NS Pharma Inc.
Protocol #: NS-018-201

A Phase 2b, Open-label, Multicenter, Randomized, Controlled, 2-Arm Study to Assess the Efficacy and Safety of Orally Administered NS-018 versus Best Available Therapy in Subjects with Primary Myelofibrosis, Post Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis with Severe Thrombocytopenia (Platelet Count <50,000/µL)

Statistical Analysis Plan

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List of abbreviations terms and Definitions of Terms

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BAT	best available therapy
BCR-ABL1	Breakpoint Cluster Region- Abelson 1
BID	twice daily (“bis in die” Latin)
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	Contract Research Organization
CT	computed tomography
CTCAE v5.0	Common Terminology Criteria for Adverse Events version 5.0
CYP	cytochrome P450
DIPSS	Dynamic International Prognostic Scoring System
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ET	essential thrombocythemia
EMH	extramedullary hematopoiesis
ETMF	essential thrombocythemia myelofibrosis
FLT3	Fibromyalgia syndrome -like tyrosine kinase 3
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IPSS	International Prognostic Scoring System
ITT	Intention-to-treat
IWG	International Working Group
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
IWRS	interactive web response system
JAK	Janus kinase
MF	myelofibrosis
MFSAF v4.0	Myelofibrosis Symptom Assessment Form version 4.0
mITT	Modified intention-to-treat
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
PcD	pharmacodynamic(s)
PK	pharmacokinetics

Abbreviation	Definition
PMF	primary myelofibrosis
PV	polycythemia vera
PVMF	polycythemia vera myelofibrosis
QD	once daily
QoL	Quality of Life
QTcF	QT Interval Corrected Using Fridericia's Correction
RNA	ribonucleic acid
mRNA	messenger ribonucleic acid
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
STAT3	signal transducer and activator of transcription (3)
SVR	spleen volume reduction
TEAE	treatment-emergent adverse event
TSS	total symptom score
ULN	upper limit of normal
WHO	World Health Organization

I. Introduction

A. Background

Myelofibrosis (MF) is a BCR-ABL1-negative myeloproliferative neoplasm (MPN) characterized by bone marrow fibrosis, anemia, progressive splenomegaly, extramedullary hematopoiesis (EMH), debilitating constitutional symptoms, cachexia, leukemic progression, shortened survival, and compromised quality of life (QoL). Myelofibrosis may be de novo or secondary to polycythemia vera (PV) or essential thrombocythemia (ET). Approximately 90% of subjects with MF carry mutations in any of the 3 driver genes: Janus kinase 2 (JAK2) in approximately 60% of cases, calreticulin in approximately 20%, and myeloproliferative leukemia virus oncogene in approximately 10%. Mutant proteins activate the JAK/signal transducers and activators of transcription pathway and other pathways downstream, leading to myeloproliferation, proinflammatory cytokine expression, and bone marrow remodeling.

MF is associated with a heterogenous clinical phenotype, stratifying subjects by prognosis can facilitate choice of appropriate treatment and identify candidates for high-risk procedures such as transplant. The International Prognostic Scoring System (IPSS), used at diagnosis, utilizes 5 independent predictors of inferior survival to determine disease risk in primary MF: age >65 years, hemoglobin <10 g/dL, white cell count >25 × 10^9/L, circulating blasts ≥1%, and presence of constitutional symptoms. The presence of 0, 1, 2, or ≥3 adverse features indicates low-, intermediate 1-, intermediate 2-, or high-risk disease, respectively, and corresponding median survival times range from approximately 11.3 to 2.3 years. The Dynamic International Prognostic Scoring System (DIPSS) can be used to stratify prognosis at any time during the disease course. The DIPSS includes the same 5 prognostic factors as the IPSS but ascribes greater weight to low hemoglobin (2 points instead of 1); risk scoring is modified accordingly, and corresponding median survival estimates for low-, intermediate 1-, intermediate 2-, and high-risk diseases range from not reached to 1.5 years. The subsequent DIPSS-Plus includes 3 additional independent prognostic factors: red blood cell (RBC) transfusion dependence, platelet count <100 × 10^9/L, and unfavorable karyotype.

Until 2019, ruxolitinib, a dual JAK1/JAK2 inhibitor that was approved by the United States (US) Food and Drug Administration (FDA) in 2011 and by the European Medicines Agency in 2012, was the only available drug

indicated for treatment of intermediate- and high-risk MF. Evidence suggests there may be a survival benefit with ruxolitinib compared with conventional therapies. Subjects treated with ruxolitinib frequently experience gradual loss of response, have a suboptimal response, or develop cytopenias during treatment, resulting in ruxolitinib discontinuation within a few months and therefore, a subsequent risk of disease rebound. In the Phase III COMFORT-I and COMFORT-II trials, pooled ruxolitinib discontinuation rates at 3 and 5 years were approximately 50% and approximately 70%, respectively. Suboptimal ruxolitinib dosing to avoid treatment-related AEs, at least initially, appears to be relatively common.

Fedratinib is an oral JAK2 inhibitor with activity against wild-type and mutationally activated JAK2 and Fibromyalgia syndrome-like tyrosine kinase 3 (FLT3). In August 2019, the US FDA approved fedratinib for treatment of adult subjects with intermediate-2 or high-risk primary or secondary MF. The National Comprehensive Care Network (NCCN) clinical practice guidelines for treatment of MPNs now includes fedratinib as an option for subjects with intermediate-2 or high-risk MF with platelet count ≥50 × 10^9/L, used as initial therapy or as second-line therapy for subjects previously treated with ruxolitinib.

Despite the benefits reported with ruxolitinib as the first-line treatment, a high proportion of subjects discontinue treatment; the 1-, 2-, and 3-year discontinuation rates are 49%, 71%, and 86%, respectively. For subjects who discontinue treatment with ruxolitinib, the median overall survival is dismal and ranges from 13 to 16 months. There remains a great unmet need for subjects who are nonresponsive to and have discontinued treatment with a JAK inhibitor.

A detailed description of the chemistry, pharmacology, safety, and key findings of nonclinical and clinical studies for NS-018 is provided in the current Investigator's Brochure (IB).

NS-018 is currently being developed as a therapeutic agent for MPN including MF. NS-018 has been shown to have specificity for inhibiting activated JAK2 and is expected to have a wide therapeutic range, providing a satisfactory margin of safety between its efficacy and its safety. In the Phase 2 part of the Phase 1/Phase 2 study, 15 out of 20 subjects had an SVR of 0% to 50% at Cycle 7 since baseline. One subject who had a baseline platelet count of <50,000/μL, achieved ≥35% SVR at Cycle 7. The available safety data in the Phase 1/Phase 2 study indicate an overall acceptable safety and tolerability profile for NS-018. Based on these data, NS-018 is considered to have a positive benefit-risk ratio for the treatment of subjects with MF and with platelet count of <50,000/μL.

Treatment with specific therapy such as the JAK inhibitor, ruxolitinib, was observed in minority of subjects with platelets below 100,000/μL, which is in line with previous reports. Although there are case reports and series in which JAK inhibitors have been used successfully with improvement of platelet count, JAK inhibitors are not recommended for subjects with severe thrombocytopenia according to the NCCN clinical practice guidelines for treatment of MPNs. The management of severe thrombocytopenia remains unresolved, and future studies focused on subjects with low platelets are deeply needed, to extend their extremely limited treatment armamentarium. Several reports showed additional significant negative impact of severe thrombocytopenia (<50,000/μL) on prognosis of these subjects, but little is known about the impact of severe thrombocytopenia on the outcome of subjects with PMF versus post-PVMF versus post-ETMF. The fact that 1 subject with a baseline platelet count of <50,000/μL achieved ≥35% SVR at Cycle 7 of the NS-018 clinical study as well as the current clinical situation described above, it would be worth considering that NS-018 may have a positive benefit-risk ratio for the treatment of subjects with MF with platelet count of <50,000/μL.

The protocol, NS-018-201, describes the general approach to analysis of data from the study. This Statistical Analysis Plan outlines the statistical principles which will be used to analyze and present the data, including definition of endpoints, stopping rules, and analysis populations. Table, Figure, and Listing shells will be supplied in an accompanying document.

B. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on the Protocol Amendment version 3.0 dated 07 August 2023.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE				
Document	**Date**	**Amendment No.**	**Substantial**	**Region**
Version 3.0	07 August 2023	2	Yes	Europe, North America, Turkey, Poland, and Asia
Version 2.0	15 September 2022	1	Yes	Poland, Turkey, North America, and Asia
Original Protocol	13 October 2021	-	-	Europe, North America, and Asia.

