NS-018-101: A Phase 1/2, Open-label, Dose-escalation, Multi-center Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Orally Administered NS-018 in Patients with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis

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CLINICAL STUDY PROTOCOL

A Phase 1/2, Open-label, Dose-escalation, Multi-center Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Orally Administered NS-018 in Patients with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis

Investigational Product: NS-018

Protocol Number: NS-018-101

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SIGNATURE PAGE

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We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature

PPD

Date

PPD

NS Pharma, Inc.

PPD

PPD

Associate Professor

PPD

PPD

SYNOPSIS

TITLE: A Phase 1/2, Open-label, Dose-escalation, Multi-center Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Orally Administered NS-018 in Patients with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis

PROTOCOL NUMBER: NS-018-101

INVESTIGATIONAL PRODUCT: NS-018

PHASE: 1/2

INDICATION(S): Primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), or post-essential thrombocythemia myelofibrosis (post-ET MF)

OBJECTIVES:

Phase 1: The primary objective of the Phase 1 portion of the study is to evaluate the safety, tolerability, maximum tolerated dose (MTD), and clinically active dose of NS-018 when orally administered in patients with PMF, post-PV MF, or post-ET MF.

The secondary objectives of the Phase 1 portion of the study are to determine plasma pharmacokinetics (PK), evaluate pharmacodynamic (PD) correlates, and evaluate preliminary efficacy of NS-018 in patients with PMF, post-PV MF, or post-ET MF.

Phase 2: The primary objective of the Phase 2 portion of the study is to further evaluate the safety and efficacy of the selected dose(s) of NS-018 in patients with PMF, post-PV MF, or post-ET MF.

The secondary objectives of the Phase 2 portion of the study are to further determine plasma PK and evaluate PD correlates of NS-018 in patients with PMF, post-PV MF, or post-ET MF.

POPULATION:

The population for this study includes male and female patients ≥18 years of age with PMF, post-PV MF, or post-ET MF that requires therapy, including patients with intermediate-1, intermediate-2, or high-risk MF according to the International Prognostic Scoring System (IPSS). Patients must have symptomatic palpable splenomegaly. Patients must have Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 3 at study entry (screening).

STUDY DESIGN AND DURATION:

This is a Phase 1/2, open-label study of NS-018 in patients with PMF, post-PV MF, or post-ET MF. Approximately 24 evaluable patients will be enrolled during the Phase 1 portion. Sequential cohorts of 3 to 6 patients each will be treated with escalating doses of NS-018 until MTD is established. Patients in the first cohort will self-administer NS-018 orally at a starting dose of 75 mg daily; additional planned daily doses are 125 mg, 200 mg, and 300 mg. A twice daily (BID) dosing schedule may be initiated by the Safety Review Committee based on results from PK analysis. Patients will remain on NS-018, administered continuously as daily therapy in cycles of 28 days duration, in the absence of progressive disease and demonstration of acceptable product tolerance. Once the MTD or clinically active dose (CAD) is determined, a Phase 2 portion that will include up to an additional 20 patients will be initiated (treated at the MTD). Consideration by the Safety Review Committee will also be given to suspending Phase 2 enrollment at the MTD, and instead adding the same total number of patients at a second dose level, the CAD. The expansion cohorts for the MTD and CAD, should they both be pursued, will not be concurrently open for enrollment. The two dose levels would instead be expanded sequentially. Consideration will also be given to enroll patients only at the CAD but not MTD level, based on the risk/benefit of therapy as judged by the investigator/medical monitor and sponsor.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

NS-018 will be self-administered orally as daily therapy in cycles of 28 days in duration. NS-018 will be self-administered 2 hours or more after the last meal and at least 1 hour before the next meal. The starting dose cohort (first cohort) will receive 75 mg daily. Appropriate numbers of 25 mg and/or 100 mg tablets will be supplied to the patients to enable self-administration at their assigned dose level. Additional planned daily doses are 125 mg, 200 mg, and 300 mg. If twice daily dosing requires evaluation, dosing would start at one total daily dose level below the last once per day dose level that was declared safe. For example, if 300 mg QD was declared safe, the starting dose for BID dosing would be 100 mg twice daily, 12 hours apart [representing a total daily dose 200 mg]).

SAFETY:

Adverse events (AEs) occurring after any administration of NS-018 will be followed until the event resolves, until the event is judged stable and not expected to resolve completely, or until the patient begins alternative treatment. Investigators will record and grade AEs using the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. Safety assessments also include laboratory tests, electrocardiograms (ECGs), vital signs, and physical examinations.

EFFICACY:

The responses to treatment assessed using the IWG consensus criteria (Phase I) and the IWG MRT and ELN Response Criteria (Phase II) will be tabulated by dose level and visit. The number and percentage of patients achieving the response will be provided for each response

level. The objective response rate (the percentage of patients with confirmed CR, PR, or CI during the treatment period) and its 95% exact binomial confidence interval will be provided by dose level. Quality of life assessed using the MF SAF during Phase I or MPN-SAF (MPN-10) during Phase II will be summarized by dose level and visit. Change in spleen size by magnetic resonance imaging (MRI; computed tomography [CT] scan for patients not able to tolerate MRI) for the Phase 2 portion will be summarized for the cohort.

PHARMACOKINETIC/PHARMACODYNAMIC AND QUALITY OF LIFE:

Pharmacokinetic parameters to be estimated include observed maximum concentration (Cmax), time to maximum plasma concentration (Tmax), area under the plasma concentration-time curve (AUC), terminal elimination half-life (t1/2), and accumulation ratio (R). Pharmacodynamic parameters include Janus kinase 2 (JAK2) V617F allele burden, phosphorylated signal transducer and activator of transcription 3 (phospho-STAT3), and cytokine levels.
Quality of life will be assessed using the Myelofibrosis Symptom Assessment Form (MF SAF) or Myeloproliferative Neoplasm Symptom Assessment Form [MPN-SAF (MPN-10)].

STATISTICAL ANALYSES:

Continuous variables will be summarized with descriptive statistics, including the number of observations, arithmetic mean, standard error/deviation, median, minimum, and maximum values. Frequency counts and percentage will be provided for categorical data.

Adverse events will be summarized by dose level. Clinical laboratory evaluations at each visit and change from baseline (Cycle 1 Day 1) will be summarized by dose level. A laboratory value shift table will be provided. Vital signs and ECG parameters at each assessment time will be summarized by dose level. Other safety variables and their changes from baseline (when applicable) will be summarized by dose level at each of the scheduled assessment times.

Plasma concentrations of NS-018 and its metabolites will be summarized by dose level with descriptive statistics. Individual patient and mean plasma concentrations of NS-018 and its metabolites will be plotted versus time. In addition, the relationship between plasma concentrations of NS-018 and its metabolites and each efficacy and toxicity outcome measure as well as any biomarker endpoints will be explored.

Pharmacodynamic parameters including JAK2 V617F allele burden, phospho-STAT3, cytokine levels and their changes from baseline will be summarized by dose level and listed. The relationship between NS-018 dose level and JAK2 or phospho-STAT3 levels over time will be explored.

Responses to treatment assessed using the IWG consensus criteria (Phase I) and the IWG MRT and ELN Response Criteria (Phase II) will be tabulated with the number and percentage of patients for each response level. The objective response rate (the percentage of patients with confirmed complete or partial responses during the treatment period) and its

95% exact binomial confidence interval will be provided by dose level. Quality of life assessed using the MF SAF (Phase I) or MPN-SAF (MPN-10) (Phase II) will be summarized by dose level and visit.

SITES: Multisite in the United States

SPONSOR:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area under the plasma concentration time curve
BID	“bis in die" Latin - twice a day
BSA	Body surface area
BUN	Blood urea nitrogen
CAD	Clinically active dose
CFR	Code of Federal Regulations
CI	Clinical improvement
Cmax	Maximum concentration
CR	Complete remission
CrCl	Creatinine clearance
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CV	Coefficient of variation
CYP	Cytochrome p450
DLT	Dose-limiting toxicity
DRL	Drug Reference List
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ELN	European LeukemiaNet
ET	Essential thrombocythemia
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IND	Investigational New Drug (application)
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
IUD	Intrauterine device
IWG	International Working Group
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK2	Janus kinase 2
K_i	inhibitory constant

LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MF SAF	Myelofibrosis Symptom Assessment Form
MM	multiple myeloma
MPN	Myeloproliferative neoplasm
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
PD	Pharmacodynamic; progressive disease
PK	Pharmacokinetic
PMF	Primary myelofibrosis
PR	Partial response
PV	Polycythemia vera
QD	Once daily
QTcB	Bazett's correction of the QT interval formula
SAE	Serious adverse event
SD	Stable disease
STAT	Signal transducer and activator of transcription
STD_{10}	Severely toxic dose in 10% of the animals
t1/2	Half-life
TEAE	Treatment emergent adverse event
Tmax	Time to maximum concentration
ULN	Upper limit of normal
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background

Nippon Shinyaku has developed a novel Janus kinase 2 (JAK2) inhibitor, NS-018, for the treatment of patients with myeloproliferative neoplasm (MPN). MPN, including polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF), is a clonal hematopoietic stem cell malignancy characterized by the abnormal proliferation and survival of one or more myeloid cell types.

Until recently the molecular etiology of MPN remained elusive. However, understanding was greatly expanded when a somatic point mutation of JAK2 tyrosine kinase (JAK2 V617F) was described in more than 90% of PV patients and about 50% of ET and MF patients in 2005.[1,2,3] JAK2 V617F is a constitutively activated kinase that activates the JAK/signal transducer and activator of transcription (STAT) signaling pathway and dysregulates cell growth and function. Another point mutation, in the thrombopoietin receptor, whose signaling is known to be mediated by JAK2, has been identified in 1% to 5% of ET and MF patients. These findings suggest that aberrant JAK2 activation is responsible for the molecular pathogenesis of MPN.

The clinical courses of PV and ET are relatively indolent with a fairly long life expectancy. Polycythemia vera can be managed by treatment with phlebotomy and hydroxyurea and ET by treatment with low-dose aspirin and hydroxyurea. Myelofibrosis can arise de novo as primary myelofibrosis (PMF) or can develop as a terminal stage of PV (post-PV MF) or ET (post-ET MF). Myelofibrosis has a progressive clinical course and is associated with a shorter life expectancy, with median survival after diagnosis of about 5 years. Patients with MF have anemia, splenomegaly, or constitutional symptoms such as weight loss and fatigue. Since the only currently available curative therapy for MF is hematopoietic stem cell transplantation, it is hoped that alternative therapies that will ameliorate the clinical symptoms of MF can be developed.

1.2 Rationale

1.2.1 Summary of non-clinical studies

JAK2 associates with the cytoplasmic domain of the erythropoietin receptor, thrombopoietin receptor, and several kinds of cytokine receptors in hematopoietic cells, and plays an essential role in intracellular signal transduction. JAK2 V617F is an activated JAK2 which constitutively phosphorylates downstream molecules such as STATs, signal transducer and activator of transcription, activates multiple signaling pathways and leads to cell proliferation, survival and anti-apoptosis. Cells expressing JAK2 V617F acquired cytokine-dependent growth ability and erythropoietin-hyper-responsiveness.1 Mice transplanted with bone marrow cells expressing JAK2 V617F developed a closely resembled feature of PV pathology including a striking elevation of hematocrit, leukocytosis, splenomegaly, and

reticulinfibrosis in the bone marrow.[4] A line of JAK2 V617F transgenic mice progressed into a myelofibrosis-like disease including anemia, bone marrow fibrosis, splenomegaly and shortened life time.[5] Although JAK2 V617F mutation is probably the most frequent genetic alteration in MF, additional mutations have been detected in exon 12 of JAK2 (F537-K539delinsL, H538QK539L, K539L, etc.)[6]and in the FERM (Four-point-one, Ezrin, Radixin, Moesin) domain of JAK2 (R430Q)[7] among JAK2 V617F negative patients. Likewise, mutations in the thrombopoietin receptor such as W515L/K, were identified in a small population of MF patients. Ligand-independent activation of mutated thrombopoietin receptor results in a constitutive activation of JAK2 kinase. Moreover, excess production of inflammatory cytokines is believed to relate to constitutional symptoms of splenomegaly and a hypermetabolic state in MF. Interleukin-6, whose signal is mediated by JAK2, was notably elevated in MPN patients especially during progression of MF to acute myelogenous leukemia, and ET and PV to MF.[8] This evidence collectively indicates that up-regulated JAK2 signaling is of importance in the development of MF pathology, regardless of the presence of specific genetic alterations, and that there is a strong rationale for the application of JAK2 inhibitors for MF treatment.

NS-018 is an orally available, potent and specific JAK2 inhibitor. NS-018 is a potential therapeutic agent for the treatment of MF, is expected to suppress the aberrant proliferation of bone marrow cells which express activated JAK2.NS-018 demonstrated a potent *in vivo* effect on the prolongation of life and the reduction of splenomegaly at low dosages in a JAK2 V617F-bearing mouse model. Therefore, NS-018 can be expected to have specificity for activated JAK2 and a wide therapeutic range *in vivo*, providing a satisfactory margin of safety between its efficacy and its toxicity.

The following is a summary of the key findings in the areas of nonclinical studies for NS-018.[9]

Pharmacology

- NS-018 inhibited JAK2 kinase with IC_{50}values of subnanomolar range at both ATP = K_m and ATP = 1 mmol/L, with selectivity for JAK2 over JAK1, JAK3, and Tyk2 kinases.
- NS-018 showed potent antiproliferative activity against JAK2-driven cell lines such as BaF3/JAK2V617F with IC_{50} values of around 100 nmol/L and showed only minimal cytotoxicity against non-target cells.
- NS-018 significantly prolonged survival at doses of over 6.25 mg/kg twice daily (bid) and reduced splenomegaly at dosages over 1.5 mg/kg bid in a mouse BaF3/JAK2V617F leukemia model.
- NS-018 inhibited IL-6-induced STAT3 phosphorylation in a dose-dependentmanner in MM cell lines such as PCM6, U266 and RPMI8226, and inhibitedthe IL-6-induced proliferation of PCM6 cells with an IC_{50} value of140 nmol/L.

