or PR is considered to have undergone relapse when he or she when he or she no longer fulfills the criteria for even CI. However, changes from either CR to PR or CR/PR to CI should be documented and reported.

* Because of subjectivity in peripheral blood smear interpretation, CR does not require absence of morphologic abnormalities of red cells, platelets, and neutrophils.

† In subjects with CR, a complete cytogenetic response is defined as failure to detect a cytogenetic abnormality in cases with a pre-existing abnormality. A partial cytogenetic response is defined as 50% or greater reduction in abnormal metaphases. In both cases, at least 20 bone marrow- or peripheral blood-derived metaphases should be analyzed. A major molecular response is defined as the absence of a specific disease-associated mutation in peripheral blood granulocytes of previously positive cases. In the absence of a cytogenetic/molecular marker, monitoring for treatment-induced inhibition of endogenous myeloid colony formation is encouraged. Finally, baseline and post-treatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process.

‡ Transfusion dependence is defined as receiving an average of ≥2 units of RBC transfusions/month over 3 months per Gale RP, et. al (2).

It is acknowledged that worsening cytopenia might represent PD, but its inclusion as a formal criterion was avoided because of the difficulty distinguishing disease-associated from drug-induced myelosuppression. However, a decrease in hemoglobin level of 20 g/L or more, a 100% increase in transfusion requirement, and new development of transfusion dependency, each lasting for more than 3 months after the discontinuation of protocol therapy, can be considered disease progression.

Appendix B Classification and diagnosis of myeloproliferative neoplasms according to the 2008 World Health Organization criteria

Criteria for primary myelofibrosis are presented below. Diagnosis requires meeting all 3 major criteria and 2 minor criteria.

Major criteria

1. Presence of megakaryocyte proliferation and atypia*, usually accompanied by either reticulin or collagen fibrosis

or,

in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease).

2. Not meeting WHO criteria for polycythemia vera†, BCR-ABL1–positive chronic myelogenous leukemia‡, myelodysplastic syndrome§, or other myeloid disorders.

3. Demonstration of $JAK2^{V617F}$ or other clonal marker (eg, MPLW515K/L)

or,

in the absence of the above clonal markers, no evidence that bone marrow fibrosis is secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Minor criteria

1. Leukoerythroblastosis

2. Increase in serum lactate dehydrogenase level

3. Anemia

4. Palpable splenomegaly

* Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering.

† Requires the failure of iron replacement therapy to increase hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels. Red cell mass measurement is not required.

‡ Requires the absence of BCR-ABL1.

§ Requires the absence of dyserythropoiesis and dysgranulopoiesis. It should be noted that subjects with conditions associated with reactive myelofibrosis are not immune to primary myelofibrosis and the diagnosis should be considered in such cases if other criteria are met. The degree of abnormality could be borderline or marked.

Appendix C International Working Group for Myelofibrosis Research and Treatment Recommended Criteria for post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis

Criteria for post-PV myelofibrosis:

Required criteria:
1. Documentation of a previous diagnosis of PV as defined by the WHO criteria.
2. Bone marrow fibrosis Grade 2–3 (on 0–3 scale) or Grade 3–4 (on 0–4 scale)[a].

Additional criteria (2 are required):
1. Anemia[b] or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis.
2. A leukoerythroblastic peripheral blood picture.
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of >5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly.
4. Development of at least 1 of 3 constitutional symptoms: >10% weight loss in 6 months, night sweats, or unexplained fever (>37.51°C).

Criteria for post-essential thrombocythemia myelofibrosis:

Required criteria:
1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria.
2. Bone marrow fibrosis Grade 2–3 (on 0–3 scale) or Grade 3–4 (on 0–4 scale)[a]

Additional criteria (2 are required):
1. Anemia[b] and a >2mg/ml decrease from baseline hemoglobin level.
2. A leukoerythroblastic peripheral blood picture.
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of >5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly.
4. Increased lactate dehydrogenase (above reference level).
5. Development of at least 1 of 3 constitutional symptoms: >10% weight loss in 6 months, night sweats, or unexplained fever (>37.51°C).

a Grade 2–3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain).

Grade 3–4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

b Below the reference range for appropriate age, sex, gender and altitude considerations.