This SAP will govern the analysis of data from this study. The plan can be modified up to the database lock to reflect any changes to the protocol because of amendments. Any amendments to the protocol, which do not affect the statistical analyses, will not necessitate an update to this document. Additional post-hoc or unplanned analyses, which are not defined in this SAP, may be performed to support the clinical development program. Such analyses will be documented in the CSR as deviations from the analysis plan.

II. Protocol Objectives

A. Primary Objectives

The primary objective is to compare the efficacy of the dose of 300 mg *bis in die* (BID) of NS-018 to the Best Available Therapy (BAT) in subjects with primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (post-PVMF), or post essential thrombocythemia myelofibrosis (post-ETMF) with severe thrombocytopenia and to also compare the effect of the dose of 300 mg BID of NS-018 on MF-associated symptoms as measured by Myelofibrosis Symptom Assessment Form version 4.0 (MFSAF v4.0) to the BAT.

B. Secondary Objectives

Secondary objectives of the study are to evaluate whether the dose of 300 mg BID of NS-018 is safe and demonstrates probable benefit for the best splenic response as compared to BAT.

C. Exploratory Objectives

Exploratory objectives of the study are:

- To evaluate the effect of NS-018 on fatigue, on health-related QoL and utility using the EQ-5D-5L, on a bone marrow fibrosis, phosphorylation of STAT3, on platelet, RBC, and transfusion.
- To evaluate plasma PK of NS-018 in the study population.
- To evaluate efficacy, as measured by the rates of complete response (CR), partial response (PR), clinical improvement, stable disease (SD), progressive disease (PD) and relapse, based on the IWG-MRT response criteria.
- To explore changes in the expression profile of mRNA by NS-018 versus baseline assessment.

- To evaluate the splenic response and the effect on improvement of MF-associated symptoms and fatigue up to Week 48.
- To evaluate the splenic response and the effect on improvement of MF-associated symptoms and fatigue after transitioning from BAT to NS-018.

III. Study Endpoints and Estimands

A. Primary Endpoints

The study has co-primary endpoints:

- Proportion of subjects who achieve ≥35% reduction in spleen volume from baseline to Week 24 as measured by MRI (or by CT for applicable subjects).
- Proportion of subjects who achieve ≥50% reduction in total symptom score from baseline to Week 24 as measured by the MFSAF v4.0.

B. Secondary Endpoints

The protocol describes as secondary endpoints the following:

- Proportion of subjects who achieve ≥35% reduction in spleen volume from baseline at any time up to Week 24 as measured by MRI (or by CT for applicable subjects)
- Comparison of the safety of NS-018 versus BAT

C. Exploratory Endpoints

The following exploratory endpoints will be evaluated:

- Improvement in fatigue as measured by Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form (F-SF) 7b.
- Change on health-related QoL and utility using EQ-5D-5L
- Plasma concentration of NS-018.
- Improvement of bone marrow fibrosis.
- Inhibition of phospho-STAT3.
- Rates of CR, PR, clinical improvement, SD, PD and relapse as measured by the IWG-MRT response criteria.
- Proportion of subjects with platelet count of ≥50,000/μL at Weeks 12 and 24.
- Proportion of platelet transfusion-independent subjects at baseline with improvement in grade of thrombocytopenia at Week 24.

- Proportion of transfusion-dependent subjects at baseline who achieve transfusion independence and 50% reduction in transfusion rate at Week 24.
- Improvement in platelet count without transfusion at Week 24.
- Rate of RBC transfusion through Week 24 (defined as the average number of RBC units/subject/month).
- RBC transfusion independence rate and RBC transfusion dependence rate at Week 24.
- Improvement in hemoglobin level without transfusion at Weeks 24.
- Change of mRNA expressions by using mRNA sequencing
- Improvement in splenic response, MF-associated symptoms and fatigue up to Week 48 by NS-018.
- Improvement in splenic response, MF-associated symptoms and fatigue by NS-018 after transitioning from BAT to NS-018.

D. Estimands Considerations

The primary objective of this study can be restated as estimating the treatment effects of NS-018 compared to the Best Available Treatment (BAT) in patients with PMF, post-PVMF, or post-ETMF with severe thrombocytopenia. The primary estimands that are to support regulatory decisions are described below.

Table 1: Lists of Estimands

Endpoint	Estimand Definition	Attributes		
		Population	Variable/endpoint	Population-level summary
Co-Primary	The co-primary estimand of this study is the effect of NS-018 compared to the BAT as measured by ≥35% reduction in spleen volume from baseline to Week 24.	Subjects with PMF, PPV-MF, or PET-MF	Proportion of responders, defined as subjects with at least 35% reduction in spleen size at Week 24 compared to baseline.	Difference in proportion of responders at Study Week 24 between NS-018 and BAT treatment arms will be analyzed as described in Section VIII.B

Co-Primary	The co-primary estimand of this study is the effect of NS-018 compared to the BAT as measured by ≥50% reduction in total symptom score of MFSAF v4.0 from baseline to Week 24	Subjects with PMF, PPV-MF, or PET-MF.	Proportion of responders, defined as subjects who achieved at least 50% reduction in total symptom score at Week 24 compared to baseline.	Difference in proportion of responders for the key secondary endpoint between NS-018 and BAT treatment arms will be analyzed as described in Section VIII.B

Intercurrent events are patient-level events that either change the meaning of a patient's data or make it impossible to collect that data. Values of endpoints can also be missing for reasons other than intercurrent events. Consideration of intercurrent events and strategies to assess their impact are described here:

- Subjects who take prohibited medication during the study will be analyzed by the treatment policy strategy, i.e., data collected after the initiation of prohibited medications will be included in analysis as collected.
- Subjects with dosing adjustments, missing doses or severe treatment non-compliance during the study will be analyzed by the treatment policy strategy.
- Any major protocol deviations that could influence spleen size or TSS will be analyzed with a composite strategy: 1) The Main Analytical Approach: Treatment Policy strategy; 2) Supplementary Analyses: exclusion from Per Protocol (PP) set.
- Week 24 spleen size or TSS data are not available. For example, a subject withdraws from the study prior to Week 24 with or without giving a reason or becomes lost to follow-up. A composite strategy will be adopted: The Main Analytical Approach is, per the protocol and to be conservative, subjects missing the Week 24 assessments will be considered as non-responders for the Primary Analysis. In addition, sensitivity analysis related to imputation of missing data will be performed, as described in Section VIII.C.

IV. Study Design

A. Design Overview

This is a Phase 2b, open-label, multicenter, randomized, controlled, 2-arm study intended to compare the efficacy and safety of NS-018 versus BAT in subjects with PMF, post-PVMF, or post-ETMF. A total of 120 subjects who meet eligibility criteria and consent to participate in the study will be stratified at baseline by spleen volume and by history of prior JAK inhibitor treatment and randomly assigned in a 1:1 ratio to receive either NS-018 or BAT (control arm). The stratification factors will be as follows:

1) spleen volume (≥[redacted] cm^3 vs <[redacted] cm^3)
2) JAK inhibitor (naïve vs prior treatment).

Subjects will have regularly scheduled study visits at Screening, Day 1 and Day 15 of Cycles 1, 2, 3, 4, 5, and 6, and Day 1 of every cycle thereafter.

Subjects in South Korea only will have additional visits on Day 8 and Day 22 of the first cycle for safety laboratory assessments.

The screening period is 28 days before start of treatment. One cycle is 28 days.

During screening, all subjects will be evaluated for active tuberculosis (except in UK). Additionally, inactive (latent) tuberculosis testing will be done in UK and South Korea by local laboratory for all subjects. At Cycle 1 Day 1, before the subject starts study treatment, all eligibility criteria including the subject's status for coronavirus disease 2019 (COVID-19) should be reviewed and confirmed. All subjects will be treated from Cycle 1 Day 1 through the end of the study. There will be an indefinite period from Cycle 7 Day 1 until the subject meets the criteria for the discontinuation of study treatment (see protocol Section 7.1), or until 3 years (expected) after the first subject is enrolled at any of the study centers, whichever comes first.

Subjects who complete the treatment period will complete the end of study procedures within 14 days after the last dose.
Subjects who discontinue prior to completing the treatment period will be asked to complete the end of study procedures within 14 days after the last dose.
If the end of study procedures occurs at a regularly scheduled visit, these procedures may be performed at that time.
A 30-day follow-up phone call will be scheduled after completion of the end of study procedures.

An IDMC will be set up to oversee safety across the life span of the study and all specifics will be captured in the IDMC charter. IDMC data review meetings will be scheduled quarterly intervals during the study timeline, resulting in a minimum of eight (8) planned data review meetings. The first data review meeting will happen after 3 subjects randomized to NS-018 treatment arm have been enrolled and completed Cycle 2 Day 1 of the study. Subsequent meetings will be held quarterly.
The IDMC will also review the results of the interim analysis for futility.

