CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Open-label, Translational Biology Study of Momelotinib in Transfusion-Dependent Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA	
IND Number:	101155	
EudraCT Number:	Not Applicable	
Indication:	Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)	
Protocol ID:	GS-US-352-1672	
Clinical Program Manager:	Name: Telephone:	Ryan Athearn (650) 378-3104
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Protocol Version/Date:	Original:	18 May 2015

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Dr.
Foster City, CA 94404

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IND Number:	101155
EudraCT Number:	Not Applicable
Study Centers Planned:	Approximately 20 centers in North America
Objectives:	The primary objective of this study is: • To determine the transfusion independence response rate for transfusion dependent myelofibrosis (MF) subjects treated with momelotinib (MMB) The secondary objectives of this study are: • To evaluate baseline levels and changes in markers of iron metabolism in transfusion dependent MF subjects treated with MMB • To assess inhibition of JAK1/2 in transfusion dependent MF subjects treated with MMB • To evaluate MMB pharmacokinetics (PK) in transfusion dependent MF subjects • To evaluate changes in circulating cytokine and inflammatory markers in transfusion dependent MF subjects treated with MMB
Study Design:	This is a single-arm, open-label study of MMB in transfusion-dependent subjects with PMF or Post-PV/ET MF. Subjects will receive MMB for 24 weeks (± 7 days) on study. After completion of the 24 week (± 7 days) treatment phase visit procedures, subjects who respond to treatment, at the investigator's discretion, will have the option of maintenance therapy with MMB on Study GS-US-352-1154 at the MMB dose they tolerated and/or derived clinical benefit from during the 24-week treatment period.

Number of Subjects Planned:	Approximately 40
Target Population:	Subjects with PMF or Post-PV/ET MF who are transfusion dependent
Duration of Treatment:	The planned duration of study treatment is 24 weeks (±7 days).
Diagnosis and Main Eligibility Criteria:	**Inclusion Criteria:** 1) Age ≥ 18 years old 2) Diagnosis of PMF or Post PV/ET-MF 3) Requires myelofibrosis therapy, in the opinion of the investigator 4) High risk or intermediate-2 risk defined by the Dynamic International Prognostic Scoring System (DIPSS) or intermediate-1 risk defined by DIPSS and associated with symptomatic splenomegaly and/or hepatomegaly 5) Transfusion dependent at baseline, defined as ≥ 4U RBC transfusion in the 8 weeks prior to first dose of MMB 6) Acceptable organ function as evidenced by the following: a) Platelet Count ≥ 50 x 10^9/L b) AST/SGOT and ALT/SGPT ≤ 3 x upper limit of normal (ULN) or AST/SGOT or ALT/SGPT ≤ 5 x ULN if liver is involved by disease process as judged by the investigator c) Serum creatinine ≤ 2.0 mg/dL or calculated creatinine clearance of ≥ 60mL/min d) Direct bilirubin ≤ 2.0 x ULN 7) Peripheral blood blast count < 20% 8) Expected Life expectancy of > 24 weeks 9) A negative serum pregnancy test for female subjects (unless surgically sterile or greater than two years postmenopausal) 10) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3

11) Lactating females must agree to discontinue nursing before MMB administration

12) Able to understand and willing to sign the informed consent form

Exclusion Criteria:

1) Prior splenectomy
2) Splenic irradiation within 3 months prior to the first dose of MMB
3) Prior treatment with MMB
4) Known positive status of human immunodeficiency virus (HIV)
5) Chronic active or acute viral hepatitis A, B, or C infection (testing required for hepatitis B and C), or hepatitis B or C carrier
6) Use of strong CYP3A4 inducer within 2 weeks prior to the first dose of MMB
7) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician
8) History of a prior diagnosis of any malignancy other than PMF or Post PV/ET-MF except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate specific antigen for >1 year prior to enrollment, or any other cancer that has been in complete remission without treatment for ≥ 5 years prior to enrollment.
9) Treatment with a JAK inhibitor within 21 days of the planned first dose of MMB
10) Documented myocardial infarction or unstable/uncontrolled cardiac disease (eg, unstable angina, congestive heart failure [New York Heart Association > Class III]) within 6 months of randomization
11) Presence of peripheral neuropathy ≥ CTCAE Grade 2
12) Unwilling or unable to undergo Magnetic Resonance Imaging (MRI) per requirements in Section 6.2.11.2
13) Unwilling to consent to genomics sampling
14) Pregnant or breast-feeding
15) Known hypersensitivity to the study investigational medicinal products, the metabolites, or formulation excipients