Safety Pharmacology

- NS-018 had no effect on the central nervous system or the respiratory system of conscious male rats at doses up to 100 mg/kg.
- NS-018 inhibited human ether-a-go-go-related gene (hERG) currents in human embryonic kidney cells (HEK293) in a concentration-dependent manner with an $IC_{50}$of 0.6 μmol/L.
- Single doses of NS-018 up to 80 mg/kg in conscious dogs had no biologically significant effect on blood pressure, heart rate, or electrocardiogram (ECG) parameters, but caused loose stool at 5 mg/kg or more, and vomiting and/or diarrhea at 20 mg/kg or more.

Pharmacokinetics and Metabolism

- The bioavailability of NS-018 after a single oral administration to fasting male rats was 8.63%, and the bioavailability of NS-018 after a single oral administration to overnight fasting male dogs was 50.8%.
- ^{14}C-NS-018 was well absorbed after a single oral administration to male and female rats.
- The extent of binding of ^{14}C-NS-018 to serum protein *in vitro* was more than 95% in rats, dogs, monkeys, and humans.
- The distribution study of ^{14}C-NS-018 in pigmented rats suggested there was an affinity of drug-related materials for melanin.
- NS-018 was converted to several metabolites in hepatic microsomes and cryopreserved hepatocytes from preclinical species and humans, and human specific metabolites were not detected.
- After a single intravenous and oral administration of ^{14}C-NS-018 to male rats, radioactivity was excreted mainly into the feces. Following a single intravenous administration to bile duct-cannulated male rats, only a relatively small portion (approximately 6% of the dose) was reabsorbed to undergo enterohepatic recycling.
- The effect of NS-018 on human cytochrome P450 enzymes (CYP) isoforms revealed that NS-018 inhibited CYP1A2 potently (IC_{50}value of 0.65 μmol/L) and moderately inhibited CYP3A4, CYP2C8, CYP2C9, CYP2C19, and CYP2D6.The K_i values were assayed for CYP1A2 and CYP3A4 and were 0.428 μmol/L and 1.66 μmol/L. A time-dependent inhibitory effect was also seen for CYP3A4. NS-018 also induced CYP3A4.CYP3A4 and CYP2D6 were considered to be mainly involved in the metabolism of NS-018.
- NS-018 did not interact with P-glycoprotein (P-gp) as a substrate but interacted as an inhibitor.

Toxicology

- Hematological changes attributable to the pharmacological effect of NS-018 were observed in a 4-week repeated-dose oral toxicity study in rats. Those changes were almost recovered at the end of the 4-week recovery period. One animal in the 150 mg/kg group died.

- Hematological, renal and gastrointestinal tract changes were also observed in a 4-week repeated-dose oral toxicity study in dogs. All 6 animals in the 150 mg/kg group died.
- In the 4-week repeated-dose studies, the maximum tolerated dose (MTD) of NS-018 was 50 mg/kg/day in both rats and dogs. No observed adverse effect level (NOAEL) was determined to be 15mg/kg/day in male rats. The severely toxic dose in 10% of rats (STD_{10} of rats) was 150 mg/kg and the highest non-severely toxic dose (HNSTD) in dogs was 50 mg/kg/day.
- In the 13-week repeated dose studies, the MTD of NS-018 was 30 mg/kg/day in rats and 50 mg/kg/day in dogs, respectively. NOAEL was not determined in both rats and dogs.
- NS-018 did not induce gene mutations.
- NS-018 induced numerical aberration in the *in vitro*chromosomal aberration test. On the contrary, NS-018 did not induce structural chromosome aberration.
- NS-018 increased the incidence of micronucleated immature erythrocytes in the *in vivo* micronucleus assay in rats, whereasNS-018 did not cause deoxyribonucleic acid (DNA) damage in the liver or peripheral blood cells in the rat comet (single-cell gel electrophoresis) assay.
- NS-018 did not induce phototoxic response in the in vitro 3T3 NRU photo toxicity test.

1.2.2 Speculation from non-clinical study results

Based on the nonclinical studies, the first-in-patient clinical trials will be conducted to evaluate the safety, tolerability, pharmacokinetics and clinical efficacy of NS-018.

NS-018 is a competitive inhibitor of CYP1A2 and a non-competitive inhibitor of CYP3A4, and an inducer of CYP3A4 (based on an increase in activity of more than 40% at 1 μmol/L) and a moderate inducer of CYP1A2, as is presented in the following tables.

IC50 and *K*i values and inhibition type of NS-018 for each CYP isoforms:			
CYP Isoform	IC50 (**μmol/L**)	*K*i(**μmol/L**)	**Inhibition type**
CYP1A2	0.648	0.428	Competitive
CYP2A6	>50	-	-
CYP2B6	23.5	-	-
CYP2C8	4.05	1.38	Competitive
CYP2C9	5.31	2.81	Competitive
CYP2C19	5.77	2.86	Competitive
CYP2D6	6.63	1.74	Competitive
CYP2E1	>50	-	-
CYP3A4 (midazolam)	7.46	-	-
CYP3A4 (testosterone)	1.61	1.66	Noncompetitive

-: no data

NS-018 potential to induce CYP1A2 and CYP3A4 activity.		
Phenacetin *O*-deethylase activities of NS-018:		
0.1 µmol/L	322.5% vehicle	3.7% positive control
1 µmol/L	1774.7% vehicle	27.6% positive control
3 µmol/L	1094.9% vehicle	16.4% positive control
Testosterone 6β-hydroxylase activities of NS-018:		
0.1 µmol/L	131.7% vehicle	8.1% positive control
1 µmol/L	319.8% vehicle	56.2% positive control
3 µmol/L	154.8% vehicle	14.0% positive control

Phenacetin *O*-deethylase for a substrate of CYP1A2
Testosterone 6β-hydroxylase for a substrate of CYP3A4

Plasma C_{max} levels following repeated oral administration of well tolerated doses of NS-018 of 150 mg/kg/day in the rat (Report B091357) [10] and 50 mg/kg/day in the dog (Report B091358),[11] were approximately 15 (M)-20 (F) µmol/L and 4.5 (M)-5.1 (F) µmol/L, respectively, and are within the range of concentrations considered likely to inhibit or induce CYP1A2 and/or 3A4 activity. Therefore, the use of concomitant medications that are substantially metabolized by CYP1A2 and CYP3A4 should be cautioned as described in Section 4.2.

While NS-018 was determined to be metabolized by CYP3A4 and CYP2D6 from the study using the human P450-expressing microsomes, CYP3A4 was considered to be mainly involved in the metabolism of NS-018 from the result of the chemical inhibition study. In the investigation of inhibitory effects on the metabolism of NS-018 after addition of specific inhibitors of each P450 isoform to human liver microsomes, only ketoconazole (an inhibitor of CYP3A4) inhibited the formation of metabolites and the disappearance of NS-018. The percentage of inhibition on the disappearance of NS-018 was 53.6% for CYP3A4.[12]Therefore, the use of concomitant medications known to be strong inhibitors or inducers of CYP3A4 should be cautioned as described in Section 4.2.

The starting dose of NS-018 was selected based on the results of 4-week repeated dose, daily administration, oral gavage toxicity studies conducted in rats and dogs. The STD_{10} of rats was 150 mg/kg (estimated human equivalent dose was 24.2 mg/kg) and the HNSTD in dogs was 50 mg/kg (the estimated human equivalent dose was 27.8 mg/kg). Taking into account the human equivalent dose of 1/10 of the STD_{10} of rats and 1/6 of the HNSTD in dogs, the starting dose in this first-in-human study was determined to be 75 mg.

Dose conversion: Rat to Human

Animal Dose	Human Equivalent Dose	Human Equivalent Dose of 1/10 STD_{10}
150 mg/kg	24.2 mg/kg	2.42 mg/kg (145.2 mg at 60 kg)
STD_{10} = severely toxic dose to 10%		

Dose conversion: Dog to Human

Animal Dose	Human Equivalent Dose	Human Equivalent of 1/6 HNSTD
50 mg/kg	27.8 mg/kg	4.63mg/kg (278 mg at 60 kg)
HNSTD = highest non-severely toxic dose		

2 STUDY OBJECTIVES AND HYPOTHESES

2.1 Study Objectives

2.1.1 Phase 1

The primary objective of the Phase 1 portion of the study is to evaluate the safety, tolerability, and to determine the maximum tolerated dose (MTD), and clinically active dose (CAD, as defined in Section 6.1.1) of NS-018 when orally administered in patients with PMF, post-PV MF, or post-ET MF.

The secondary objectives of the Phase 1 portion of the study are to determine the plasma PK, evaluate PD correlates, and evaluate preliminary efficacy of NS-018 in patients with PMF, post-PV MF, or post-ET MF.

2.1.2 Phase 2

The primary objective of the Phase 2 portion of the study is to further evaluate the safety and efficacy of the selected dose(s) in patients with PMF, post-PV MF, or post-ET MF.

The secondary objectives of the Phase 2 portion of the study are to further determine the plasma PK and evaluate PD correlates of NS-018 in patients with PMF, post-PV MF, or post-ET MF.

3 STUDY DESIGN

3.1 Summary of Study Design

This is a Phase 1/2, open-label study of NS-018 in patients with PMF, post-PV MF, or post-ET MF. Patients in the first cohort will self-administer NS-018 orally at a starting dose of 75 mg daily. Doses will be increased in later cohorts based on safety data. Treatment will be administered continuously as daily therapy in cycles of 28 days in duration.

Approximately 24 patients will be enrolled during the Phase 1 portion (treated with escalated doses in a standard 3+3 cohort design) and 20 patients will be enrolled during the Phase 2 portion (treated at the MTD). Consideration by the Safety Review Committee will also be given to suspending Phase 2 enrollment at the MTD, and instead adding the same total number of patients at a second dose level, the CAD. The expansion cohorts for the MTD and CAD, should they both be pursued, will not be concurrently open for enrollment. The two dose levels would instead be expanded sequentially. Consideration will also be given to enroll patients only at the CAD but not MTD level, based on the risk/benefit of therapy as judged by the investigator/medical monitor and sponsor.

For the purpose of scheduling procedures and evaluations, a treatment cycle is defined as 28 days. A patient may continue to receive treatment with NS-018 until the patient experiences unacceptable toxicity that precludes any further treatment, disease progression, and/or as long as the patient is benefiting from treatment, at the discretion of the investigator.

This study will be conducted at selected sites in the United States.

4 STUDY POPULATION

4.1 Inclusion Criteria

Patients meeting the following criteria will be eligible to participate in the study:

1. Primary myelofibrosis, post-PV MF, or post-ET MF (As defined in Appendix B) that requires therapy, including patients with intermediate-1, intermediate-2, or high-risk MF according to the International Prognostic Scoring System (IPSS)[13] (Appendix C), regardless of their JAK2 mutation status. Patients must have symptomatic palpable splenomegaly (at least 5 cm below the left costal margin in the mid-clavicular line by physical examination).For the Phase 2 portion, MF patients must have received prior JAK2 inhibitor therapy, and been found to be intolerant, or refractory/relapsed from prior JAK2 inhibitor therapy, based on investigator assessment.
2. ≥18 years old.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤3 (see Appendix D).
4. Estimated life expectancy of ≥12 weeks.
5. Male or non-pregnant, non-lactating female patients. Male and female patients who are fertile and their partners must agree to use one of the following methods of contraception from screening through 90 days following discontinuation of study drug.
    - Complete abstinence from sexual intercourse
    - Double-barrier method (condom with spermicide in conjunction with the use of an intrauterine device [IUD] or diaphragm)
    - Tubal ligation or vasectomy (surgical sterilization)
6. Negative serum or urine pregnancy test within 7 days prior to the first dose of study drug (if patient is a female of childbearing potential).
7. Serum creatinine of ≤ 1.5 ×the upper limit of normal (ULN) OR estimated creatinine clearance (CrCl) ≥40 ml/min/1.73 m^2 calculated using the Cockcroft and Gault equation:

    CrCl (mL/min) = [(140-age (years)) x weight (kg)] / (serum creatinine (mg/dL) x 72)
    For females, multiply result by 0.85

    Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × ULN and total bilirubin ≤ 1.5 × ULN. If the total bilirubin is elevated

between 1.5 x and 3 x ULN, patients with a direct bilirubin ≤1.5 X ULN are eligible during the Phase 2 portion.

8. Adequate bone marrow reserve, as demonstrated by:
    - Absolute neutrophil count (ANC) >1000/µL and
    - Platelet count ≥25,000/µL without the assistance of growth factors or platelet transfusions.
9. QTcB≤480 msec.
10. No MF-directed treatment for at least 2 weeks prior to initiation of NS-018, including any use of corticosteroids for Myelofibrosis symptom or blood count management. Low dose corticosteroids ≤ 10 mg/day prednisone or equivalent is allowed for non-myelofibrosis purposes.
11. No treatment with any investigational agent or anticancer agents within 2 weeks prior to initiation of NS-018.
12. Able to provide written informed consent prior to enrollment into the study.