B. Study Population

Eligible subjects for this study are male or female (non-pregnant and non-lactating female for Germany and UK) aged 18 years or older who have been diagnosed with the DIPSS risk categories of intermediate -2 or high-risk PMF, post-PVMF, or post-ETMF with severe thrombocytopenia (platelet count <50,000/μL) with life expectancy >6 months. Subjects must have had no MF-directed (other than JAK inhibitor) for at least 2 weeks prior to initiation of NS 018 or BAT and met pre-specified laboratory values for selected parameters (spleen volume of at least 450 cm^3 measured by MRI or by CT, TSS ≥10 on MFSAF v4.0, Peripheral blood blast count <10%, Estimated creatinine clearance ≥40 mL/min/1.73 m^2, AST and ALT ≤3 × ULN and a direct bilirubin ≤1.5 × ULN, Absolute neutrophil count >500/μL) in addition to multiple other required eligibility criteria (ECOG performance status ≤2, QTcF ≤480 msec). Subjects may or may not have received prior therapy for MF including JAK inhibitor.

Subjects who are **not** eligible for this study are subjects with Active, uncontrolled systemic infection including active tuberculosis infection, subjects with active hepatitis A, B, C or who are HIV-positive, and subjects with serious cardiac condition within the past 6 months or who have been diagnosed with another malignancy within 2 years prior to enrollment or who have had surgery within 4 weeks of screening. Subjects with suspected, probable, or confirmed diagnosis of COVID-19 are excluded from study participation.

C. Sample Size Predictions

A total of 120 randomized subjects (60 in each treatment arm) is planned.

Assuming a splenic response rate of 20% in the NS-018 arm and 1% in the BAT arm, there is 93.5% power at the final analysis to maintain a type I error rate of 5% (i.e., a 2-sided significance level using Fisher's exact test is 5%). Similarly, assuming a symptom response rate of 33% in the NS-018 arm and 8% in the BAT arm, the power of the final analysis to maintain a type I error rate of 5% is 91.0%. Assuming that there is no correlation between spleen volume reduction and TSS reduction, the power to reject the null hypothesis for both endpoints is 85.1%.

D. Treatment Randomization and Blinding

This study is an open-label design in which Investigators, subjects, Sponsor and CRO will know the treatment assignment.

When screening assessments are completed and eligibility is confirmed, subjects will be randomized to a study arm in 1:1 ratio using centralized IWRS.
Randomization will be stratified by spleen volume (≥[redacted] cm^3 vs [redacted] cm^3) and a history of prior JAK inhibitor treatment (naïve vs prior treatment).

Spleen volume will be assessed by the central reader who will be blinded to treatment assignments.

E. Assessment Schedule

All subjects will be treated from Cycle 1 Day 1 through the end of the study. The acceptable visit window for scheduled visits is ± 3 days.
The following table provides the different assessment across the visit schedules.

Table 2 : Summary of the schedule of study procedures.

Visit Timing		Study procedure
Screening	Day -28 to Day 0	Informed consent, Review/confirm eligibility criteria, COVID-19 status verification, Genetic substudy informed consent (optional), Medical history, Physical examination, MRI/CT (spleen volume measurement), Vital signs, ECOG PS, Active tuberculosis, Clinical laboratory (by central lab), Latent tuberculosis** (local laboratory), Pregnancy test, 12-lead ECG, Bone marrow assessment, AEs, Concomitant therapies/procedures/medication.

Cycle 1	Day 1 (Day 1/ WK 0)	Review/confirm eligibility criteria, Vital signs, ECOG PS, Clinical laboratory (by central lab), 12-lead ECG, Genetic profiling, EQ-5D-5L, Randomization, Dispense study treatment/diary, AEs, Concomitant therapies/procedures/medication. NS-018 treatment arm only: PK sampling, Phospho-STAT3, mRNA sequencing.
	Day 8 (Day 8/ WK 1)	Clinical laboratory*(by local lab)
	Day 15 (Day 15/ WK 2)	Clinical laboratory (by central lab), 12-lead ECG, AEs, Concomitant medication.
	Day 22 (Day 22/WK3)	Clinical laboratory*(by local lab)
Cycle 2	Day 1 (Day 29/ WK 4)	Physical examination, Vital signs, Clinical laboratory, 12-lead ECG, Response assessment (IWG MRT and ELN), Dispense study treatment/diary, AEs, Concomitant therapies/procedures/medication. NS-018 treatment arm only: PK sampling, Phospho-STAT3, mRNA sequencing.
	Day 15 (Day 43/ WK 6)	Clinical laboratory (by central lab), AEs, Concomitant medication
Cycle 3	Day 1 (Day 57/ WK 8)	Physical examination, Vital signs, Clinical laboratory, Response assessment (IWG MRT and ELN), Dispense study treatment/diary, AEs, Concomitant medication
	Day 15 (Day 71/ WK 10)	Clinical laboratory (by central lab), AEs, Concomitant medication
Cycle 4	Day 1 (Day 85/ WK 12)	Physical examination, MRI/CT (spleen volume measurement), Vital signs, Clinical laboratory, 12-lead ECG, Response assessment (IWG MRT and ELN), Dispense study treatment/diary, AEs, Concomitant medication
	Day 15 (Day 99/ WK 14)	Clinical laboratory (by central lab), AEs, Concomitant medication
Cycle 5	Day 1 (Day 113/ WK 16)	Vital signs, Clinical laboratory (by central lab), Dispense study treatment/diary, AEs, Concomitant medication
	Day 15 (Day 127/ WK 18)	Clinical laboratory (by central lab), AEs, Concomitant medication
Cycle 6	Day 1 (Day 141/ WK 20)	Vital signs, Clinical laboratory (by central lab), Dispense study treatment/diary, AEs, Concomitant medication
	Day 15 (Day 155/ WK 22)	Clinical laboratory (by central lab), AEs, Concomitant medication
Cycle >=7	Day 1 (Every +Day 28/ WK 4)	Vital signs, Clinical laboratory (by central lab), AEs, Concomitant medication. Cycle 7 and Every 3 cycles: Physical examination, 12-lead ECG, Response assessment (IWG-MRT and ELN), Dispense study treatment/diary. Cycles 7, 10 and 13: MRI/CT (spleen volume measurement) Cycle 7 and Every 6 cycles: EQ-5D-5L Cycles 7, 13 and every 12 cycles: Bone marrow assessment

Complete End-of-Study Procedures		Physical examination, MRI/CT (spleen volume measurement), Vital signs, ECOG PS, Clinical laboratory (by central lab), Pregnancy test (serum), 12-lead ECG, Response assessment (IWG MRT and ELN), AEs, Concomitant medication
End of Study	30-Day Follow-up (Phone call)	AEs, Concomitant medication

* For South Korean Sites Only.
** For UK and South Korean Sites Only.

During the screening period, subject will complete the **MF-SAF v4.0** assessment daily. The first 7 consecutive days of diary data will be used for eligibility assessment. Subject will complete the MF-SAF from Day −7 of Cycle 1 Day 1 to the end of Cycle 6 (Day 168) and the last 7 days in each cycle thereafter until the end of Cycle 12 (Day 336) for efficacy assessment.

The **PROMIS** questionnaire must be completed daily during the screening period and the last 7 days of each cycle until the end of Cycle 12 (Day 336). This assessment will be performed for all subjects including subjects transitioning from BAT to NS-018.

V. Interventions

A. Clinical Trial Material (CTM)

The drug product is NS-018 (ilginatinib), a potent and specific JAK2 inhibitor which was designed and synthesized by Nippon Shinyaku Co., Ltd. NS-018 is being developed as a therapeutic agent for MPN including MF.

NS-018 is provided in film-coated tablets orally administrated. The tablet contains 100 mg of active NS-018 drug substance and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. Additionally, the coating film Opadry OY-L-28900 contains polyethylene glycol, hypromellose, titanium dioxide and lactose monohydrate.

Subjects will self-administer 300 mg BID of NS-018 2 hours or more after the last meal and at least 1 hour before the next meal. Each dose must be administered 8 to16 hours apart.

The BAT will be administered according to manufacturer’s instructions and Investigator discretion. The Investigator will decide the BAT that will be administered to the subject during the screening period based on

subject's condition. The BAT may include hydroxyurea, danazol, fedratinib, ruxolitinib, interferon, corticoid, erythropoietin, purinethol, thalidomide, lenalidomide or 'supportive care/therapy'. The BAT 'supportive care/therapy' refers to use of blood products, fluids (crystalloids), pain medications, and/or antibiotics, that subjects will need to manage myelofibrosis symptoms and complications. Subjects in the control group will receive BAT at doses and schedules selected by the Investigator based on the subject's condition and according to the manufacturer's instructions or the Investigator's discretion. The BAT must be a single agent and cannot be combined with other agents. JAK inhibitor can be allowed as BAT if the JAK inhibitor was administered as a standard of care based on the product label or Investigator's discretion. The BAT may be changed at any time during the randomized treatment period based on the Investigator's clinical assessment of the subject's condition. However, it is not allowed to change the BAT to JAK inhibitor if it was not used as standard of care treatment prior to study participation. No experimental agents (those not approved for any indication) may be used at any time.