Appendix D Clinically relevant inducers and inhibitors of CYP3A4 isoenzymes

CYP3A4 sensitive **Substrates**	CYP3A4 Substrates with narrow therapeutic range	CYP3A4 **Inducers**	CYP3A4 **Inhibitors**
aprepitant budesonide buspirone conivaptan darifenacin darunavir dasatinib dronedarone eletriptan eplerenone everolimus felodipine indinavir fluticasone lopinavir lovastatin lurasidone maraviroc midazolam nisoldipine quetiapine saquinavir sildenafil simvastatin sirolimus tolvaptan tipranavir triazolam vardenafil	alfentanil astemizole* cisapride* cyclosporine dihydroergota mine ergotamine fentanyl pimozide quinidine sirolimus tacrolimus terfenadine* * Withdrawn from the United States market because of safety reasons	carbamazepine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's wort* troglitazone	HIV Antivirals: indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone erythromycin grapefruit juice verapamil diltiazem cimetidine amiodarone fluvoxamine mibefradil Troleandomycin

This is not an exhaustive list of sensitive and narrow therapeutic index CYP3A substrates. It is periodically updated at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Coadministration of SAR302503 can alter the concentrations of other drugs and other drugs may alter the concentrations of SAR302503. The potential for drug-drug interactions must be considered before and during therapy. In patients taking CYP3A4 sensitive substrates (with a wider therapeutic range), close monitoring of laboratory parameters is recommended.

Appendix E Eastern Cooperative Oncology Group performance status scale

CALGB (ECOG) Performance Status Scale

PS	0	Normal, fully functional
PS	1	Fatigue without significant decrease in daily activity
PS	2	Fatigue with significant impairment of daily activities or bed rest < 50% of waking hours
PS	3	Bed rest/sitting > 50% of waking hours
PS	4	Bedridden or unable to care for self

Appendix F New York Heart Association classification of functional capacity and objective assessment

In 1928 the New York Heart Association published a classification of subjects with cardiac disease based on clinical severity and prognosis. This classification has been updated in 7 subsequent editions of Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (Little, Brown & Co.). The ninth edition, revised by the Criteria Committee of the American Heart Association, New York City Affiliate, was released March 4, 1994. The classifications are summarized below.
Functional Capacity

Class I. Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
Class II. Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
Class III. Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
Class IV. Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Appendix G Modified myelofibrosis symptom assessment form diary

Instructions: Please fill out all questions, as best able, reflecting how these symptoms affected you at their worst moment over the past 24 hours. Use a scale of 0 to 10, marking "0" if the symptom is absent, 1 or above if the symptom is present, "10" being the symptom severity at its worst imaginable.

- Night sweats Absent ⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩ Worst imaginable

- Itching (pruritus) Absent ⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩ Worst imaginable

- Abdominal discomfort Absent ⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩ Worst imaginable

- Filling up quickly when you eat (early satiety) Absent ⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩ Worst imaginable

- Pain under ribs on left side Absent ⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩ Worst imaginable

- Bone or muscle pain Absent ⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩ Worst imaginable

Appendix H Brief fatigue inventory

Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL# _____

Date: ____/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General Activity
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

C. Walking ability
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

F. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

BFI - English - Formatted March 19, 2008

Appendix I Myeloproliferative neoplasm symptom assessment form

Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) ©

Instructions: Please fill out all questions, as best able, reflecting how these symptoms affected you over the LAST WEEK unless directed otherwise.

Item	Symptom	1 to 10 (0 if absent) ranking* (1 is most favorable and 10 least favorable)
	Circle the one number that describes how, during the past week how much difficulty you have had with each of the following symptoms	
1	Filling up quickly when you eat (Early Satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
2	Abdominal pain	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
3	Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
4	Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
5	Problems with Headaches	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
6	Problems with Concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
7	Dizziness/ Vertigo/ Lightheadedness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
8	Numbness/ Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
9	Difficulty sleeping	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
10	Depression or sad mood	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
11	Problems with Sexual Desire or Function	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
12	Cough	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
13	Night Sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
14	Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
15	Bone Pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
16	Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
17	Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
18	What is your Overall Quality of Life?	(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As bad as it can be)

Appendix J EORTC QLQ C-30 questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix K Patient's global impression of change scale

Since the start of the study, my overall status is:

✓*one box only:*

[1] ☐ Very Much Improved

[2] ☐ Much Improved

[3] ☐ Minimally Improved

[4] ☐ No Change

[5] ☐ Minimally Worse

[6] ☐ Much Worse

[7] ☐ Very Much Worse

(US/English)

ARD12181 Amended Protocol 3

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
DiJohnson, Celeste	Clinical Approval	29-Nov-2012 17:39 GMT+0
Lebedinsky, Claudia	Clinical Approval	29-Nov-2012 18:34 GMT+0