4.2 Exclusion Criteria

Patients are excluded from participation in the study if any of the following criteria apply:

1. Active, uncontrolled systemic infection.
2. Patients with any unresolved toxicity (regardless of organs) greater than Grade 1 from previous anticancer therapy.
3. Prior treatment with JAK2 inhibitors that necessitated discontinuation specifically due to gastrointestinal toxicity.
4. Potentially curative therapy is available:
    - Candidates for hematopoietic stem cell transplant in which transplant is an available and viable option and of higher priority than this study are excluded;
    - If the patient has declined hematopoietic stem cell transplant, has no donor for transplant, or in the judgment of the investigator is not suitable for transplant, the patient may be enrolled.
5. Currently taking medication that is substantially metabolized by cytochrome P450 (CYP) 1A2 or CYP3A4 (see Appendix E) or taking medication known to be strong inhibitors or inducers of CYP3A4 (see Appendix E).
6. Patients with a serious cardiac condition within the past 6 months such as uncontrolled arrhythmias, myocardial infarction, angina or heart disease as defined by the New York Heart Association (NYHA) Class III or IV (see Appendix F).
7. Pregnant or lactating.
8. Radiation therapy for splenomegaly within 6 months prior to study entry (screening).
9. Splenectomy (applicable to patients enrolling in the Phase 2 portion of the study only).
10. Known HIV positive status.
11. Known active hepatitis, or a history of viral hepatitis B or hepatitis C (during Phase II portion)

12. Other concurrent disease and/or medical condition, which, in the judgment of the investigator, would prevent the patient's participation.
13. Patients diagnosed with another malignancy, unless they are disease free. Patients with early stage squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or cervical intraepithelial neoplasia may be eligible for participation at the investigator's discretion.
14. Patients who have had surgery (other than placement of vascular access and bone marrow biopsy) within 4 weeks of study entry (screening), or patients with incomplete recovery from any prior surgical procedures.
15. Patients actively receiving a concurrent investigational agent.
16. Unwilling or unable to comply with the protocol.

4.3 Patient Enrollment

When a patient has met the study requirements and is ready to be enrolled in the study, the site will send a Patient Enrollment Request Form to PAREXEL (Billerica, MA). PAREXEL will input the patient's assigned dose cohort onto the form and send the form back to the site. The site will treat the patient at the assigned dose.

4.4 Patient Discontinuation

Patients will be discontinued from the study under the following circumstances:

- Disease progression or no clinical benefit after 6 cycles;
- Patient's physician considers a change of therapy would be in the best interest of the patient;
- Patient requests discontinuation;
- Continued unacceptable toxicities despite optimal treatment or dose reduction;
- Need for any treatment not allowed by the protocol;
- Non-compliance; and
- Female patients who become pregnant during the study or who fail to use adequate birth control if applicable. (See Section 8.3 for more information regarding pregnancies).

Patients who are discontinued will be asked to undergo the end of study procedures within 30 days after the last dose of study drug or within 30 days after withdrawal from the study, as outlined in Section 5.1.8 for the Phase 1 portion and Section 5.2.10 for the Phase 2 portion.

5 STUDY PROCEDURES

5.1 Assessment Schedule – Phase 1

5.1.1 Phase 1: Screening (Day -14 to Day 0)

- Signed, written informed consent;
- Medical history including concurrent baseline conditions. Document concomitant medications used within 14 days prior to study drug administration and blood products transfused within 3 months prior to study drug administration;
- Complete physical examination including weight and spleen size by clinical assessment (palpation) (must be done within 7 days prior to Cycle 1, Day 1);
- Vital signs (blood pressure, pulse, respiratory rate, and temperature);
- ECOG Performance Status;
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G);
- Serum or urine pregnancy test for female patients of childbearing potential (must be done within 7 days prior to Cycle 1 Day 1);
- Electrocardiogram (ECG) - triplicate; QTcB must be ≤480 msec, locally read for eligibility determination and centrally read for safety analysis;
- Bone marrow assessment by aspiration and biopsy, according to standard practice at the site, (within 28 days prior to the first dose of study drug)
- Determine if the patient meets the inclusion/exclusion criteria.

5.1.2 Phase 1: Cycle 1, Day 1

- Review eligibility criteria and laboratory test results;
- Vital signs (blood pressure, pulse, respiratory rate, and temperature) obtained before the first dose of study drug is taken;
- ECOG Performance Status (may be obtained within 24 hours prior to study drug administration);
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G) (may be obtained within 24 hours prior to study drug administration);
- ECG – triplicate (pre-dose and approximately 2, 4, 6, and 8 hours post-dose; centrally read);
- Obtain blood samples for PK assessment (sampling time points are pre-dose and approximately 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-dose);
- JAK2 V617F allele burden (pre-dose may be obtained within 24 hours prior to study drug administration);
- Phospho-STAT3 (pre-dose and approximately 3 and 6hours post-dose) (pre-dose may be obtained within 24 hours prior to study drug administration);
- Cytokine level(pre-dose only; may be obtained within 24 hours prior to study drug administration);
- Myelofibrosis Symptom Assessment Form (MF SAF) questionnaire (may be obtained within 24 hours prior to study drug administration);

- Distribute study drug and instruct patient regarding completion of the study drug dosing diary (may be done within 24 hours prior to study drug administration);
- Assessment of AEs using the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0 (published 28 May 2009) (see Appendix H) (may be obtained within 24 hours prior to study drug administration and following study drug administration); and
- Concomitant medication notation (may be obtained within 24 hours prior to study drug administration).

5.1.3 Phase 1: Cycle 1, Days 8, 15, and 22 (±2 days)

- Directed physical examination including weight and spleen size by palpation;
- Vital signs (blood pressure, pulse, respiratory rate, and temperature; pre-dose);
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G);
- ECG – triplicate (Day 8 only; pre-dose and approximately 2 hours post-dose; centrally read);
- Obtain blood samples for PK assessment (Day 8 only; sampling time points are pre-dose and approximately 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose);
- Phospho-STAT3 (Day 8 only; pre-dose and approximately 3 and 6hours post-dose);
- Review patient study drug dosing diary for compliance;
- Assessment of AEs using the NCI CTEP CTCAE, version 4.0 (published 28 May 2009) (see Appendix H); and
- Concomitant medication notation.

5.1.4 Phase 1: Cycles 2, 3, and 4, Day 1 (±3 days)

- Directed physical examination including weight and spleen size by palpation;
- Vital signs (blood pressure, pulse, respiratory rate, and temperature; pre-dose);
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G);
- Serum or urine pregnancy test (female patients of childbearing potential only);
- ECG – triplicate (at Cycle 2, pre-dose and approximately 2 hours post-dose, centrally read; at Cycles 3 and 4, pre-dose, locally read);
- Obtain blood sample for PK assessment (Cycle 2 only; sampling time points are pre-dose and approximately 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-dose);
- Bone marrow assessment (Cycle 4 only);
- Response assessment using the International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid

metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT);
- JAK2 V617F allele burden if mutation present prior to start of therapy (Cycle 2 and Cycle 4, pre-dose);
- Phospho-STAT3 (Cycle 2 only: pre-dose and approximately 3 and 6 hours post-dose; – refer to study lab manual for subset of patients to which this applies);
- Cytokine (pre-dose);
- MF SAF (Cycle 2 and Cycle 4, pre-dose);
- Review patient study drug dosing diary for compliance and distribute study drug;
- Assessment of AEs using the NCI CTEP CTCAE, version 4.0 (published 28 May 2009) (see Appendix H); and
- Concomitant medication notation.

5.1.5 Phase 1: Cycles 2, 3, and 4, Day 15; Cycles 5 and 6, Days 1 and 15 (±3 days)

- Hematology and serum chemistry are to be obtained at the referring/local doctor's office and the results faxed to the study site.

5.1.6 Phase 1: Cycle 7 and 10, Day 1, (±1 week)

If a patient remains on study drug beyond 4 cycles, he/she will only be required to return to the clinic every 3 months

- Directed physical examination including weight and spleen size by palpation;
- Vital signs (blood pressure, pulse, respiratory rate, and temperature; pre-dose);
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G);
- ECG – triplicate (pre-dose, locally read);
- Bone marrow assessment (pre-dose), Cycle 7 only;
- Response assessment (IWG-MRT);
- JAK2 V617F allele burden if mutation present prior to start of therapy (pre-dose);
- MF SAF (pre-dose);
- Review patient study drug dosing diary for compliance and distribute study drug, Cycle 7 only;
- Assessment of AEs using the NCI CTEP CTCAE, version 4.0 (published 28 May 2009) (see Appendix H); and
- Concomitant medication notation.

5.1.7 Phase 1: Cycle 8, 9 11 and 12 Day 1(±3 days)

- Hematology and serum chemistry are to be obtained at the referring/local doctor's office and faxed to the study site, unless the patient is scheduled for a site visit.

5.1.8 Phase 1: Cycle 13, Day 1 and Day 1 of every 3 cycles thereafter (±1 week)

- Directed physical examination including weight and spleen size by palpation;
- Vital signs (blood pressure, pulse, respiratory rate, and temperature; pre-dose);
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G);
- ECG – single reading (pre-dose, locally read);
- Bone marrow assessment (pre-dose) Cycle 13 only, then annually;
- Response assessment (IWG-MRT);
- JAK2 V617F allele burden if mutation present prior to start of therapy (pre-dose);
- MF SAF (pre-dose);
- Assessment of AEs using the NCI CTEP CTCAE, version 4.0 (published 28 May 2009) (see Appendix H); and
- Concomitant medication notation.

5.1.9 Phase 1: End of Study Assessments

The following procedures will be performed within 30 days after the last dose of study drug or within 30 days after withdrawal from the study:

- Complete physical examination including weight and spleen size clinical assessment;
- Vital signs (blood pressure, pulse, respiratory rate, and temperature);
- ECOG Performance Status;
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G);
-
- ECG – triplicate or single reading if Cycle 13 and thereafter (locally read);
- Response assessment (IWG-MRT);
- MF SAF;
- Collect any unused study drug and review patient study drug dosing diary for compliance (if applicable);
- Assessment of AEs using the NCI CTEP CTCAE, version 4.0 (published 28 May 2009) (see Appendix H); and
- Concomitant medication notation.

All efforts will be made to complete the end of study visit for early termination patients however review of laboratory tests obtained from referring/local doctor's office and a follow-up phone call to the patient may take place at a minimum for those patients refusing to return to the study site.

5.1.10 Phase 1: Follow-up

If an unresolved AE was observed at the end of study visit, patients must be followed until the event resolves, until the event is judged stable and not expected to resolve completely, or until the patient begins alternative treatment.

5.2 Assessment Schedule – Phase 2

5.2.1 Phase 2: Screening (Day -14 to Day 0)

- Signed, written informed consent;
- Medical history including concurrent baseline conditions. Document concomitant medications used within 14 days prior to study drug administration and blood products transfused within 3 months prior to study drug administration;
- Complete physical examination including weight and spleen size by palpation (within 7 days prior to Cycle 1, Day 1);
- Vital signs (blood pressure, pulse, respiratory rate, and temperature);
- ECOG Performance Status;
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G);
- Serum or urine pregnancy test for female patients of childbearing potential (must be done within 7 days prior to Cycle 1 Day 1);
- ECG – triplicate. QTcB must be ≤480 msec locally read for eligibility determination and central reading for safety analysis;
- Bone marrow assessment by aspiration and biopsy, according to standard practice at the site(within 28 days prior to first dose of study drug)
- Spleen size measurement by magnetic resonance imaging (MRI; computed tomography [CT] scan for patients not able to tolerate MRI) within 14 days prior to study drug administration. Imaging will be transmitted to a central imaging center for central reading;
- Determine if the patient meets the inclusion/exclusion criteria.

5.2.2 Phase 2: Cycle 1, Day 1

- Review eligibility criteria and laboratory test results;
- Vital signs (blood pressure, pulse, respiratory rate, and temperature) obtained before the first dose of study drug is taken;
- ECOG Performance Status (may be obtained within 24 hours prior to study drug administration);
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G) (may be obtained within 24 hours prior to study drug administration);
- ECG – triplicate (pre-dose and approximately 2, 4, 6, and 8 hours post-dose; centrally read);
- Obtain blood samples for PK assessment (sampling time points are pre-dose and approximately 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-dose);
- JAK2 V617F allele burden (pre-dose may be obtained within 24 hours prior to study drug administration);
- Phospho-STAT3 (pre-dose and approximately 2 and 3hours post-dose) (pre-dose may be obtained within 24 hours prior to study drug administration);
- Cytokine level(pre-dose only; may be obtained within 24 hours prior to study drug administration);

- MPN SAF (MPN-10) (may be obtained within 24 hours prior to study drug administration);
- Distribute study drug and instruct patient regarding completion of the study drug dosing diary (may be done within 24 hours prior to study drug administration);
- Assessment of AEs using the NCI CTEP CTCAE, version 4.0 (published 28 May 2009) (see Appendix H) (may be obtained within 24 hours prior to study drug administration and following study drug administration); and
- Concomitant medication notation (may be obtained within 24 hours prior to study drug administration).

5.2.3 Phase 2: Cycle 1, Day 8 (±2 days)

- Laboratory tests (hematology, serum chemistries, as listed in Appendix G)
- ECG – triplicate; pre-dose and approximately 2 hours post-dose; centrally read);
- Review patient study drug dosing diary for compliance;
- Assessment of AEs using the NCI CTEP CTCAE, version 4.0 (published 28 May 2009) (see Appendix H); and
- Concomitant medication notation.

5.2.4 Phase 2: Cycle 1, Day 15 (±2 days)

- Directed physical examination, including weight and spleen size by palpation;
- Vital signs (blood pressure, pulse, respiratory rate, and temperature);
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G);
- ECG – triplicate (pre-dose and approximately 2 hours post-dose; centrally read);
- Obtain blood samples for PK assessment (pre-dose and approximately 2 hours post-dose);
- Phospho-STAT3 (pre-dose and approximately 2 and 3hours post-dose);
- Review patient study drug dosing diary for compliance;
- Assessment of AEs using the NCI CTEP CTCAE, version 4.0 (published 28 May 2009) (see Appendix H); and
- Concomitant medication notation.

5.2.5 Phase 2: Cycle 1, Day 22 (±2 days)

- Hematology and serum chemistry are to be obtained at the referring/local doctor's office and faxed to the study site.