B. Study Procedures

Subjects meeting the eligibility criteria were screened for the study after the nature and purpose of the protocol were explained to them, and they or a legally authorized representative voluntarily granted written informed consent to participate.

Subjects will receive NS-018 or BAT according to treatment assignment from Cycles 1 to 6 until one of the following criteria for disease progression is met:

1. Increase in spleen volume of ≥15% measured by MRI (or by CT for applicable subjects) from the baseline for subjects who are randomized to NS-018 or transitioned to NS-018.
2. Splenic irradiation or splenectomy.
3. Leukemic transformation defined by an increase in peripheral blood blast percentage to ≥20% that is sustained for at least 8 weeks.
4. Leukemic transformation defined by bone marrow blast count of ≥20%.
5. Death.

Subjects who meet the criteria for increase in spleen volume of >15% measured by MRI (or by CT for applicable subjects), leukemic transformation, or have had splenic irradiation will be discontinued from

the study treatment and will be asked to complete the end of study procedures. Subjects randomized to the BAT arm (ie, subjects already on BAT or 'supportive care/therapy') and met all of the following criteria may transition to NS-018 treatment:

- Subject has completed at least 24 weeks on BAT or had progression of disease prior to Week 24; progression must be declared based only on an increase in splenic volume of >15% measured by MRI (or by CT for applicable subjects) from baseline.
- Subject has not undergone splenic irradiation or splenectomy.
- Subject does not meet criteria for leukemic transformation.

For subjects receiving BAT and transitioning to NS-018 before Cycle 7 Day 1, subjects will be required to taper off or washout this treatment before initiation of NS-018.

Procedures conducted at each visit time to assess the study drug safety, pharmacodynamics, and pharmacokinetics to achieve the study objectives are summarized in the Study procedure column of the Table 2 in section IV.E.

VI. General Analytical Considerations

A. Data Sources

All data are collected via electronic case report forms (eCRFs) defined by and provided by the Sponsor or designee through remote data entry; subject data necessary for analysis and reporting will be entered into a validated database or data system. Appendix 2 of the protocol provides additional details regarding data recording and handling.

B. Visit Windows

The visit number for analysis purposes will be the visit number assigned by the investigator at the time of the visit (i.e., nominal visits).

C. Definition of Baseline

Cycle 1 Day 1 is the date of initiation of NS-018.The day before initiation of NS-018 will be Day -1.

For analysis purposes, baseline is defined as of the last data available within 28 days prior to initiation of NS-018. For BAT, unless otherwise

specified, it is the last data available up to and including the Cycle 1 Day 1 visit.
Bone marrow assessment performed within 6 months prior to the first dose can be used as baseline.

For spleen size (palpation) and spleen volume assessment, baseline values should be obtained within 14 days prior to the first dose of study treatment.

MFSAF v4.0 assessment will be assessed daily for the first 7 consecutive days of entry through the screening period for eligibility.

For Genetic Profiling, Phospho-STAT3 and mRNA sequencing assessment, baseline will be the value on Cycle 1 Day 1 and may be obtained within 24 hours prior to study treatment administration.

For SAF2 (Second Safety) population, baseline will consist of the last data available prior to initiation of NS-018.

D. Missing Data

Any subjects who discontinue study treatment will not be replaced. If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a subject withdraws from the study, the subject may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records. Subjects who do not reach Week 24 will be considered treatment non-responders (i.e., did not achieve ≥35% SVR from baseline to Week 24).

Unless stated otherwise, missing data will not be replaced with imputed values.

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month.

"COVID-19 VACCINE" and AEs missing date will be analyzed under the same rule as above.

Incomplete start and stop dates will be listed as collected without imputation.

E. Multiple Study Centers

There will be no adjustment for multiple study centers in the analysis.

F. Covariate Adjustment in Primary Analysis

This study uses a stratified randomization schedule when enrolling subjects. The stratification factors will be included as covariates in efficacy analysis. The main statistical analyses of primary and secondary efficacy outcomes comparing NS-018 with BAT will be adjusted by spleen volume strata (≥ [redacted] cm^3 vs < [redacted] cm^3), and history of prior JAK inhibitor strata (naïve vs prior treatment).

G. Multiplicity Adjustment

The efficacy of SVR and TSS, as co-primary endpoints, will be confirmed when the null hypotheses of SVR and TSS are rejected simultaneously.

As we have co-primary endpoints, multiplicity issue can arise and then the adjustment needs to be made. Hochberg procedure for multiple comparisons will be used for the evaluation of the primary endpoints. For the two endpoints, the Hochberg procedure results in the following rule: if the maximum of the two p-values is less than 0.05 (2-sided tests), then both hypotheses are rejected and claim the statistical significance for both endpoints. Otherwise, the minimum of the two p-values needs to be less than 0.025 for claiming the statistical significance.

If both primary endpoints are significant, then the secondary efficacy endpoint will be tested at 0.05 significance level (two-sided).

H. Interim Analyses or Timing of Analyses

The primary efficacy analyses will be conducted after all subjects have completed assessments at Week 24 (Cycle 7 Day 1).

An Interim Analysis for CSR will be conducted after all subjects have reached 24 weeks of follow-up.

A final analysis will be conducted at the end of the study.

An IDMC will be set up to oversee safety across the life span of the study and all specifics will be captured in the IDMC charter. The scope of the analysis will be Demographics, disposition, AE/SAE, VS and Lab data.

According to the IDMC Charter,

An interim analysis for futility on splenic response will be carried out when 60 subjects (50% of randomized subjects) have completed assessments at Week 24 (Cycle 7 Day 1). The IDMC will additionally review the results of the interim analysis for futility and will make appropriate recommendations based on those results. Conditional power will be used as the statistical rule to guide the decision of whether to stop the trial early for futility.

Note (details) on Conditional Power (CP) [4]:

Conditional power quantifies the probability that the null hypothesis of no treatment effect will be rejected at the end of the study with a given statistical test, given the primary endpoint data observed thus far.If this quantity is very small, a conclusion can be reached that it would be futile to continue the investigation[3].

I. Analysis Populations

Analysis sets define the subjects to be included in an analysis.
Six analysis sets/populations will be defined for use with various analyses and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

Intent-to-treat (ITT) Population. The ITT population will include all randomized subjects.

Modified Intent-to-treat (mITT) Population.The mITT population will consist of all randomized subjects who receive at least 1 dose of study treatment and have a baseline assessment and at least 1 post-baseline efficacy assessment. Subjects will be analyzed as randomized.
This will be the primary analysis population for the evaluation of efficacy.

Safety (SAF) Population. All randomized subjects who receive at least one dose of the study treatment will be included in the (SAF) population.

For BAT subjects who do not receive therapy, a Cycle 1 Day 1 visit is required to be included in the SAF. Subjects will be analyzed as treated. This will be the primary analysis population for the evaluation of exposure and safety.

Second safety (SAF2) population. A SAF2 population will consist of subjects randomized to BAT who complete BAT through 6 cycles and go on to receive at least 1 dose of NS-018. Baseline will consist of the last data available prior to initiation of NS-018.

Per-Protocol population (PP). The PP population consist of subjects treated for the first 4 weeks without a major protocol violation that might affect the efficacy assessment.

PK concentration Population. The PK concentration population will consist of all randomized subjects who received at least 1 dose of study treatment and have at least 1 plasma concentration value forNS-018. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.

J. Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures.

All observed and derived variables (e.g., change from baseline, percentage change from baseline, and response status) that are analyzed or summarized will be listed by subject. Descriptive statistics will provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentage will be appropriate for the purpose of the analysis. For continuous parameters, descriptive statistics will include number of subjects, mean, standard deviation (SD), median, minimum, and maximum.

The summaries and listings will be separated by treatment arm.

All calculations and analyses will be conducted using SAS® Version 9.4.

VII. Subject Accountability

A. Disposition

Enrolled. A hierarchical table of the populations will summarize the relationship of the analysis populations. Given population definitions, the ITT population will be treated as the starting, parent population. The summary will present the number and percentage of subjects in each of the categories listed below:

- Subjects Signed Inform Consent (Overall only)
- Screen Failures (Overall only)
- Screened and Randomized subjects (ITT)
- The numbers and percentages of mITT *population* will be presented for each treatment arm.
- The numbers and percentages of *SAF population* will be presented for each treatment arm.
- The numbers and percentages of *SAF2 population* will be displayed only for NS-018 arm.