5.2.6 Phase 2: Cycle 2, 3, and 4, Day 1 (±3 days)

- Directed physical examination including weight and spleen size by palpation;
- Spleen size measurement by MRI (CT scan for patients not able to tolerate MRI) (Cycle 4 only). Imaging will be transmitted to a central imaging center for central reading;

- Vital signs (blood pressure, pulse, respiratory rate, and temperature);
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G);
- Serum or urine pregnancy test (female patients of childbearing potential only);
- ECG – triplicate (Cycle 2: pre-dose and approximately 2 hours post-dose, centrally read; Cycle 3 and 4: pre-dose, locally read);
- Obtain blood sample for PK assessment (Cycle 2 only; sampling time points are pre-dose and approximately 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose);
- Bone marrow assessment (Cycle 4 only);
- Response assessment (IWG-MRT and ELN);
- JAK2 V617F allele burden if mutation present prior to start of therapy (Cycle 2 and Cycle 4, pre-dose);
- Phospho-STAT3 (Cycle 2 only: pre-dose and approximately 2 and 3 hours post-dose;);
- Cytokine (pre-dose);
- MPN SAF (MPN-10) (Cycle 2 and Cycle 4, pre-dose);
- Review patient study drug dosing diary for compliance and distribute study drug;
- Assessment of AEs using the NCI CTEP CTCAE, version 4.0 (published 28 May 2009) (see Appendix H); and
- Concomitant medication notation.

5.2.7 Phase 2: Cycles 2, 3, and 4, Day 15; Cycles 5 and 6, Days 1 and 15 (±3 days)

- Hematology and serum chemistry are to be obtained at the referring/local doctor's office and faxed to the study site.

5.2.8 Phase 2: Cycle 7 and 10 Day 1 (±1 week)

If a patient remains on study drug beyond 4 cycles, he/she will only be required to return to the clinic every 3 months.

- Directed physical examination including weight and spleen size by palpation;
- Spleen size measurement by MRI (CT scan for patients not able to tolerate MRI). Imaging will be transmitted to a central imaging center for central reading;
- Vital signs (blood pressure, pulse, respiratory rate, and temperature);
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G);
- ECG – triplicate (pre-dose only; locally read);
- Bone marrow assessment, Cycle 7 only;
- Response assessment (IWG-MRT and ELN);
- JAK2 V617F allele burden if mutation present prior to start of therapy (pre-dose);
- MPN SAF (MPN-10) (pre-dose);
- Review patient study drug dosing diary for compliance and distribute study drug, Cycle 7 only;

- Assessment of AEs using the NCI CTEP CTCAE, version 4.0 (published 28 May 2009) (see Appendix H); and
- Concomitant medication notation.

5.2.9 Phase 2: Cycle 8, 9, 11 and 12 Day 1 (±3 days)

- Hematology and serum chemistry are to be obtained at the referring/local doctor's office and faxed to the study site, unless the patient is scheduled for a site visit.

5.2.10 Phase 2: Cycle 13, Day 1 and Day 1 of every 3 cycles thereafter (±1 week)

- Directed physical examination including weight and spleen size by palpation;
- Spleen size measurement by MRI (CT scan for patients not able to tolerate MRI). Cycle 13 and after completion of months 18 and 24 treatment cycles (i.e. Cycle 19 and 25). Imaging will be transmitted to a central imaging center for central reading; After 24 treatment cycles, MRI will be performed as clinically indicated; however is not required to be transmitted to a central imaging center for central reading.
- Vital signs (blood pressure, pulse, respiratory rate, and temperature);
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G);
- ECG – single reading (pre-dose only; locally read);
- Bone marrow assessment (pre-dose) Cycle 13 only, then annually;
- Response assessment (IWG-MRT and ELN);
- JAK2 V617F allele burden if mutation present prior to start of therapy (pre-dose);
- MPN SAF (MPN-10) (pre-dose);
- Assessment of AEs using the NCI CTEP CTCAE, version 4.0 (published 28 May 2009) (see Appendix H); and
- Concomitant medication notation.

5.2.11 Phase 2: End of Study Assessments

The following procedures will be performed within 30 days after the last dose of study drug or within 30 days after withdrawal from the study:

- Complete physical examination including weight and spleen size by palpation;
- Spleen size measurement by MRI (CT scan for patients not able to tolerate MRI) if not done within the past 8 weeks.
- Vital signs (blood pressure, pulse, respiratory rate, and temperature);
- ECOG Performance Status;
- Laboratory tests (hematology, serum chemistries, and urinalysis, as listed in Appendix G);
- ECG – triplicate or single reading if Cycle 13 or thereafter (locally read);
- Response assessment (IWG-MRT and ELN);
- MPN SAF (MPN-10);

- Collect any unused study drug and review patient study drug dosing diary for compliance, if applicable;
- Assessment of AEs using the NCI CTEP CTCAE, version 4.0 (published 28 May 2009) (see Appendix H); and
- Concomitant medication notation.

All efforts will be made to complete the end of study visit for early termination patients however review of laboratory tests obtained from referring/local doctor's office and a follow-up phone call to the patient may take place at a minimum for those patients refusing to return to the study site.

5.2.12 Phase 2: Follow-up

If an unresolved AE was observed at end of study visit, patients must be followed until the event resolves, until the event is judged stable and not expected to resolve completely, or until the patient begins alternative treatment.

6 TREATMENTAND RESTRICTIONS

6.1 Treatment

6.1.1 Treatment Regimen, Dosage, and Duration

Patients will be treated at the dose cohort level to which they are assigned. All study drug will be self-administered orally. NS-018 will be self-administered 2 hours or more after the last meal and at least 1 hour before the next meal.

The dose levels planned and the numbers of patients in each dose level are presented below.

Once Daily (QD) Cohort [completed]			Twice Daily (BID) Cohort		
Cohort	**NS-018Total Daily Dose(mg)**	**No. of Patients Per Cohort**	**Cohort**	**NS-018 Total Daily Dose(mg)**	**No. of Patients Per Cohort**
Phase 1			Phase 1		
QD 1#	75	3-6			
QD 2#	125	3-6			
QD 3#	200	3-6	BID 1#	200 (100×2) £	3-6
QD 4#	300	3-6		—	—
	—	—	BID 2#	400 (200×2) £	3-6
	—	—	BID 3#	600 (300×2) £	3-6
	—	—	BID 4#§	800 (400×2) £	3-6
Phase 2	MTD or lower Up to 20 patients				

MTD = maximum tolerated dose.
£ BID dosing must be administered 12 hours apart
If a DLT is experienced at any dose level, an intermediate cohort at a lower dose may be considered, as recommended by Safety Review Committee
§ Additional cohorts at doses > 400 mg BID (800 mg/day) may be considered by the Sponsor if agreed by the Safety Review Committee after review of PK, PD, and safety data. The maximum planned increase in dose between cohorts will be 200 mg as the total daily dose (e.g., the dose level above 400 mg BID will not exceed 500 mg BID)

During the study, a Safety Review Committee will review data from each cohort and may make dosing schedule changes based on the data review. The Safety Review Committee is described in detail in Section 13.9.

In the Phase 1 portion of the study, sequential cohorts of 3 to 6 patients will be treated with escalating doses until the MTD is established (see Section 6.1.1.3). The first patient in each cohort must be observed for at least 7 days of dosing with NS-018. If there is no clinically significant toxicity observed in that patient, enrollment in the cohort may continue. If a significant toxicity occurs, including any possible dose-limiting toxicity (DLT, see Section 6.1.1.2), the Safety Review Committee must meet and determine whether additional patients may be entered at that dose or an intermediate cohort at a lower dose should be considered. Each cohort can be assessed after at least 3 patients have completed 28 days of study drug dosing.

The Safety Review Committee can make dosing schedule changes (twice daily dosing rather than once daily dosing; intermediate dose levels if toxicity occurs that does not rise to the level of a DLT) based on pharmacodynamic, pharmacokinetic, and safety review. If twice daily dosing requires evaluation, dosing would start at one total daily dose level below the last once per day dose level that was declared safe. For example, when 300 mg QD was declared safe,

the starting dose for BID dosing would be 100 mg twice daily, 12 hours apart [representing a total daily dose 200 mg]).

Should BID dosing commence during the Phase I portion of the study, the SRC will meet after the last patient in that cohort has completed 28 days of dosing to assess the safety of that dosing schedule. Should the BID cohort be declared safe, the next BID cohort may begin. However, during the Phase 1 escalation portion of study, intrapatient schedule changes are not permitted (i.e., patients who start QD dosing regimen must remain on QD dosing and patients who start on BID dosing must remain on BID dosing).

If DLTs are seen in the 75 mg cohort, a cohort, labeled -1 and dosed at 50 mg, may be considered by the Safety Review Committee. Cohorts at doses >400 mg BID(800 mg/day) may be considered by the Sponsor if agreed by the Safety Review Committee after review of PK, PD, and safety data. The maximum planned increase in dose between cohorts will be 200 mg as the total daily dose (e.g., the dose level above 400 mg BID will not exceed 500 mg BID).

Once a cohort is declared safe, patients treated at lower doses in earlier cohorts can be considered for intrapatient dose escalation. Intrapatient dose escalation is permissible in individual patients if the patient has received at least 3 months of study drug at a given dose and has not experienced any Grade 3 or 4 drug-related toxicity and no evidence of significant clinical efficacy and the next highest dose cohort has already been declared safe by the Safety Review Committee. Intrapatient dose escalation depends on the total daily dose and the confirmation of safety based on QD and/or BID dose regimen at a dose level. For example a patient at 100mg BID can increase by up to 200 mg BID only when 200 mg BID is declared safe by the Safety Review Committee. In the event that intrapatient dose escalation would result in a patient escalating more than one dose at a time, the eligibility of the patient for dose escalation would be reviewed and the dose level determined by the investigator and the medical monitor.

After intrapatient dose escalation, patients will return to the study site after 1 month of treatment at the higher dose to undergo physical examination (including assessment of spleen size by palpation) and safety laboratory tests (hematology and chemistry). Patients will return to 3-month visit schedule after this visit.

When the MTD is reached, the Phase 2 portion of the study will commence. Additional patients will be added at the MTD level to confirm tolerability and explore efficacy, for a total of 20 patients. Consideration by the Safety Review Committee will also be given to suspending Phase 2 enrollment at the MTD, and instead adding the same total number of patients at a second dose level, the CAD. The CAD is defined as a dose level below the MTD with a clinically significant response rate and an acceptable toxicity profile as determined by the

investigator/medical monitor and sponsor. The expansion cohorts for the MTD and CAD, should they both be pursued, will not be concurrently open for enrollment. The two dose levels would instead be expanded sequentially. Consideration will also be given to enroll patients only at the CAD but not MTD level, based on the risk/benefit of therapy as judged by the investigator/medical monitor and sponsor. After Phase 2 has started, patients who are continuing treatment from the Phase 1 portion of the study are able to change to the Phase 2 dose as intrapatient dose escalation, and based on risk/benefit as judged by the investigator. A change of schedule is allowed, such as a change from a QD Phase 1 dose to a BID Phase 2 dose. Since a patient could potentially be escalated by more than one dose upon crossing over from Phase 1 to the Phase 2 dosing schedule, the eligibility of the patient for dose escalation would be reviewed and the dose level determined by the investigator and the medical monitor. A patient must receive at least 3 months of study drug at the Phase I dose and not experience any Grade 3 or 4 drug-related toxicity before being escalated to the Phase 2 dosing schedule.

During the Phase 2 portion of the study, the Safety Review Committee will meet when a DLT-equivalent AE occurs, in order to determine whether additional patients may be enrolled at the same dose level or at a lower dose thereafter. In addition, the Safety Review Committee will meet when the number of patients completing Cycle 1 reaches 10 to review the pooled safety information to determine if further enrollment is warranted. Any DLTs that occur at a dosing schedule will be evaluated separately.

6.1.1.1 Dose Reductions/Delays

Patients who experience a DLT, as defined in Section 6.1.1.2, **must** have study drug administration interrupted: 1) when a Grade 4 drug related toxicity returns to ≤Grade 1 or to baseline within 4 weeks of study drug interruption, the investigator may recommence treatment, but at one dose level below that at which the toxicity occurred; 2) when a Grade 3 drug related toxicity returns to ≤Grade 1 or to baseline within 4 weeks of study drug interruption, the investigator may recommence treatment at one dose level below that at which the toxicity occurred, or after discussion with the medical monitor, at the same dose at which the toxicity occurred. Discussion on the appropriateness of the patient continuing in the study will also include an evaluation of the current clinical response.

At each step, the investigator must carefully evaluate the relevant risks and benefits to the patient of continued study participation. A second dose reduction can be considered by the investigator if a second significant toxicity occurs, to one further cohort dose below. Patients whose baseline dose has been reduced for toxicity cannot be dose escalated back to the prior dose.

Study drug administration may be interrupted for clinically significant toxicities of ≥Grade 1 that do not meet DLT criteria, at the discretion of the investigator. Once the toxicity has resolved to Grade 0 or 1, or to baseline level within 4 weeks of study drug interruption, study drug may be resumed at either the same dose or one dose level below, at the discretion of the investigator. Furthermore, subjects who experience Grade 4 life-threatening non-hematological toxicity will not be eligible for further treatment, unless reviewed by the Safety Review Committee and deemed appropriate for continued follow up and possible re-initiation of study drug.

Antidiarrheal or antiemetic therapy must be administered before interrupting therapy for Grade 1 or 2 nausea, vomiting, and/or diarrhea.

Patients whose dose is reduced will continue the regular schedule of assessments.

Patients requiring a >4 week interruption in study drug administration should be withdrawn from the study, unless reviewed by the Safety Review Committee and deemed appropriate for continued follow up and possible re-initiation of study drug.

These guidelines for dose reductions or delays also apply to patients in Phase 2 who experience a drug related toxicity

6.1.1.2 Definition of Dose-Limiting Toxicity

A DLT is defined as any one or more of the following events that is unrelated to underlying disease, intercurrent illness, or concomitant medications:

- Grade 4 neutropenia, thrombocytopenia, anemia, or lymphopenia
- Grade 3 or 4 hematologic toxicity other than the above
- Grade 3 or 4 non-hematologic toxicity,

For nausea, vomiting, and/or diarrhea to be considered a DLT, the event must persist for at least 72 hours despite the use of an optimal antiemetic or antidiarrheal regimen. The optimal antiemetic regimen is to be determined by each investigator and should at a minimum include a 5-HT_3 antagonist. The optimal antidiarrheal regimen is to be determined by each investigator and should at a minimum include Imodium®(Loperamide hydrochloride) or Lomotil®(diphenoxylate hydrochloride and atropine sulfate). Grade 3 nausea, vomiting, and/or diarrhea will not be considered a DLT in patients who did not receive optimal treatment with antiemetics or antidiarrheals.

Important medical events other than those listed above may be considered a DLT based upon appropriate medical judgment and discussion by the Safety Review Committee (e.g., the same clinically significant toxicity not qualifying

as a DLT, but observed in multiple patients, or chronic Grade 2 toxicity that persists for more than 4 weeks despite interruption of therapy).

6.1.1.3 Definition of Maximum Tolerated Dose

The MTD is defined as the dose at which ≤1 of 6 patients experience a DLT, with the next higher dose having at least 2 patients experiencing a DLT.

Rules for Determination of MTD

Number of Patients Experiencing DLT During Study Treatment	Action
0/3	Escalate to the next higher dose level.
1/3	Up to 3 additional patients will be added before treating patients at a higher dose. If none of the additional patients experience a DLT, the dose will be escalated. If one of the additional patients has a DLT, the MTD will have been exceeded and 3 additional patients will be added at the previous dose to determine the MTD and recommended Phase 2 dose.
2/3	If 2 of the first 3 patients at a dose level experience a DLT, the MTD will have been exceeded and 3 additional patients will be added at the previous dose to determine the MTD and recommended Phase 2 dose.
DLT = dose-limiting toxicity; MTD = maximum tolerated dose.	

6.1.2 Compliance Control

Patient compliance will be monitored by assessing the tablet count from the drug packages returned at each visit. Patients will complete a study drug dosing diary daily that will document the time of day they took their study drug. Tablet counts will be compared by the site to the dosing diary to further assess compliance and aid patient education regarding compliance. Documentation on the electronic Case Report Form (eCRF) will account for patient compliance during each cohort. Patients will be instructed to return any unused study drug and packaging when attending clinic visits or if the patient is discontinued before the study is complete.

Patients who take <80% of the expected prescribed regimen will be counseled on the importance of taking the study drug appropriately. If compliance is <80% during the first month of therapy, the patient will be counseled, remain on study drug and will follow the study assessment schedule. The patient will be included in all final study analysis populations (See Section 12.2), however the patient will not be included in the data from each cohort that is reviewed by the Safety Review Committee to determine dosing schedule changes. In the event that a patient's compliance is <80% during the first month of therapy, an additional patient will be enrolled in the cohort and their data will be included in the cohort review by the Safety Review Committee as well as in all final study analysis populations.

6.2 Study Restrictions

6.2.1 Concomitant Medications

Any medication taken within 14 days of study drug administration will be considered a concomitant medication. The site will also enter the patient's prior therapies for MF. Patients taking medications chronically should be maintained on the same dose and dosing schedule, if medically feasible.

Necessary supportive measures for optimal medical care will be given throughout the study, including intravenous antibiotics to treat infections, blood components, antidiarrheals, and antiemetics. Additional care will be administered as indicated by the treating physician and the patient's medical need. No concomitant cytotoxic therapy, whether conventional or investigational, will be allowed during this study. All concomitant medications and supportive therapy must be recorded in the eCRF.

Routine prophylactic use of growth factors (G-CSF, GM-CSF, and erythropoietin) or high dose steroids (>10 mg/day of prednisone or prednisone equivalent) is not permitted. Therapeutic use may be considered at the treating physician's discretion in patients who develop complications secondary to cytopenias (e.g., overt sepsis).

Blood products can be administered as needed.

The potential for drugs which are metabolized by cytochrome p450 enzymes being affected by NS-018 is considered possible. The plasma concentration of these drugs may increase or decrease when administered concomitantly with NS-018.

Patients currently taking medication that is substantially metabolized by cytochrome P450 (CYP) 1A2 or CYP3A4 (see Appendix E) are not eligible for this study. Every effort should be made to change these medications to acceptable alternatives to allow patient enrollment.

Patients taking strong CYP3A4 inducers or strong CYP3A4 inhibitors (see Appendix E) who cannot be safely switched to an acceptable alternative are excluded from the study.

If a patient requires administration of a medication that is substantially metabolized by CYP1A2 or CYP3A4 or requires the administration of a strong CYP3A4 inhibitor after enrollment, and is benefiting from study treatment, the NS-018 dose will be decreased by 50%. When the course of treatment with a medication that is substantially metabolized by CYP1A2 or CYP3A4 or is a strong CYP3A4 inhibitor has been completed, the patient will resume their previous dose of NS-018 beginning the next day.

Use of moderate or weak CYP3A4 inducers or moderate or weak CYP3A4 inhibitors (see Appendix E) is discouraged (alternative therapies should be considered), but does not disqualify the patient from study participation and does not require dose modification.

No other drugs that directly treat myelofibrosis are allowed during this study. No other investigational agents and anticancer agents are permitted while on study. Herbal medications should be discontinued and not initiated while participating in the study.

7 INVESTIGATIONAL PRODUCT

7.1 Clinical Trial Material

NS-018 will be supplied by NS Pharma.

The lot numbers and expiration dates (if available) of the drugs supplied will be recorded in the final report.

7.2 Pharmaceutical Formulation(s)

NS-018 is provided in 25 mg and 100 mg film-coated tablets. The tablet contains 25 mg or 100 mg of NS-018 drug substance and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate.

7.3 Administration

The patient will be instructed to take study drug 2 hours or more after the last meal and at least 1 hour before the next meal. When the twice daily (BID) dosing schedule is initiated, NS-018 doses must be administered at least 12 hours apart.

7.4 Labeling and Packaging

Open-label supplies will have a label indicating the number of tablets, storage conditions, directions for use, and sponsor study number and identification, as well as appropriate cautionary language for investigative material. Each bottle will contain 40 tablets. The labels will include space for the patient number and initials to be entered by the investigator.

7.5 Dispensing Procedures and Storage Conditions

7.5.1 Dispensing Procedures

NS-018 will be dispensed to patients in high density polyethylene bottles with polypropylene caps containing 40 tablets. NS-018 will be dispensed at Cycle 1 Day 1 and all other applicable visits.

At each visit, patients will bring the bottles of study drug dispensed to calculate study drug compliance.

Patients will be instructed not to split, crush, or chew tablets.

7.5.2 Storage Conditions

NS-018 tablets should be stored away from light at 2 to 8 °C.

Study drug must be stored in a pharmacy or a locked and secure storage facility, accessible only to those individuals authorized by the investigator to dispense the investigational drug.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

8.1.1 Collection of Adverse Events

It is responsibility of the investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of patients, by observation and by routine open questionings e.g., "How have you felt since I last saw you?"

8.1.2 Definition of Adverse Events

An AE is any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE.

All AEs, including intercurrent illnesses, occurring during the study will be documented in the eCRF. Concomitant illnesses, which existed before entry into the study, will not be considered AEs unless they worsen during the treatment period. All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, reported by patient), must be documented.

Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page.

A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study drug has been administered.

8.1.3 Assessment of Adverse Events

Each AE will be assessed by the investigator with regard to the following categories.

8.1.3.1 Seriousness

A serious AE (SAE) is defined as an AE that meets **any** of the following criteria:

- Results in death;
- Is life-threatening;
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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;
  NOTE: In general, hospitalization for treatment of a pre-existing condition(s) that did not worsen from baseline is not considered an AE and should not be reported as an SAE.
- Results in disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event.
  NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.1.3.2 Intensity

Investigators should assess the severity of AEs according to CTCAE (see Appendix H). In general, CTCAE v4.0 Severity Grades are:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
Grade 2: Moderate; minimal, local or noninvasive intervention indicated;
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care;
Grade 4: Life-threatening consequences; urgent intervention indicated;
Grade 5: Death related to AE.

8.1.3.3 Causality

The causal relationship of the AE to study drug will be described as follows:

- Probable: the AE:
  - Follows a reasonable temporal sequence from administration of the study drug.
  - Could not be reasonably explained by the patient's clinical state, environmental or toxic factors or other therapies administrated to the patient.
  - Disappears or decreases on cessation or reduction in dose of the study drug.

  - Follows a known pattern of response to the study drug.
  - Reappears or worsens upon rechallenge.

- Possible: the AE:
  - Follows a reasonable temporal sequence from administration of the study drug.
  - Could be reasonable explained by the patient's clinical state, environmental or toxic factors or other therapies administrated to the patient.
  - Follows a known pattern of response to the study drug.

- Unlikely: the AE
  - Does not follow a reasonable temporal sequence from administration of the study drug.
  - Could be reasonably explained by the patient's clinical state, environmental or toxic factors or other therapies administrated to the patient.
  - Does not follow a known pattern of response to the study drug.
  - Does not reappear or worsen upon rechallenge.

- Not related:
  - The AE does not meet the above criteria.
  - There is sufficient information that the etiology of the AE is not related to the study drug.

8.1.4 Recording Adverse Events

Patients should be instructed to report any AE that they experience to the investigator. Investigators should assess for AEs at each visit. Adverse events occurring during the clinical study and the follow-up period should be recorded in the eCRF. To capture the most potentially relevant safety information during a clinical study, it is important that investigators record accurate AE terms in the eCRF.

In addition to the above AEs, patients will be instructed to report any changes in skin or vision in order to assess possible phototoxicity of NS-018. During the periodic safety monitoring, investigators should be reminded to inquire of the patients about any changes in their skin or vision.

Investigators are required to document all AEs occurring during the clinical study, commencing with the first dose of NS-018 and including the protocol-defined post-treatment follow-up period in the eCRF. The AEs occurring following the signature of the informed consent, but prior to the first dose of NS-018 will not be reported as AEs unless the event is related to a study procedure. This information (events occurring following the signature of the informed consent but prior to the first dose of NS-018, and not related to a study procedure) will be collected within the medical history section of the eCRF. It is

also important to record all AEs that result in permanent discontinuation of NS-018, whether serious or non-serious.

All AEs occurring after any administration of NS-018 will be followed until the event resolves, until the event is judged stable and not expected to resolve completely, or until the patient begins alternative treatment.

All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to study drug, action taken with the study drug, outcome, and whether the event is classified as serious.

8.2 Serious Adverse Event Reporting - Procedure for Investigators

Initial Reports

All SAEs occurring from the time of the administration of the first dose of study drug until 30 days following the last administration of study drug must be reported to PAREXEL **within 24 hours** of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). Serious AEs that the investigator considers related to study drug occurring after the 30-day follow-up period will also be reported to PAREXEL. Events that occur after signing consent that are considered related to a required study procedure will also be captured as AEs/SAEs.

To report the SAE, fax the completed SAE report form to PAREXEL (fax number listed below) within 24 hours of awareness. PAREXEL safety personnel are available for SAE reporting on a 24-hour basis. Reports are reviewed during normal business hours.

Safety Contact Information:
PAREXEL International
1 Federal Street
Billerica, MA 01821-3559

SAE Contact Information:
PPD

Serious AEs should be reported to the reviewing Institutional Review Board (IRB) according to individual requirements. A copy of that report must be retained at the investigative site and filed in the investigator Site File.

The sponsor will notify FDA and all participating investigators in an IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected or of potentially serious risks from clinical trials or any other source, as soon as possible, but no later than 15 calendar days after the

sponsor receives the safety information and determines that the information qualifies for reporting.

Follow-Up Reports

The investigator must continue to follow the patient until the SAE has subsided, or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. Within 48 hours of receipt of new information, the updated follow-up SAE report form, along with any supporting documentation (e.g., laboratory test reports, patient discharge summary, or autopsy reports), should be faxed to PAREXEL clinical safety personnel.

8.3 Exposure *In Utero* During Clinical Studies

The sponsor has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to the study drug.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

All pregnancies must be reported by the investigator to the sponsor on the initial pregnancy report form within 24 hours after becoming aware of the pregnancy. The investigator must follow up and document the course and the outcome of all pregnancies even if the patient was discontinued from the study or if the study has finished.

All outcomes of pregnancy must be reported by the investigator to the sponsor on the pregnancy outcome report form within 30 days after he or she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy (including SAEs occurring after last administration of study drug) must be recorded on the SAE report form (e.g., maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs

If a female partner of a male study patient who has been exposed to the study drug becomes pregnant, the pregnancy and outcome of pregnancy should be monitored.

8.4 Laboratory Assessments

Safety laboratory assessments (hematology, chemistry, and urinalysis) will be performed locally at each center's laboratory by means of their established

methods. Before starting the study, the investigator will supply the sponsor with a list of the normal ranges and units of measurement.

8.5 Vital Signs

The following vital signs will be assessed in accordance with the Schedule of Procedures (Appendix A):

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

8.6 Electrocardiograms

To determine whether NS-018 causes prolongation of the QTc interval, 12-lead ECG tracings will be collected as outlined below from all patients treated with NS-018:

- Screening (locally read for eligibility determination; centrally read for analysis);
- Cycle 1 Day 1: pre-dose and 2, 4, 6, and 8 hours after administration of NS-018; centrally read;
- Cycle 1 Day 8 (Phase 1 and Phase II), Cycle 1 Day 15 (Phase 2): pre-dose and 2 hours after administration of NS-018; centrally read;
- Cycle 2 Day 1: pre-dose and 2 hours after administration of NS-018; centrally read; and
- Cycle 3 Day 1, Cycle 4 Day 1, Cycle 7 Day 1 and every 3 cycles thereafter and End of Study: pre-dose; locally read.