For each column, the denominator for the percentage calculation will be the total number of randomized subjects analyzed (ITT) for that column.

An additional summary of enrolled subjects will display the numbers and percentages of the disposition including the following:

- Primary reason subjects discontinued of study treatment
- Primary reason subjects' withdrawal from the study

Percentages of subjects who withdrew for each of these reasons will be calculated using all members of the relevant population in the relevant treatment arm for the denominator.

In addition, the number of patients by site and investigator will be presented by treatment group and overall.

B. Protocol Deviations and Population Inclusions

A major protocol deviation is a protocol deviation that may significantly affect the completeness, accuracy, and/or reliability of the study data (major data protocol deviation) or that may significantly affect a subject's rights, safety, or well-being (major GCP protocol deviation). Prior to database lock, all documented protocol deviations will be reviewed to identify major protocol deviations by a data review team including representatives from clinical operations, medical, data management, and statistics. Major protocol deviations will be categorized as either major data protocol deviations or major GCP protocol deviations.

All protocol deviations will be listed. Major protocol deviations will be flagged. A listing will identify subjects who were enrolled even though they did not meet one or more eligibility criteria, and subjects who met withdrawal criteria discernible from recorded data during the study but were not withdrawn. A separate listing of subjects in the ITT population who were excluded from the Efficacy Population will indicate the reason for the exclusions.

C. Subject Characteristics

Demography. Subject demographic variable including age, gender (Male, Female), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported) and race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Unknown) and will be summarized by treatment arm and overall by appropriate descriptive statistics for all ITT, mITT and Safety populations.

Where date of birth is collected, age will be calculated as the number of years between the date of birth and the date of informed consent. Where date of birth is not collected due to country-specific regulations, the subject's age as provided by the investigator will be used.

A by-subject demographic listing will be provided by subject ID number in ascending order.

Other Baseline Characteristics. Baseline characteristics including weight at baseline, ECOG performance status (score =0, 1, 2, 3, 4), spleen volume, history of prior JAK inhibitor treatment and transfusion dependence status (Yes, No) will be summarized by treatment arm and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order.

Disease history. Disease history and disease characteristics include type of MF, time since initial diagnosis, diagnostic classification, DIPSS Adverse Prognostic Factors, DIPSS risk category, time since DIPSS Assessment, screening platelet results - based on 2 consecutive measurements (first platelet count, second platelet count and average platelet count at screening).

Qualitative data will be described using frequency and percentages and continuous data will be summarized by appropriate descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

A by-subject listing will be provided.

Medical History.
Subjects with any condition entered on medical-history elements prior to consent will be listed with the description of medical condition and onset and resolution dates.

Surgical History
A by-subject listing with any disease-specific surgical procedures prior to consent will be provided with the description of surgical procedure and the procedure start and end dates.

Prior Disease Treatment*.* Any prior myelofibrosis therapy including transfusions prior to consent will be presented with the number (lines) of the therapy, its indication (PMF, post-PMF, post-ETMF and other), the time (month) between last treatment and the start of the study treatment, the number of days of interruption and its reason, and the best response of the therapy. Also, it will be indicated if the therapy is a JAK inhibitor. In addition, a by-subject listing of other prior disease treatment will be provided by subject ID number in ascending order.

COVID-19 Assessment. The number and percentages of subjects assessed for COVID-19 infection with their vaccination status will be tabulated and a by-subjects listing of COVID-19 status will be provided.

VIII. Efficacy Analyses

Efficacy data collected after Week 24 will be presented separately

A. Definition of Efficacy Outcomes

Reduction of ≥35% in spleen volume. Subjects who achieve ≥35% reduction in spleen volume from baseline to Week 24 as measured by MRI (or by CT for applicable subjects) will be defined as a responder, otherwise they will be considered as a non-responder. The responder rate will be based on the percentage change in spleen volume (SpV) from baseline (B) in the 24 Week treatment (T), which is defined as follows:

% SpV Change = [(SpV (T) - SpV (B)) / SpV (B)] x100%

Reduction of ≥50% in TSS. Subjects who achieve ≥50% reduction in Total Symptom Score from baseline to Week 24 as will be defined as a responder, otherwise they will be considered as a non-responder. The responder rate will be based on the percentage change in TSS from baseline (B) in the 24 Week treatment (T), which is defined as follows:

% TSS Change = [(TSS (T) - TSS (B)) / TSS (B)] x100%

The MFSAF v4.0 assesses the severity of 7 core symptoms of myelofibrosis: fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side, early satiety, and bone pain. The MFSAF v4.0 asks respondents to report symptom severity at its worst for each of the 7 items on a 0 (Absent) to 10 (Worst Imaginable) numeric rating scale. The MFSAF v4.0 is scored as a unidimensional scale to create a TSS.

The TSS for the 24-hour recall (i.e., daily diary) format is calculated as the sum of the 7 individual item responses on the 0 to 10 scale for a possible TSS range of 0 to 70.

- The daily TSS is the sum of the scores for the following symptoms: tiredness, early satiety, abdominal discomfort, night sweats, pruritus, bone pain, and pain under ribs on the left side (excludes the inactivity score).

- The baseline TSS is the mean of the daily TSS over the 7 consecutive days prior to the start of treatment. A similar approach will be performed when defining the TSS values for Cycles 7, 8, 9, 10, 11 and 12. Missing values during these days are handled as described below.

- Week 24 TSS is the mean of the daily TSS obtained during the 28 consecutive days at Cycle 6. A similar approach will be performed when defining the TSS values for Cycles 2, 3, 4 and 5.

Handling of Missing TSS Values

- If any of the seven individual symptoms scores are missing, the TSS for that day will be considered as missing.

- The baseline TSS is set to missing if fewer than 4 daily TSS are available out of the 7 consecutive days prior to the start of study

treatment. A similar approach will be performed when defining the TSS values for Weeks 28, 32, 36, 40, 44 and 48.

- The Week 24 TSS is set to missing if fewer than 20 daily TSS are available out of the 28 consecutive days prior to Week 24 spleen volume scan date (or Week 24 visit date if scan date is missing). In sensitivity analyses where Week 24 TSS is derived from the mean of 7 consecutive days of daily TSS, the Week 24 TSS is set to missing if fewer than 4 daily TSS are available out of the 7 consecutive days prior to Week 24 spleen volume scan date (or Week 24 visit date if scan date is missing). Missing TSS at other post-baseline time-points is similarly handled. A similar approach will be performed when defining the TSS values for Weeks 8, 12, 16 and 20.

Best splenic response. Subjects who achieve ≥35% reduction in spleen volume (SpV) from baseline (B) compared to Cycle 4 Day 1 or Cycle 7 Day 1 will be considered as responders. subjects who do not achieve ≥35% reduction in spleen volume (SpV) from baseline (B) compared to Cycle 4 Day 1 and Cycle 7 Day 1 will be considered as non-responders.

$$\% \text{ SpV Change (i)} = [(\text{SpV (Ti)} - \text{SpV (B)}) / \text{SpV (B)}] \times 100\%$$

Improvement in fatigue. Fatigue will be measured daily by PROMIS F-SF 7b and subjects will be asked to evaluate their fatigue since waking up. The PROMIS Fatigue item banks assess a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles. Fatigue is divided into the experience of fatigue (frequency, duration, and intensity) and the impact of fatigue on physical, mental, and social activities. Improvement in fatigue will be indicated by a negative deviation over baseline.

Change on Health-Related (H-R) QoL and utility using EQ-5D-5L. The EQ-5D-5L questionnaire is a generic measure of health status that provides a descriptive profile and a simple index value. It includes 5 items assessing mobility, self-care, usual activities, pain / discomfort, anxiety / depression. Each dimension has 5 levels response scored on a scale of 1 to 5: no problems, slight problems, moderate problems, severe problems, and extreme problems. For each item, a lower score indicates better health status. A negative change in outcome measures at a post-baseline visit indicates an improvement of H-R QoL over the baseline.

Improvement of bone marrow fibrosis. Bone marrow will be assessed by aspiration and biopsy, according to standard practice at the site at baseline (Screening), Cycle 7 Day 1, Cycle 13 Day 1 and at every 12 cycles thereafter. The parameters in cellular composition of the bone marrow aspirate and biopsy include %Blasts, Cellularity (Cellularity, %Cellularity), Morphology (M:E Ratio, Megakaryocytes, Degree of Dysplasia Present), Cell differential (Total Cells Counted, Promyelocytes, Myelocytes, Mature Granulocytes, Eosinophils, Erythroid Cells, Monocytes). Also, as a part of Bone marrow assessment, Fibrosis score (grade) will be graded using European Consensus Criteria for Grading Myelofibrosis (Thiele et al., 2005) and reported from worst case to better case scale as MF-0, MF-1, MF-2, and MF-3 in Bone Marrow Biopsy. Shift in fibrosis Grade in the bone marrow from Baseline is defined as the status change of fibrosis at time of worst/best response (whenever it occur) compared to fibrosis status at baseline.

Treatment response. Treatment response will be assessed during the study at Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, and at every 3 cycles thereafter (Day 1) using the IWG-MRT and ELN Response Criteria for treatment response in myelofibrosis. The criteria are provided in

Appendix 1. The response, to be assessed following each bone marrow sampling, will be categorized as Complete Response (CR), Partial Response (PR), Clinical Improvement (CI), Anaemia Response, Spleen Response, Symptoms Response, Progressive Disease (PD), Stable Disease (SD), Relapse, Cytogenetic Remission, Molecular Remission, Cytogenetic/Molecular Relapse. The subject who discontinues without post-baseline response assessment will be categorized as Not Evaluable (NE) during final data analysis. Objective response rate (ORR) is the proportion of responders with MF. Clinical advantage rate (CAR) is the proportion of MF subjects with clinical benefit (Complete Remission (CR), Partial Remission (PR), Clinical Improvement (CI), Anaemia Response, Spleen Response, Symptoms Response, Stable Disease).

Change in platelet counts. Subjects with platelet count of ≥50,000/μL at Weeks 12 and 24 will be defined as a responder, otherwise they will be considered as a non-responder.

Change in blood transfusion dependency. For the purposes of this assessment, we will consider these following definitions.

- ***Transfusion dependence at baseline*** will be defined as subject who received at least 6 units of packed red blood cells (PRBC), in the 12 weeks prior to first study drug, for a hemoglobin level of <85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study drug administration.
- ***Transfusion dependence at Week 24*** will be defined as the use of 6 or more units of red blood cell product(s) during any consecutive 12 weeks prior to Week 24 for a hemoglobin level of <85 g/L, in the absence of bleeding or treatment-induced anemia.
- ***Transfusion independency at baseline*** will be defined as subject who didn't meet the definition of transfusion dependence at baseline.
- ***Transfusion independency at Week 24*** will be defined as no (0) use of PRBC during any consecutive rolling 12 weeks interval during the treatment phase, capped by a hemoglobin level of ≥85 g/L for subjects who met the definition of transfusion dependence at baseline. Subjects who were not transfusion-dependent at baseline and who required transfusions during the study, but not during the last 12 weeks of observation, will be considered transfusion independent.
- ***Improvement in platelet count*** is marked by an increase of platelet count from baseline.

- ***Improvement grade of thrombocytopenia*** is marked by an increase in the number of platelets which make change in grade defined as *Grade 3* (<50,000/μL), *Grade 2* (50,000 -<75,000/μL), *Grade 1* (75,000/μL – <LLN).
- ***Improvement in hemoglobin level*** is indicated by an increase of hemoglobin level.
- ***Rate of RBC transfusion at Week 24.*** Rate of RBC transfusion will be calculated as the total number of RBC units across all subjects divided by the total exposure time among these subjects through Week 24. excluding cases due to overt bleeding per subject month from the first dose.
- ***Improvement grade of hemoglobin*** is marked by an increase in the level of hemoglobin which make change in grade defined as *Grade 3* (<8 – 6.5 g/dL), *Grade 2* (<10 – 8 g/dL), *Grade 1* (10 g/dL – <LLN).

Pharmacokinetics and Pharmacodynamics. The PK and PcD assessments will be performed with PK population. The PK parameters to be estimated include observed C_{max}, time to maximum plasma concentration (T_{max}), AUC, terminal elimination half-life ($t_{1/2}$), and accumulation ratio (AR). The PcD assessment include Phospo-STAT3 assessment and mRNA sequencing.

B. Analysis Methods for Primary Efficacy Analysis

The study has co-primary endpoints. The primary efficacy analyses will be performed on the mITT population.

A Firth-corrected logistic regression model will be used to compare the **proportion of subjects who achieve ≥35% SVR from baseline to Week 24** and the **proportion of subjects who achieve ≥50% reduction in TSS from baseline to Week 24** between the NS-018 arm and the BAT arm. Baseline spleen volume and a history of prior JAK inhibitor treatment as recorded on the CRF will be included as covariates. A secondary analysis using the stratification factors at the time of randomization may be added. Model-based point estimates for the treatment effects, and p-values, and odds ratio with its 95% confidence interval will be reported for each treatment arm.

The null hypothesis (H_0) and the alternative hypothesis (H_A) are:

> H_0: The proportion of subjects who achieve ≥35% SVR (resp. ≥50% reduction in TSS as measured by MFSAF v4.0) from baseline to Week 24 in each treatment arm is the same.

H_A: The alternative hypothesis is that the proportion of subjects who achieve ≥35% SVR (respectively ≥50% reduction in TSS as measured by MFSAF v4.0) from baseline to Week 24 is different by treatment arm.

Subgroup analyses may be performed by age, gender, stratification factors, diagnostic classification and DIPSS risk category. Other baseline characteristics may be included in the analysis depending on the data.

Subjects who do not reach Week 24 for any cause including death prior to Week 24 will be considered treatment nonresponders (i.e., did not achieve ≥35% SVR from baseline to Week 24 and did not achieve ≥50% reduction in TSS from baseline to Week 24, respectively).

As descriptive purposes, the count and the percentage of subjects who achieve ≥35% SVR from baseline to Week 24 and subjects who achieve ≥50% reduction in TSS from baseline to Week 24 will bepresented by treatment arm. In addition, descriptive statistics will be presented by treatment arm for **Spleen Volume** and **TSS as measured by MFSAF v4.0** will be summarized by using descriptive statistics. The actual value, the change and the percentage change from baseline will be presented.

C. Sensitivity and Supporting Analysis

Using the mITT population, as sensitivity analysis of the primary endpoint of SVR at Week 24, imputation will be used to evaluate the impact of missing data. Subjects who experience death from any cause prior to Week 24, the last SVR will be imputed to Week 24 for the first primary endpoint.
A second sensitivity analysis will be performed for missing Week 24 spleen volume/TSS where subject data will be imputed using the last non-missing value, except for death or initiation of other MF or anti-cancer therapy where missing will be imputed as non-responders.

The analysis described above (Section B) will be repeated for the PP Population.
Other supporting analysis will include Fisher's exact test, chi-square test and Cochran-Mantel-Haenszel (CMH) test of the co-primary and key secondary endpoints.

D. Analysis Methods for Secondary Efficacy Analysis

The **proportion of subjects who achieve ≥35% SVR at any time up to Week 24** will be compared between the NS-018 arm and the BAT arm using Firth-corrected logistic regression model. Covariates of baseline spleen volume and a history of prior JAK inhibitor treatment will be included.

Subjects who do not reach Week 24 for any cause including death prior to Week 24 will be considered treatment nonresponders (i.e., did not achieve ≥35% SVR at any time up to Week 24).

E. Analysis Methods for Exploratory Analysis

For **EQ-5D scores** and each of **PROMIS symptoms/items scores**, for each of the parameters in cellular composition of the **bone marrow aspirate and biopsy**, descriptive statistics will be presented by treatment arm for actual value, change from baseline, and percentage change from baseline by visit, and for the maximum and minimum percentage change from baseline.
In addition, the mean and its 95% confidence interval (CI) will be presented for the actual value, its change from baseline, and its percentage change from baseline by visit; and for the maximum and minimum percentage change from baseline.

Also, For **EQ-5D scores** and each of **PROMIS symptoms/items scores**, and **bone marrow fibrosis grade**, the shift of the score from baseline to post-baseline will be summarized by the visit day and greatest reduction. Additionally, change from baseline will also be displayed using a line plot with time point (scheduled visit) on the x-axis, mean change score on the y-axis, and standard errors around each mean score. Separate lines will be presented for each treatment arm.

The counts and the percentage of **subjects showing improvement** compared to baseline (i.e., the responder) will be presented for each visit for **QoL,** for **fatigue,** for **bone marrow fibrosis grade** and for **platelet counts**.

The **overall response rate** will be presented by treatment arm and the numbers and percentages of subjects who have best overall response as CR, PR, CI, SD, and PD will also be provided. ORR and CAR and their Binomial exact 95% confidence interval will be presented.

Descriptive statistic of **rate of RBC transfusion through Week 24**, **independence** and **dependence** RBC transfusion rate at Week 24 will be presented by treatment arm. Transfusions due to clinically overt bleeding will be excluded from this analysis.

The count and the percentage of subjects showing **improvement in platelet count without transfusion** will be presented by treatment arm for each visit.