All ECGs up to Cycle 13 will be taken in triplicate about 1 minute apart and the median QTc value will be evaluated at the respective study site for inclusion criterion 10 (Section 4.1), for compliance with study protocol-defined procedures and safety. After Cycle 13, all ECGs will be single reading only.

When time points for ECG measurements coincide with the time points for pharmacokinetic sampling, triplicate ECG collection should take place immediately prior to the collection of the plasma sample for pharmacokinetics.

All ECGs will be read locally and/or centrally. The ECGs for central reading will be sent after local reading; transmission will not be done immediately.
Details regarding the ECG collection and reading will be provided in the study reference manual.

Following the analysis of the PK data from the first cohort of patients, the ECG schedule may be modified so that tracings are taken around the time of peak plasma concentrations.

8.7 Physical Examinations

Physical examinations, including weight and spleen size, will be performed in accordance with the Schedule of Procedures (Appendix A).

9 EFFICACY ASSESSMENTS

9.1 Treatment Response

Efficacy will be assessed using the IWG-MRT[14]during the Phase I portion of the study and IWG-MRT and ELN[15] during the Phase II portion of the study. The criteria are provided in Appendix I.

9.2 Spleen Size Assessment

In the Phase 1 portion of the study, spleen size will be assessed clinically, by palpation.

In Phase 2, spleen size will be assessed by palpation and by MRI (CT scan for patients not able to tolerate MRI), which will be transmitted to the central reading center and read centrally. Details regarding the MRI/CT protocol will be provided in the study reference manual.

9.3 Bone Marrow Assessment

Bone marrow will be assessed by aspiration and biopsy, according to standard practice at the site.

10 PHARMACODYNAMIC AND PHARMACOKINETIC ASSESSMENTS

Instructions for the processing, handling, and shipment of samples for central analysis will be provided in the study reference manual.

10.1 Pharmacodynamic Assessments

10.1.1 JAK2 V617F Allele Burden Assessment

The intended time points for JAK2 V617F allele burden assessment in both the Phase 1 and Phase 2 portion of the study are specified below.

- Cycle 1 Day 1: pre-dose;
- Cycle 2 Day 1: pre-dose (if mutation present prior to start of therapy);
- Cycle 4 Day 1: pre-dose (if mutation present prior to start of therapy); and
- Cycle 7 Day 1 and every 3 cycles thereafter: pre-dose (if mutation present prior to start of therapy).

10.1.2 Phospho-STAT3 Assessment

The intended time points for Phospho-STAT3 assessment are specified below for each phase of the study.

Phase 1:

- Cycle 1 Day 1: pre-dose and approximately 3 and 6 hours after administration of NS-018 ;
- Cycle 1 Day 8: pre-dose and approximately 3 and 6 hours after administration of NS-018 ;

- Cycle 2 Day 1: pre-dose and approximately 3 and 6 hours after administration of NS-018 ;

Phase 2:

- Cycle 1 Day 1: pre-dose and approximately 2 and 3 hours after administration of NS-018 ;
- Cycle 1 Day 15: pre-dose and approximately 2 and 3 hours after administration of NS-018 ;
- Cycle 2 Day 1: pre-dose and approximately 2 and 3 hours after administration of NS-018 ;

10.1.3 Cytokine Assessment

The intended time points for cytokine assessment in both the Phase 1 and Phase 2 portions of the study are specified below.

- Cycle 1 Day 1: pre-dose
- Cycle 2 Day 1: pre-dose
- Cycle 3 Day 1: pre-dose
- Cycle 4 Day 1: pre-dose

Additional analysis of excess plasma PD samples may be performed for other pharmacodynamic marker evaluations.

10.2 Pharmacokinetic Assessment

Blood samples will be obtained for PK assessments to analyze NS-018 and its metabolites. The intended time points are specified below for each phase of the study.

Phase 1:

- Cycle 1 Day 1: pre-dose and approximately 0.5, 1, 2, 3, 4, 6, 8, and 24 hours after administration of NS-018;
- Cycle 1 Day 8: pre-dose and approximately 0.5, 1, 2, 3, 4, 6, and 8 hours after administration of NS-018; and
- Cycle 2 Day 1: pre-dose and approximately 0.5, 1, 2, 3, 4, 6, 8, and 24 hours after administration of NS-018.

Phase 2:

- Cycle 1 Day 1: pre-dose and approximately 0.5, 1, 2, 3, 4, 6, 8, and 24 hours after administration of NS-018;
- Cycle 1 Day 15: pre-dose and approximately 2 hours after administration of NS-018; and
- Cycle 2 Day 1: pre-dose and approximately 0.5, 1, 2, 3, 4, 6 and 8 hours after administration of NS-018.

Pharmacokinetic parameters to be estimated include observed maximum concentration (Cmax), time to maximum plasma concentration (Tmax), area under the plasma concentration-time curve (AUC), terminal elimination half-life (t1/2), and accumulation ratio (R).

A twice daily dosing schedule may be initiated based on results from PK analysis.

Additional analysis of excess plasma PK samples may be performed for the further understanding of drug metabolites and for the understanding of drug levels of concomitant medications which might have effected levels (or interfered with measurement) of the experimental product.

11 OTHER ASSESSMENTS

During the Phase I portion of the study, the Myelofibrosis Symptom Assessment Form (MF SAF, see Appendix J) will be completed at baseline and repeated at Cycle 2 Day 1 and Cycle 4 Day 1 and every 3 months thereafter, including End of Study.

During the Phase II portion of the study, the Myeloproliferative Neoplasm Symptom Assessment Form [MPN SAF(MPN-10), see Appendix L] will be completed at baseline and repeated at Cycle 2 Day 1 and Cycle 4 Day 1 and every 3 months thereafter, including End of Study.

Analysis of urine samples from patients in the Phase 2 portion of the study (C1D1, Pre-Dose and Single point, 100ml, 2-6 hours post dose on Cycle 2 Day 1, first 6 patients) will be performed for the further understanding of drug metabolites and for the understanding of drug levels of concomitant medications which might have effected levels (or interfered with measurement) of the experimental product.

12 STATISTICS

Additional statistical analyses, other than those described in this section, may be performed if deemed appropriate. A description of the statistical analysis performed on the study data will be outlined in the Statistical Analysis Plan.

Each phase of this study will be analyzed separately. All tables, figures and listings will therefore be separated by study phase.

Interim analyses of PK, PD, and safety data from the Phase 1 portion of the study will be conducted after the MTD has been established.

An analysis of all existing PK, PD, and safety data from the Phase 2 portion of the study will be conducted 6 months after the last patient is enrolled in this part of the study.

The complete analysis of all study data will be contained in the clinical study report at the end of the study.

12.1 Sample Size Determination

Approximately 24 patients will be enrolled during the Phase 1 portion (treated with escalated doses in a standard 3+3 cohort design) and 20 patients will be enrolled during the Phase 2 portion (treated at the MTD). In the Phase 1 portion, additional cohorts at doses >400 mg BID(800 mg/day) may be considered by the Sponsor if agreed by the Safety Review Committee after review of PK, PD, and safety data; if additional cohorts are considered the total number of patients in Phase 1 may increase beyond the approximately 24 projected patients. The maximum planned increase in dose between cohorts will be 200 mg as the total daily dose (e.g.,, the dose level above 400 mg BID will not exceed 500 mg BID). Consideration by the Safety Review Committee will also be given to suspending Phase 2 enrollment at the MTD, and instead adding the same total number of patients at a second dose level, the CAD. The expansion cohorts for the MTD and CAD, should they both be pursued, will not be concurrently open for enrollment. The two dose levels would instead be expanded sequentially. Consideration will also be given to enroll patients only at the CAD but not MTD level, based on the risk/benefit of therapy as judged by the investigator/medical monitor and sponsor.

The probability of observing at least one event with a prevalence rate of e.g. 30% is greater than 99% in the Phase 2 portion.

Probabilities for observing at least one event/one response for other scenarios are presented in the table below:

Prevalence rate / Response rate	Probability of observing at least one AE / one response
	Phase 2 portion (N=20)
5 %	64,2 %
10 %	87,8 %
15 %	96,1 %
20 %	98,8 %
30 %	> 99,9 %

12.2 Analysis Populations

12.2.1 Safety Population

The Safety Population consists of all patients who receive at least one dose of study drug.

12.2.2 Pharmacokinetic Population

The PK Population includes all patients who receive at least one dose of study drug and have at least one evaluable PK profile.

12.2.3 Pharmacodynamic Population

The PD Population includes all patients who receive at least one dose of study drug and have baseline and at least one post-baseline PD assessment.

12.2.4 Efficacy Population

The Efficacy Population includes all patients who receive at least one dose of study drug and have baseline and at least one post-baseline efficacy assessment.

12.3 Demographic and Baseline Characteristics

Baseline and demographic characteristics will be summarized by dose level. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized with frequency tables.

12.4 Efficacy Analyses

Since the primary objective of this study is to evaluate the safety, tolerability, MTD, and clinically active dose of NS-018 in patients with PMF, post-PV MF, or post-ET MF, no formal hypothesis testing will be performed for efficacy parameters. Efficacy analysis will be based on the Efficacy Population.

The responses to treatment assessed using the IWG consensus criteria(Phase I) and the IWG MRT and ELN Response Criteria (Phase II)will be tabulated by dose level and visit. The number and percentage of patients achieving the response will be provided for each response level. The objective response rate (the percentage of patients with confirmed complete remission (CR), partial response (PR), or clinical improvement (CI) during the treatment period) and its 95% exact binomial confidence interval will be provided by dose level. Quality of life assessed using the MF SAF (Phase I) or MPN SAF (MPN-10) (Phase II) will be summarized by dose level and visit. Change in spleen size by MRI (CT scan for patients not able to tolerate MRI) for the Phase 2 portion will be summarized for the cohort.

12.5 Safety Analyses

All safety analyses will be based on the Safety Population. Adverse events, vital sign measurements, clinical laboratory information, ECG measurements, and concomitant medications will be summarized by dose level.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of all AEs will be graded according to the NCI CTEP CTCAE version 4.0. A summary of all AEs will be provided by system organ class and preferred term. The same summaries will be performed for Grade 3/4 AEs and drug-related AEs. Listings will be presented for SAEs, Grade 3/4 AEs, and AEs leading to discontinuation from the study.

Clinical laboratory evaluations at each visit and change from baseline (Cycle 1 Day 1) will be summarized by dose level. A laboratory value shift table will be provided. Vital signs and ECG parameters at each assessment time will be summarized by dose level. Other safety variables and their changes from baseline (when applicable) will be summarized by dose level at each of the scheduled assessment times.

12.6 Pharmacokinetic Analyses

Blood samples for PK analysis of NS-018 and its metabolites will be collected at designated study visits. All PK analyses will be based on the PK population.

Plasma concentrations of NS-018 and its metabolites will be summarized descriptively by dose level and time point of collection. Summary statistics including number of patients, arithmetic mean, geometric mean, geometric CV, standard deviation, minimum, maximum, median, coefficient of variation, and standard error of the mean will be presented. Individual patient and mean plasma concentrations of NS-018 and its metabolites will be plotted vs. 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 its metabolites.

12.6.1 Relationship between PK data and endpoints

The relationship between plasma concentrations of NS-018 and its metabolites and each efficacy and toxicity outcome measure as well as any biomarker endpoints will be explored. The details will be outlined in the Statistical Analysis Plan.

12.7 Pharmacodynamic Analyses

All PD analyses (JAK2 V617F allele burden, phospho-STAT3, and cytokine levels) will be based on the PD Population. JAK2 V617F allele burden and phospho-STAT3 values and cytokine levels at each time point and changes from baseline will be summarized descriptively by dose level and listed. The relationship between NS-018 dose level and JAK2 V617F allele burden or phospho-STAT3 levels over time will be explored.

13 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

13.1 Data Quality Assurance

The sponsor will conduct a site visit to verify the qualifications of each investigator, inspect the site facilities, and inform the investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the eCRF/electronic data

capture (EDC) system for this study must be consistent with the patients' source documentation (i.e., medical records).

13.1.1 Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study center using eCRF. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manger will raise a query in the EDC application. The appropriate staff at the study site will answer queries sent to the investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF.

The specific procedures to be used for data entry and query resolution using the eCRF/EDC system will be provided to study sites in a training manual. In addition, site personnel will receive training on the eCRF/EDC system.

13.2 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the CRFs or EDC system promptly. All source documents from which eCRF/EDC entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available include laboratory assessments, and ECG recordings.

Data that will be entered directly into the eCRF/EDC system (i.e., for which there is no prior written or electronic record of data, such as Quality of Life assessments) are considered to be source data.

The original eCRF/EDC entries for each patient may be checked against source documents at the study site by the site monitor.

After review by the site monitor, completed eCRF/EDC entries will be uploaded. Instances of missing or uninterpretable data will be discussed with the investigator for resolution.

The specific procedures to be used for data entry and query resolution using the eCRF/EDC system will be provided to study sites in a training manual. In addition, site personnel will receive training on the eCRF/EDC system.

13.2.1 Data Collection

The investigators (and appropriately authorized staff) will be given access to an online web-based EDC) system which is 21 Code of Federal Regulations (CFR) Part 11 compliant. This system is specifically designed for the collection of the clinical data in electronic format. Access and right to the EDC system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the investigator and authorized staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each patient included in the study and should reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or immediately after the patient's visit or assessment. The investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the investigator should indicate this in the eCRF.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on-line directly by the investigator or by authorized staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the investigator will be required to electronically sign off the clinical data

Data about all study drug dispensed to the patient and any dosage changes will be tracked on the eCRF.