The proportion of **subjects** whose **transfusion status** (dependent or independent) **changed** over baseline (from dependent to independent or vice versa), will be tabulated with summary statistics.

The number and percent of subjects who received any blood component transfusions will be summarized by blood component (PRBC (Packed Red Blood Cells), platelets), and visit when the transfusion data were collected.

Proportion of **platelet transfusion-independent subjects** at baseline with **improvement in grade of thrombocytopenia** at Week 24; proportion of transfusion-dependent subjects at baseline who achieve **transfusion independence and 50% reduction in transfusion rate** at Week 24 will be tabulated with summary statistics.

A by-subject listing will be provided by treatment arm and visit for all the items cited above.

IX. Safety Analyses

The primary safety analyses will be performed on the safety (SAF) population. Safety data from the SAF2 population will be presented separately.

A. Exposure to NS-018

Exposure to the NS-018 will be summarized as the duration of exposure, the amount of drug exposure and the compliance. Study drug in this section refers to NS-018.

Duration of Exposure to Study Drug. The duration of study drug administration is defined as the time interval from first (non -zero)

dose of study drug administration to last study drug administration date (i.e., last known study drug administration date).
The following algorithm will be used to calculate the duration of study drug exposure for subjects who took at least 1 dose of study drug:

Duration of exposure (days) = [(last dosing date) – (first dosing date) + 1 day]

The duration includes the periods of temporary study drug interruption. For subjects who did not take any study drug, the duration of exposure is defined as zero.
If the last study drug dosing date is missing, the following rule should be used for the imputation of the last dosing date:

- If the study drug is permanently withdrawn, the latest date among the study drug end date (in EOT) will be used.
- If the study drug completion status is unknown the date of death will be used for analysis.
- If the stop date is partial then the stop date will be imputed with the earliest of the last day of the month (if only day is missing) or the last month of the year (if day and month are missing), or the death date if applicable.
- If the dose end date is completely missing and there is no EOT page and no death date, the subject is considered as on-going: The subject should be treated as on-going, and the cut-off date should be used as the last dosing date.

After imputation the imputed date will be compared with the start date of treatment, if the imputed date is less than the start date of treatment: the treatment start date will be used.

If start date is missing, then end-date should not be imputed (subjects with missing start dates are to be considered missing and no imputation will be made).

Amount of drug exposure. The total number of tablets administered, the cumulative dose, the dose intensity and the relative dose intensity will be summarized using descriptive statistics (n, mean, sd, median, min-max) by treatment arm.

The presumed total number of tablets administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

*Total number of Dose Administrated = (No. of Tablets Dispensed – No. of Tablets Returned.) * 100mg*

If a tablet is not returned or returned with unknown number of tablets, it is assumed that subject did not consume any tablet from this tablet.

Cumulative dose is defined as the total sum of all doses taken per subject for each cycle and during the study drug exposure.

Dose Intensity (mg/day) and Relative Dose Intensity (% of planned) will be calculated for per subject for each cycle as

Dose intensity (DI) = Cumulative dose (mg) / Duration of exposure (days)

*Relative dose intensity= [dose intensity / planned dose intensity] *100),*

Dose Modification*.* The number and percentage of subjects who had dose increase, dose reduction and/or dose interruption, drug permanently withdrawn, and overdose along with corresponding reasons for each will be summarized by treatment arm and overall.

Compliance. Dispensation and accountability will be presented in a by-subject listing with the planned total daily dose, the actual total daily dose, the dose action, and the reason for the dose action.

B. Exposure to BAT

Exposure to BAT will be summarized by the number and percentage of subjects with corresponding therapy types and the number of therapy cycles for which BAT was administered.

The dose and frequency of BAT therapy will be presented in a by-subject listing, including dose actions (dose interrupted, dose decreased/increased/overdose, drug withdrawn) and the reason of dose action.

C. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 will be used to classify all safety events with respect to system organ class (SOC) and preferred term (PT). Within each system organ class, the tables will display the counts and percentages of subjects reporting at least one AE, as designated by the preferred terms.

AE summaries will include treatment-emergent AEs (TEAEs), that is, AEs that first occurred or worsened in severity after the first administration of

study treatment, and up to 30 days after the last administration of study treatment. The following AE summaries will be produced:

- All TEAEs: for each study treatment, numbers of TEAEs and incidence rates will be tabulated by preferred term and system organ class.
- Serious TEAEs by System Organ Class and Preferred Term
- Serious TEAEs by Preferred Term
- TEAEs leading to death
- TEAEs leading to discontinuation of study treatment. This subset includes TEAEs with an Action Taken of “Drug Withdrawn.”
- TEAEs by Severity. On this table, treatment arms will be subdivided into five potential grades of AE severity— Mild (Grade 1), Moderate (Grade 2), Severe (Grade 3), Life threatening (Grade 4) or Death (Grade 5) based on CTCAE v5.0 and one additional category for subjects included in Grade 3-5. TEAEs missing a severity grade will not be included. An AE reported by a subject more than once will be represented in the most severe category.
- TEAEs related to CTM. This table will include TEAEs with a drug relationship of “Insufficient Data,” “Possible,” “Probable,” and “Highly Probable.” It will also include TEAEs with missing drug relationships. An AE reported by a subject more than once will be included in this table if at least one of the drug association grades is one of the grades listed here.
- AESIs that are AEs of special interest which may include bleeding of any grade, cardiac events of any grade, non-melanoma skin cancer, opportunistic infections such as herpes zoster, progressive multifocal encephalopathy, and tuberculosis. Any development of tuberculosis will be recorded as an AESI.

Subgroup analysis of TEAE and AESIs. Subgroup analysis of TEAE and AESIs will be prepared for the following factors: age group, gender, stratification factors, diagnostic classification, DIPSS risk category.

Listings will be presented as follows:

- All AEs
- Serious AEs
- Serious AEs related to Study Treatment.
- AEs Leading to Study Treatment Discontinuation
- AEs Leading to Death
- AESIs

A hierarchical listing will display the MedDRA system organ classes represented in the data. Within each system organ class, the listing will

display each unique preferred term. Within each preferred term, the listing will display each unique verbatim (recorded) term. Listed terms will be ordered alphabetically. The listing will be sorted such that each AE and its associated changes appear together. Within that constraint, the listing will display AEs for each subject in order of onset date.

A listing of SAEs will display the recorded term from the CRF and, adjacent to that, the MedDRA preferred term that appears in the tables. SAEs for each subject will appear in order of onset date.

D. Clinical Laboratory Results

The descriptive statistics will be provided for the clinical laboratory parameters including hematology, chemistry, and urinalysis:

- Hematology: Basophils, %; Basophils, Absolute; Eosinophils, %; Eosinophils, Absolute; Ery. Mean Corpuscular Volume (MCV); Ery. Mean Corpuscular Hemoglobin (MCH); Erythrocyte (RBC); Hematocrit; Hemoglobin; Lymphocytes, %; Lymphocytes, Absolute; Monocytes, %; Monocytes, Absolute; Neutrophils, %; Neutrophils, Absolute; Platelets; White Blood Cells (WBC).
- Clinical Chemistry: Alanine Aminotransferase (ALT/SGPT); Albumin; Alkaline Phosphatase (ALP); Aspartate Aminotransferase (AST/SGOT); Amylase; Blood Urea Nitrogen (BUN); Chloride; Creatinine; Glucose; Lactate Dehydrogenase (LDH); Lipase; Magnesium; Potassium; Sodium; Total Bilirubin; Total Protein; Uric Acid (Urate).
- Urinalysis: Specific gravity; PH; Protein; Glucose; Ketones; Blood; Nitrite by Dipstick; Bilirubin; Microscopic examination (if blood or protein is abnormal).

Summaries of baseline values and values at each postbaseline visit, postbaseline maximum and minimum value, change from baseline (CFB) and percentage CFB by visit, and the maximum and minimum change from baseline will be presented by treatment arm for each assessment visit.

Number and percentage of subjects with worst post-baseline CTC grade (regardless of the baseline status) will be provided. Each subject will be

counted only for the worst grade observed post-baseline.

In addition, shift tables using CTC grades to compare baseline to the worst post-baseline value will be produced for laboratory parameters with CTC grades. For laboratory parameters where CTC grades are not defined, shift tables to the worst post-baseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

Shift tables for laboratory values with respect to normal range (low, normal, high) and CTCAE toxicity grade, compared to baseline, will be summarized by visit. Overall laboratory result shift from baseline (Normal, Abnormal clinically significant (CS), and Abnormal non-clinically significant (NSC)) will be summarized.

Shift tables summarizing the counts and percentages of subjects who were normal at baseline, but who became abnormal subsequently, will also be displayed.

A by-subject listing of laboratory values will be provided by laboratory parameter. A separate listing will display notable laboratory abnormalities.