13.3 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare EDC/eCRF entries and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. EDC/eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the eCRF/EDC entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, Regulatory Authorities of certain countries, IRBs, Institutional Ethics Committees (IECs), and/or the sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The investigator assures the sponsor of the necessary support at all times.

13.4 Data Processing

All data will be entered by site personnel into the eCRF/EDC system (as detailed in Section 13.2.1).

The data-review and data-handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query/correction sheets for unresolved queries will be sent to the study monitors for resolution with the investigator. The database will be updated on the basis of signed corrections.

Previous and concomitant medications will be coded using the World Health Organization (WHO) Drug Reference List (DRL), which employs the Anatomical Therapeutic Classification (ATC) classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

Previous and concomitant diseases as well as AEs will be coded with MedDRA.

The versions of the coding dictionaries will be provided in the Clinical Study Report.

13.5 Archiving Study Records

According to International Conference on Harmonization (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

13.6 Good Clinical Practice

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

13.7 Informed Consent

Before each patient is admitted to the study, informed consent will be obtained from the patient (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country. This consent form must be dated and retained by the investigator as part of the study records. The investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the

consent and when it was obtained must also be documented in the eCRF/EDC system.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB, and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

13.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug application (IND) under which the study is being conducted.

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the investigator by PAREXEL or NS Pharma. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

13.9 Safety Review Committee

A Safety Review Committee, consisting of the actively recruiting investigators, the medical monitor overseeing the study for NS Pharma and a NS Pharma representative will meet to evaluate each cohort. If clinically significant toxicity occurs in the first patient in any cohort during their first 7 days of NS-018 dosing, the Safety Review Committee will meet and determine dosing for future patients. The Safety Review Committee must review each cohort before patients can be enrolled into the next cohort. The Safety Review Committee can make dosing schedule changes (twice daily dosing rather than once daily dosing; intermediate dose levels if toxicity occurs that does not rise to the level of a DLT) based on pharmacodynamic, pharmacokinetic, and safety review. If twice daily dosing requires evaluation, dosing would start at one total daily dose level below the last once per day dose level that was declared safe.

If DLTs are seen in the 75 mg cohort, a cohort, labeled -1 and dosed at 50 mg, may be considered by the Safety Review Committee. Cohorts at doses >400 mg BID(800 mg/day)may be considered by the Sponsor if agreed by the Safety Review Committee after review of PD, PK, and safety data. The maximum planned increase in dose between cohorts will be 200 mg as the total daily dose (e.g., the dose level above 400 mg BID will not exceed 500 mg BID).

Should BID dosing commence during the Phase I portion of the study, the SRC will meet after the last patient in that cohort has completed 28 days of dosing to assess the safety of that dosing schedule. Should the BID cohort be declared safe, the next BID cohort may begin. BID cohorts and QD cohorts may enroll simultaneously provided the previous lower dose of each cohort type has been declared safe by the SRC.

During the Phase 2 portion of the study, the Safety Review Committee will meet when a DLT-equivalent AE occurs, in order to determine whether additional patients may be enrolled at the same dose level or at a lower dose thereafter. In addition, the Safety Review Committee will meet when the number of patients who have completed Cycle 1 reaches 10 to review the pooled safety information to determine if further enrollment is warranted.

13.10 Duration of the Study

A patient may continue to receive treatment with NS-018, administered continuously as daily therapy in cycles of 28 days duration, until the patient experiences unacceptable toxicity that precludes any further treatment, disease progression, and/or as long as the patient is benefiting from treatment, at the discretion of the investigator.

13.11 Premature Termination of the Study

NS Pharma has the right to terminate the participation of either an individual site or the study at any time. Reasons for terminating the study include, but are not limited to, the following:

1. Incidence or severity of AEs in this or other studies which indicates a potential health hazard to patients;
2. Patient enrollment is unsatisfactory;
3. Data recording is inaccurate or incomplete; or
4. Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study.

13.12 Confidentiality

All study findings and documents will be regarded as confidential. The investigator and members of his/her research team must not disclose such information without prior written approval from the sponsor.

The anonymity of participating patients must be maintained. Patients will be identified on the eCRF/EDC system and other documents submitted to the

sponsor by their patient number, initials and/or birth date, not by name. Documents not to be submitted to the sponsor that identify the patient (e.g., the signed informed consent) must be maintained in confidence by the investigator.

13.13 Publication Policy

By signing the study protocol, the investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, Regulatory Authorities will be notified of the investigator's name, address, qualifications and extent of involvement.

An investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the sponsor in advance. Details are provided in a separate document.

14 LIST OF STUDY PERSONNEL

14.1 Sponsor

NS Pharma, Inc.
140 E Ridgewood Ave, 2nd Floor
Paramus, NJ 07652
PPD

14.2 Contract Research Organization

PAREXEL International
195 West Street
Waltham, MA 02451
PPD

14.3 Drug Safety

PAREXEL International
1 Federal Street
Billerica, MA 01821-3559PPD
PPD

15 REFERENCES

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16 SUPPLEMENT

16.1 Investigator's Agreement

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by NS Pharma to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to NS Pharma and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by NS Pharma, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and ICH Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Name

APPENDIX A: SCHEDULE OF PROCEDURES

Schedule of Procedures – Phase 1

Study Phase	**Screening**	**Treatment Period – Phase 1**				
Visit Timing[p]	**Day -14 to Day 0**	**Cycle 1 Day 1**	**Cycle 1 Days 8, 15, and 22**	**Cycles 2, 3, and 4 Day 1**	**Cycle 7, Day 1 and every 3 cycles thereafter**	**End of Study[o]**
Visit Window			**±2 days**	**±3 days**	**±1 week**	
Study Procedure						
Informed consent	X					
Confirm/review eligibility criteria	X	X				
Medical history	X[a]					
Physical examination	X[b]		X[k]	X[k]	X[k]	X[b]
Vital signs	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
ECOG Performance Status	X	X[f]				X
Clinical laboratory (see table next page)	X[d]	X[d,f]	X[d]	X[d]	X[d]	X[d]
Pregnancy test (serum or urine)	X			X		
12-lead electrocardiogram	X[e]	X[h]	X[l] (Day 8 only)	X[m]	X[m]	X[m]
Bone marrow assessment	X[q]			X (Cycle 4 only)	X[r]	
Response assessment (IWG-MRT)				X	X	X
Pharmacokinetic sampling		X[i]	X[i] (Day 8 only)	X[i] (Cycle 2 only)		
JAK2 V617F allele burden		X[f]		X[n] (Cycles 2 and 4)	X[n]	
Phospho-STAT3		X[f,j]	X[j] (Day 8 only)	X[j] (Cycle 2only)		
Cytokines		X[f]		X		
MF SAF		X[f]		X[g] (Cycles 2 and 4)	X[g]	X
Study drug dispensation		X[f]		X	X	
Diary dispensation		X[f]		X		
Collect unused study drug						X
Compliance check			X	X	X	X
Adverse events		X[f]	X	X	X	X
Concomitant medications		X[f]	X	X	X	X

a Including concomitant medications within 14 days prior to study drug administration, blood products transfused within 3 months prior to study drug administration, and concurrent baseline conditions.
b Complete physical examination including weight and spleen size by clinical assessment (palpation). At screening, must be done within 7 days prior to Cycle 1, Day 1 (first dose).
c Blood pressure, pulse, respiratory rate, and temperature; pre-dose during treatment.
d Hematology includes erythrocytes, MCV, MCH, neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets, leukocytes, hemoglobin and hematocrit. Serum chemistry includes BUN, LDH, creatinine, uric acid, total protein, albumin, glucose, total bilirubin, magnesium, alkaline phosphatase, AST, ALT, chloride, sodium, and potassium. Serum chemistry will also include amylase and lipase in the first 2 cycles. Urinalysis includes pH, protein, glucose, ketone, bilirubin, blood, and nitrite.
e For eligibility determination, locally read; Median QTc must be ≤480 msec. Centrally read for safety analysis.
f Pre-dose; may be obtained within 24 hours prior to study drug administration. Adverse Events on Cycle 1, Day 1 will also be collected post-dose.
g Pre-dose.
h Pre-dose and 2, 4, 6, and 8 hours post-dose; centrally read.
i Sampling times are pre-dose and approximately 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-dose. Cycle 1, Day 8 will not include 24 hour time point).

j Pre-dose and approximately 3 and 6 hours post-dose..
k Directed physical examination including weight and spleen size by palpation.
l Pre-dose and approximately 2 hours post-dose; centrally read.
m Cycle 2: pre-dose and approximately 2 hours post-dose, in triplicate and centrally read. Cycles 3 and thereafter: pre-dose, in triplicate and locally read. After Cycle 13, single reading and locally read
n If mutation present prior to start of therapy; pre-dose only.
o Within 30 days after the last dose of study drug or within 30 days after withdrawal from the study.
p For the purpose of scheduling procedures and evaluations, a treatment cycle is defined as 28 days.
q Within 28 days prior to the first dose of study drug
r Every 6 months after Cycle 7 and annually after Cycle 13

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CBC=complete blood chemistry; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; JAK2=Janus kinase 2; LDH=lactate dehydrogenase; MF SAF=Myelofibrosis Symptom Assessment Form; STAT3=signal transducer and activator of transcription 3.

Schedule of Safety Laboratory Procedures by Cycle (Site and Local Evaluations) – Phase 1

Cycle	**1**				**2**		**3**		**4**		**5**		**6**		**7**	**8**	**9**	**10**	**11**	**12**	**13**
Day	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Site visit	X	X	X	X	X		X		X						X			X			X
Local visit						X		X		X	X	X	X	X		X	X		X	X	

Local visit laboratory procedures at the indicated visits include: hematology (erythrocytes, MCV, MCH, neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets, leukocytes, hemoglobin and hematocrit) and serum chemistry (BUN, LDH, creatinine, uric acid, total protein, albumin, glucose, total bilirubin, magnesium, alkaline phosphatase, AST, ALT, chloride, sodium, and potassium). Serum chemistry will also include amylase and lipase in the first 2 cycles.
Results should be faxed to the study site.

Schedule of Procedures – Phase 2

Study Phase	**Screening**		**Treatment Period – Phase 2**				
Visit Timing[q]	**Day -14 to Day 0**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Cycle 1 Day 15**	**Cycle 2, 3, and 4, Day 1**	**Cycle 7, Day 1and every 3 cycles thereafter**	**End of Study**[o]
Visit Window			**±2 days**	**±2 days**	**±3 days**	**±1 week**	
Study Procedure							
Informed consent	X						
Confirm/review eligibility criteria	X	X					
Medical history	X[a]						
Physical examination	X[b]			X[l]	X[l]	X[l]	X[b]
Spleen size assessed by MRI (CT scan for patients not able to tolerate MRI)	X[c]				X (Cycle 4 only)	X[u]	X[p]
Vital signs	X[d]	X[d]		X[d]	X[d]	X[d]	X[d]
ECOG Performance Status	X	X[h]					X
Clinical laboratory (see table next page)	X[e]	X[e,h]	X[e]	X[e]	X[e]	X[e]	X[e]
Pregnancy test (serum or urine)	X						
12-lead electrocardiogram	X[f]	X[i]	X[m]	X[m]	X[m]	X[m]	X[m]
Pharmacokinetic sampling		X[j]		X[j]	X[j] (Cycle 2 only)		
Urine PK		X[s]			X[s] (Cycle 2 only)		
Bone marrow assessment	X[r]				X (Cycle 4 only)	X[t]	
Response assessment (IWG-MRT and ELN)					X	X	X
JAK2 V617F allele burden		X[h]			X[n](Cycles 2 and 4)	X[n]	
Phospho-STAT3		X[h,k]		X[k]	X[k] (Cycle 2 only)		
Cytokines		X[h]			X		
MPN SAF (MPN-10)		X[h]			X[g] (Cycles 2 and 4)	X[g]	X
Study drug dispensation		X[h]			X	X	
Diary dispensation		X[f]			X		
Compliance check			X	X	X	X	X
Adverse event		X[h]	X	X	X	X	X
Concomitant medication		X[h]	X	X	X	X	X

a Including concomitant medications within 14 days prior to study drug administration, blood products transfused within 3 months prior to study drug administration, and concurrent baseline conditions.
b Full physical examination including weight and spleen size by clinical assessment (palpation). At screening, must be done within 7 days prior to Cycle 1, Day 1 (first dose).
c All MRI/CT scans will be transmitted for central reading.
d Blood pressure, pulse, respiratory rate, and temperature; pre-dose during treatment.
e Hematology includes erythrocytes, MCV, MCH, neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets, leukocytes, hemoglobin; and hematocrit. Serum chemistry includes BUN, LDH, creatinine, uric acid, total protein, albumin, glucose, total bilirubin, magnesium, alkaline phosphatase, AST, ALT, chloride, sodium, and potassium. Serum chemistry will also include amylase and lipase in the first 2 cycles. Urinalysis includes pH, protein, glucose, ketone, bilirubin, blood, and nitrite (no urinalysis at C1D8). At Cycle 1, Day 15, single point, 100mL urine samples 2-8 hours post-dose should be included for at least 3 patients.
f For eligibility determination, locally read; Median QTc must be ≤480 msec. Centrally read for safety analysis.
g Pre-dose.

h Pre-dose; may be obtained within 24 hours prior to study drug administration. Adverse Events on Cycle 1, Day 1 will also be collected post-dose.
i Pre-dose and 2, 4, 6, and 8 hours post-dose; centrally read.
j Sampling times for Cycle 1 Day 1 and Cycle 2 Day 1 are pre-dose and approximately 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose; (Cycle 1, Day 1 includes 24 hour post-dose). Sampling times for Cycle 1 Day 15 are pre-dose and approximately 2 hours post-dose.
k Pre-dose and approximately 2 and 3 hours post-dose.
l Directed physical examination including weight and spleen size by palpation.
m Cycle 1, Day 8&15 and Cycle 2, pre-dose and 2 hours post-dose; in triplicate and centrally read; Cycle 3 and thereafter, pre-dose only, in triplicate and locally read. After Cycle 13, single reading and locally read
n Pre-dose JAK2 V617F allele burden, if mutation was present prior to start of therapy.
o Within 30 days after last dose of study drug or within 30 days after withdrawal from the study.
p If not done within the previous 8 weeks.
q For the purpose of scheduling procedures and evaluations, a treatment cycle is defined as 28 days.
r Within 28 days prior to the first dose of study drug
s Single point collection (100mL) Pre-dose on Cycle 1 Day 1 and 2-6 hours post dose on Cycle 2 Day 1
t Every 6 months after Cycle 7 and annually after Cycle 13
u On day 1 of cycles 7, 10, and 13, and after completion of months 18 and 24 treatment cycles (i.e. Cycle 19 and 25).