These following Others Protocol-required Screening Tests will be summarized and presented in a by-subject listing:

- Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only)
- Pregnancy test: serum or urine human chorionic gonadotropin (hCG) (as needed for women of childbearing potential)
- Serology: human immunodeficiency virus [HIV] antibody, hepatitis B, surface antigen [HBsAg], and hepatitis C virus antibody

E. Vital Signs

The vital signs include:

- Blood pressure (systolic and diastolic [mmHg])
- Heart rate (beats per minute)
- Body temperature (°C)
- Respiration rate (breaths per minute).

Weight and vital sign assessments will be summarized for the actual values, change from baseline, and percentage change from baseline by visit, and for the maximum and minimum change from baseline.

A by-subject listing including the date of visit and the result of each parameter will be provided.

F. Physical Examination

Physical examination (PE) includes weight and spleen size by clinical assessment (palpation).

The spleen size numerical results will be summarized by descriptive statistics. Categories of findings (normal, abnormal, not evaluated) on spleen size will be summarized as counts and percentages.

Additionally, for Cycle 2, Cycle 3 Day 1, Cycle 4 Day 1, Cycle7 and every 3 Cycle thereafter and Early Termination, the counts and percentages of subjects who were normal at Baseline but who presented abnormal clinically significant findings at a subsequent visit will be provided for the spleen size.

A by-subject listing will be provided including the date of visit and the spleen size assessment results for subjects whose spleen was palpable and measurable.

G. Prior and Concomitant Medications

Prior medications are defined as any medications with a stop date prior to the date of first dose of NS-018.

Concomitant medications are defined as medications or therapies taken within 14 days of study drug administration.

Medications may be flagged as both *prior and concomitant* if the start date is prior to the date of the first dose of NS-018 and the medication continued after the first dose of NS-018.

Each medication will be coded to a preferred name and an Anatomic Therapeutic Classification using the most updated version of WHO Drug at the time of study initiation (up-versioning will not occur).

The number (%) of subjects using prior, prior and concomitant, and concomitant medications will be summarized by preferred name.

A by-subject listing will be provided with the line and the name of the therapy, the reason for use, the dates of administration including start and end dates and the dosage information including dose and frequency.

H. Electrocardiograms (ECG)

The normality or abnormality of the ECG tracing will be summarized using shift tables of numbers of subjects who have a normal/abnormal ECG tracing at each scheduled time of assessment.

A by-subject listing of overall ECG evaluation by visit will also be created with all relevant information and derived variables.

X. Pharmacokinetic and Pharmacodynamic Analyses

A. Pharmacokinetics

PK analysis will be performed for subjects on the PK population.
At the Cycle 1 Day 1 (C1D1) and Cycle 2 Day 1 (C2D1) visit, blood sample will be collected at predose, 0.5, 1, 2, 3, 4, 6 and 8 hours postdose from the PK population to evaluate the plasma concentration of NS-018 and MPD-6007.
The following table displays the PK parameters assessed according to the time of visit:

PK parameters	Cycle 1 Day 1	Cycle 2 Day 1
Observed maximum plasma concentration (C_{max})	X	X
Time to maximum plasma concentration (T_{max})	X	X
Area under the plasma concentration-time curve (AUC_{0-24})	X	X
Terminal elimination phase rate constant (λ_z)	X	X
Terminal elimination half-life (t½)	X	X
Accumulation ratio (AR = [AUC_{0-24}] C2 D1/[AUC_{0-24}] C1 D1)		X
Average plasma concentration (C_{av})		X
Observed minimum plasma concentration (C_{min})		X
Percentage fluctuation		X
PTF % =100 × (Cmax − Cmin)/Cav		X
Apparent total body clearance (CL/F)	X	X
Apparent volume of distribution (Vz/F)	X	X
Lag time (Tlag)	X	X

PK parameters will be summarized descriptively at each time point of collection.

Individual subject and mean plasma concentrations of NS-018 and its metabolite MPD-6007 will be plotted versus time in linear and log-linear scale.

Derived PK parameters will be listed and summarized using the same measures as for the plasma concentrations of NS-018 and MPD-6007.

B. Pharmacodynamics

Pharmacodynamics assessments include phospho-STAT3 assessment and mRNA sequencing. The PcD analysis will be based on PK population.

Phospho-STAT3 values at each time point and changes from baseline will be summarized descriptively and listed.

XI. References

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2. Senn S. Testing for baseline balance in clinical trials. *Stat Med* 1994; 13(17): 1715-26.

3. Lachin JM. A review of methods for futility stopping based on conditional power. *Stat Med. 2005 Sep 30;24(18):2747-64.*

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Appendix 1 Revised Response Criteria for Myelofibrosis : International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) Consensus Report

Response categories	**Required criteria (for all response categories, benefit must last for ≥12 weeks to qualify as a response)**
Complete response (CR)	Bone marrow:* Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF† AND Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥100 × 10^9/L and <UNL; <2% immature myeloid cells‡ AND Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Partial response (PR)	Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥100 × 10^9/L and <UNL; <2% immature myeloid cells‡ AND Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH **OR** Bone marrow:* Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF† AND Peripheral blood: Hemoglobin ≥85 but <100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥50, but <100 × 10^9/L and <UNL; <2% immature myeloid cells‡ AND Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Clinical improvement (CI)	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia§
Anemia response	Transfusion-independent subjects: a ≥20 g/L increase in hemoglobin level‖ Transfusion-dependent subjects: becoming transfusion-independent{
Spleen response#	A baseline splenomegaly that is palpable at 5 to 10 cm, below the LCM, becomes not palpable** **OR** A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥50%** A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response. A spleen response requires confirmation by MRI or computed tomography showing ≥35% spleen volume reduction.

Response categories	**Required criteria (for all response categories, benefit must last for ≥12 weeks to qualify as a response)**
Symptoms response	A ≥50% reduction in the MPN-SAF TSS[††]
Progressive disease[‡‡]	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM **OR** A ≥100% increase in palpable disease, below LCM, for baseline splenomegaly of 5 to 10 cm **OR** A 50% increase in palpable distance, below LCM, for baseline splenomegaly of 10 cm **OR** Leukemic transformation confirmed by a bone marrow blast count of ≥20% **OR** A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 × 10^9/L that lasts for at least 2 weeks
Stable disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI **OR** Loss of anemia response persisting for at least 1 month **OR** Loss of spleen response persisting for at least 1 month
Recommendations for assessing treatment-induced cytogenic and molecular changes	
Cytogenetic remission	At least 10 metaphases must be analyzed for cytogenetic response evaluation and requires confirmation by repeat testing within 6 months window. CR: eradication of a pre-existing abnormality PR: ≥50% reduction in abnormal metaphases (partial response applies only to subjects with at least 10 abnormal metaphases at baseline)
Molecular remission	Molecular response evaluation must be analyzed in peripheral blood granulocytes and requires confirmation by repeat testing within 6 months window. CR: Eradication of a pre-existing abnormality PR: ≥50% decrease in allele burden (partial response applies only to subjects with at least 20% mutant allele burden at baseline)
Cytogenetic/molecular relapse	Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing

Abbreviations: EMH=extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven nonhepatosplenic EMH); LCM=left costal margin; MF=myelofibrosis; UNL=upper normal limit.

* Baseline and posttreatment bone marrow slides are to be interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.

† Grading of MF is according to the European classification (Thiele et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica 2005;90:1128). It is underscored that the consensus definition of a CR bone marrow is to be used only in those subjects in which all other criteria are met, including resolution of leukoerythroblastosis. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.

‡ Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized subjects, 5% immature myeloid cells is allowed.

§ See above for definitions of anemia response, spleen response, and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥20 g/L decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In addition, assignment to CI requires a minimum platelet count of ≥25,000 × 10^9/L and absolute neutrophil count of ≥0.5 × 10^9/L.

‖ Applicable only to subjects with baseline hemoglobin of <100 g/L. In subjects not meeting the strict criteria for transfusion dependency at the time of study enrolment (see as follows), but have received transfusions within the previous month, the pretransfusion hemoglobin level should be used as the baseline.

{ Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of packed red blood cells (PRBC), in the 12 weeks prior to study enrollment, for a hemoglobin level of <85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent subjects requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥85 g/L.

In splenectomized subjects, palpable hepatomegaly is substituted with the same measurement strategy.

** Spleen or liver responses must be confirmed by imaging studies where a ≥35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.

†† Symptoms are evaluated by the MPN-SAF TSS. The MPN-SAF TSS is assessed by the subjects themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). Symptoms response requires ≥50% reduction in the MPN-SAF TSS.

‡‡ Progressive disease assignment for splenomegaly requires confirmation my MRI or computed tomography showing a ≥25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to posttreatment measurements.

Source: Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. Blood 2013;122:1395-1398.