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CBC=complete blood chemistry; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; JAK2=Janus kinase 2; LDH=lactate dehydrogenase; MPN SAF (MPN-10) =Myeloproliferative Neoplasm Symptom Assessment Form; MRI=magnetic resonance imaging; STAT3=signal transducer and activator of transcription 3.

Schedule of Safety Laboratory Procedures by Cycle (Site and Local Evaluations) – Phase 2

Cycle	**1**				**2**		**3**		**4**		**5**		**6**		**7**	**8**	**9**	**10**	**11**	**12**	**13**
Day	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Site visit	X	X	X		X		X		X						X			X			X
Local visit				X		X		X		X	X	X	X	X		X	X		X	X	

Local visit laboratory procedures at the indicated visits include: hematology (erythrocytes, MCV, MCH, neutrophils, eosinophils, basophils, lymphocytes, monocytes, platelets, leukocytes, hemoglobin; and hematocrit) and serum chemistry (BUN, LDH, creatinine, uric acid, total protein, albumin, glucose, total bilirubin, magnesium, alkaline phosphatase, AST, ALT, chloride, sodium, and potassium). Serum chemistry will also include amylase and lipase in the first 2 cycles.
Results should be faxed to the study site.

APPENDIX B1: PRIMARY MYELOFIBROSIS DEFINITION

2008 WHO Diagnostic Criteria for primary myelofibrosis (PMF)

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 (e.g., *MPL*W515K/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 polycythemiavera 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 patients 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.

¶Degree of abnormality could be borderline or marked.

Reference: Vardiman J, Thiele T, Arber D, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood.2009; 114:937-951.

APPENDIX B2: POST-POLYCYTHEMIA VERA MYELOFIBROSIS DEFINITION

2008 IWG-MRT Diagnostic Criteria for post-polycythemia veramyelofibrosis (post-PV MF)

Required criteria:

1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria
2. Bone marrow fibrosis grade 2–3 (on 0–3 scale) [3] or grade 3–4 (on 0–4 scale) [4,a]

Additional criteria (two 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 $\geq$ 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 $\geq$ 1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

Abbreviations: IWG-MRT, International Working Group for Myelofibrosis Research and Treatment; LDH, lactate dehydrogenase; post-ET MF, post-essential thrombocythemiamyelofibrosis; post-PV MF, postpolycythemia veramyelofibrosis.

[a]Grade 2–3 according to the European classification:[3] 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: [4] 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.

Reference: Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemiamyelofibrosis: a consensus statement from the international working group for myelofibrosis research and treatment. Leukemia.2008; 22:437-438.

APPENDIX B3: POST-ESSENTIAL THROMBOCYTHEMIA MYELOFIBROSIS DEFINITION

2008 IWG-MRT Diagnostic Criteria for post-essential thrombocythemiamyelofibrosis (post-ET MF)

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) [3] or grade 3–4 (on 0–4 scale) [4,a]

Additional criteria (two are required):

1. Anemia[b] and a $\geq$ 2 mg ml $^{-1}$ decrease from baseline hemoglobin level
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of $\geq$ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Increased LDH (above reference level)
5. Development of $\geq$ 1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

Abbreviations: IWG-MRT, International Working Group for Myelofibrosis Research and Treatment; LDH, lactate dehydrogenase; post-ET MF, post-essential thrombocythemiamyelofibrosis; post-PV MF, postpolycythemia veramyelofibrosis.

[a]Grade 2–3 according to the European classification:[3] 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: [4] 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.

Reference: Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemiamyelofibrosis: a consensus statement from the international working group for myelofibrosis research and treatment. Leukemia.2008; 22:437-438.

APPENDIX C: INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR PRIMARY MYELOFIBROSIS

The following table determines risk level using the International Prognostic Scoring System (IPSS) for PMF (primary myelofibrosis).

Risk Level	IPSS PMF Score
Low risk	0
Intermediate risk 1	1
Intermediate risk 2	2
High risk	≥3

Factors identified as predictors of shortened survival were:

- age >65 years,
- presence of constitutional symptoms,
- hemoglobin <10 g/dL,
- leukocyte count >25x10^9/L, and
- circulating blast cells ≥1%.

Source: Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood 2009;113(13):2895-2901.

APPENDIX D: EASTERN COOPERTIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX E: PROHIBITED AND CAUTIONED MEDICATIONS – SPECIFIC CYTOCHROME P450 SUBSTRATES AND INHIBITORS/INDUCERS

The tables below list many of the medications that are prohibited or cautioned. See the website for additional medications that may not be listed. To view this website, hit CTRL+Click when your cursor is on top of this link: (http://medicine.iupui.edu/clinpharm/ddis/table.asp).

CYP1A2 and CYP3A4 Substrates
(Drugs Substantially Metabolized by CYP1A2 or CYP3A4)
Use of these drugs is prohibited

CYP1A2 Substrates

amitriptyline	ondansetron
excessive caffeine	phenacetin
clomipramine	propranolol
clozapine	riluzole
cyclobenzaprine	ropivacaine
duloxetine	tacrine
estradiol	theophylline
fluvoxamine	tizanidine
haloperidol	triamterene
imipramine N-DeMe	verapamil
mexiletine	warfarin
naproxen	zileuton
olanzapine	zolmitriptan

CYP3A4 Substrates

Macrolide antibiotics including clarithromycin, erythromycin and telithromycin (not azithromycin)

Benzodiazapines including alprazolam, diazepam, midazolam, and triazolam

Immune modulators including cyclosporine and tacrolimus

Antihistamines including astemizole, and chlorpheniramine.

Calcium channel blockers including amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, verapamil

HMG CoA reductase inhibitors (Statins) including atorvastatin, cerivastatin, lovastatin, simvastatin (not pravastatin and rosuvastatin)

Steroid 6beta-OH including estradiol, hydrocortisone, progesterone, and testosterone

Miscellaneous:

alfentanil	eplerenone	quinidine
aprepitant	fentanyl	quinine
aripiprazole	finasteride	risperidone
buspirone	haloperidol	salmeterol
cafergot	LAAM	sildenafil
excessive caffeine	lidocaine	sirolimus
cilostazol	methadone	tamoxifen
cocaine	nateglinide	trazodone
codeine N-demethylation	ondansetron	zaleplon
dexamethasone	pimozide	ziprasidone
dextromethorphan	propranolol	zolpidem
domperidone	quetiapine	

CYP3A4 STRONG Inhibitors and Inducers **Use of these drugs is prohibited**	
CYP3A4 Inhibitors	**CYP3A4 Inducers**
clarithromycin itraconazole ketoconazole nefazodone telithromycin	rifampin St. John's Wort
CYP3A4 MODERATE Inhibitors and Inducers **Use of these drugs is discouraged (alternative therapies should be considered) but does not disqualify patient participation in the study.**	
CYP3A4 Inhibitors	**CYP3A4 Inducers**
aprepitant diltiazem erythromycin fluconazole grapefruit juice verapamil	carbamazepine phenobarbital phenytoin pioglitazone rifabutin troglitazone

APPENDIX F: NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION OF HEART FAILURE

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Source: http://www.merckmanuals.com/professional/sec07/ch074/ch074a.html#CEGDEIFG

APPENDIX G: CLINICAL LABORATORY (SAFETY) TESTS

Hematology:	erythrocytes mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) neutrophils eosinophils basophils lymphocytes monocytes platelets leukocytes hemoglobin hematocrit	Urinalysis:	pH protein glucose ketone bilirubin blood nitrite
Clinical chemistry:	blood urea nitrogen (BUN) lactate dehydrogenase creatinine uric acid total protein albumin glucose total bilirubin magnesium amylase (first 2 cycles only) lipase (first 2 cycles only)	Liver enzymes:	alkalinephosphatase aspartateaminotransferase (AST) alanineaminotransferase (ALT)
Electrolytes:	chloride sodium potassium		
Pregnancy test:	Serum or urine, in women with childbearing potential		

APPENDIX H: NATIONAL CANCER INSTITUTE COMMON TOXICITY CRITERIA FOR ADVERSE EVENTS

See the following website for NCI CTEP CTCAE version 4.0 (28 May 2009). To view this website, hit CTRL+Click when your cursor is on top of this link:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX I: INTERNATIONAL WORKING GROUP CONCENSUS CRITERIA FOR TREATMENT RESPONSE IN MYELOFIBROSIS WITH MYELOID METAPLASIA

1. Complete remission (CR)	(1) Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly.
	(2) Peripheral blood count remission defined as hemoglobin level at least 110 g/L, platelet count at least 100×10^9/L, and absolute neutrophil count at least 1.0×10^9/L. In addition, all 3 blood counts should be no higher than the upper normal limit.
	(3) Normal leukocyte differential including disappearance of nucleated red blood cells, blasts, and immature myeloid cells in the peripheral smear, in the absence of splenectomy.*
	(4) 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.†
2. Partial remission (PR)	Requires all of the above criteria for CR except the requirement 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.
3. 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)
	(1) A minimum 2 -g/L increase in hemoglobin level or becoming transfusion independent (applicable only for patients with baseline hemoglobin level of less than 100 g/L).‡
	(2) Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable.§
	(3) A minimum 100% increase in platelet count and an absolute platelet count of at least $50{,}000 \times 10^9$/L (applicable only for patients with baseline platelet count below 50×10^9/L).
	(4) A minimum 100% increase in ANC and an ANC of at least 0.5×10^9/L (applicable only for patients with baseline absolute neutrophil count below 1×10^9/L).

4. Progressive disease (PD)	Requires one of the following:‖
	(1) Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at greater than 5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of greater than 10 cm.
	(2) Leukemic transformation confirmed by a bone marrow blast count of at least 20%.
	(3) An increase in peripheral blood blast percentage of at least 20% that lasts for at least 8 weeks.
5. Stable disease (SD)	None of the above.
6. Relapse	Loss of CR, PR, or CI. In other words, a patient with CR or PR is considered to have undergone relapse 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 patients 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 posttreatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process.

‡ Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the last month for a hemoglobin level of less than 85 g/L that was not associated with clinically overt bleeding. Similarly, during protocol therapy, transfusions for a hemoglobin level of 85 g/L or more is discouraged unless it is clinically indicated.

§ In splenectomized patients, palpable hepatomegaly is substituted with the same measurements.

‖ It is acknowledged that worsening cytopenia might represent progressive disease, 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.

ANC = absolute neutrophil count; CR = complete remission; CI = clinical improvement; PD = progressive disease; PR = partial response; SD = stable disease.

Source: Tefferi A, Barosi G, Mesa R, et al. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT).Blood. 2006;108:1497-1503.

APPENDIX J: MYELOFIBROSIS SYMPTOM ASSESSMENT FORM

The MF SAF is described in

Mesa RA, Schwager S, Radia D, et al. The myelofibrosis symptom assessment form (MFSAF): An evidence-based brief inventory to measure quality of life and symptomatic response to treatment in myelofibrosis. Leukemia Research. 2009;33:1199-1203.

APPENDIX K: 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 wk 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 x 10^9/L and <UNL;
		Platelet count ≥100 x 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 x 10^9/L and <UNL; platelet count ≥100 x 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 x 10^9/L and <UNL; platelet count ≥50, but <100 x 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 patients: a ≥20 g/L increase in hemoglobin level‖ Transfusion-dependent patients: becoming transfusion-independent{
Spleen response#		A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpablepp 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
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 distance, below LCM, for baseline splenomegaly of 5-10 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 x 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 cytogenetic 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 preexisting abnormality
		PR: ≥50% reduction in abnormal metaphases
		(partial response applies only to patients with at least ten 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 patients 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

EMH, extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology-or imaging study-proven nonhepatosplenic EMH); LCM, left costal margin;
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 patients 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 1 promyelocytes 1 myelocytes 1 metamyelocytes 1 nucleated red blood cells. In splenectomized patients, <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 ≥25000 x 10(9)/L and absolute neutrophil count of ≥0.5 x 10(9)/L.
‖Applicable only to patients with baseline hemoglobin of <100 g/L. In patients not meeting the strict criteria for transfusion dependency at the time of study enrollment
(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 patients 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 patients, 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.17 The MPN-SAF TSS is assessed by the patients 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

APPENDIX L: MYELOPROLIFERATIVE SYMPTOM ASSESSMENT FORM (MPN-SAF) (MPN-10)

The MPN-SAF (MPN-10) is described in

Emanuel, R.M.,Dueck, A.C., Geyer, H.L.,Kiladjian, J-J., Slot, S., Zweegman, S., ….Mesa, R.A. Myeloproliferative Neoplasm (MPN) Symptom Assessment Form Total Symptom Score: Prospective InternationalAssessment of an Abbreviated Symptom Burden ScoringSystem Among Patients With MPNs. J ClinOncol 30:4098-4103