Study Procedures/ Frequency:	Subjects may participate in the study for up to 28 weeks. This consists of up to 4 weeks (28 days) of screening and 24 weeks of study treatment. Study visits will be completed at 2 weeks and 4 weeks following initiation of MMB treatment, and thereafter every 4 weeks until week 24. During the screening period, subjects will undergo an MRI to assess spleen volume and liver iron concentration (LIC), bone marrow biopsy, and blood sampling for clinical and pharmacodynamics tests. Subjects will receive an electronic diary (eDiary) for daily completion of the modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPNSAF TSS). Subjects will complete the modified MPNSAF TSS daily through screening and 24 weeks of study participation. Patient-reported outcomes, clinical, laboratory, and disease assessments will be completed at regular study visits as defined in Appendix 2. Subjects discontinuing MMB prior to the Week 24 visit will complete an Early Study Drug Discontinuation visit within 7 days of discontinuing MMB and a Follow-up visit 30 days after the subject's last dose of MMB. Subjects completing the Week 24 visit and entering maintenance treatment on study GS-US-352-1154 will not complete the 30-Day Follow-Up visit.
Test Product, Dose, and Mode of Administration:	The starting dose of MMB for all subjects will be 200 mg in a single tablet. MMB will be orally self-administered once daily, in the morning, and thereafter at approximately the same time each day. The dose of MMB may be withheld or adjusted according to the criteria in the protocol.
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	The overall safety profile of MMB will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to MMB of any adverse events (AEs) or abnormalities of laboratory tests; serious adverse events (SAEs); or AEs leading to discontinuation of MMB.

Efficacy:

Primary Endpoints

The primary endpoint is transfusion independence response rate by Week 24, defined as becoming transfusion independent for ≥ 12 weeks at any time on study. A subject is considered as transfusion independent on study if no RBC transfusion occurs in any 12 weeks during the 24-week treatment period.

Secondary Endpoints

The secondary endpoints are:

- Transfusion response rate by Week 24, defined as becoming not transfusion dependent for ≥ 8 weeks at any time on study
- Baseline and change in markers of anemia (eg, hepcidin, ferritin)
- Change in pharmacodynamics biomarker pSTAT3
- Splenic response rate at Week 24, defined as ≥ 35% reduction in spleen volume from baseline as measured by MRI
- Response rate in total symptom score (TSS) at Week 24, defined as achieving a ≥ 50% reduction from baseline in TSS as measured by the modified MPNSAF TSS diary
- Pharmacokinetics parameters (C_{max}, C_{last}, C_{tau} and AUC_{last}, if available) for MMB
- Change in circulating cytokine and inflammatory markers (eg, IL-6, IL-8, IFN gamma, TNF alpha)

Exploratory Endpoints

The exploratory endpoints are:

- Baseline and change in markers of orthogonal or parallel signaling pathways (eg, RAS/MAPK, PI3K/AKT)
- Baseline and change in gene expression profiles in whole blood and somatic mutations in whole blood
- Baseline and change in immune subsets in whole blood
- Change in exploratory pharmacodynamics markers of signaling mediated by JAK1 and/or JAK2 (eg, pSTAT1, pSTAT5, and pSTAT6)

Pharmacokinetics: Blood samples will be collected at the time points specified in the protocol.

Statistical Methods:

The Safety Analysis Set includes all subjects who receive ≥ 1 dose of MMB. Since this study is a non-randomized study, the Safety Analysis Set will be used for subject's characteristics, efficacy and safety endpoints, and study treatment administration.

The Biomarker Analysis Set consists of all subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest. The Biomarker Analysis Set will be used for biomarkers and the correlation analyses between biomarkers and efficacy clinical endpoints.

The PK Analysis Set consists of all subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

Subject demographic and baseline characteristics will be listed and summarized as appropriate.

Transfusion independence response rate, transfusion response rate, splenic response rate and TSS response rate will be presented with corresponding 2-sided 90% exact CIs using the binomial distribution. The number and percentage of subjects in each response category (complete remission [CR] or partial remission [PR]) will also be summarized. Subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as non-responders.

All safety data collected on or after the date that MMB was first dispensed up to the date of last dose of MMB plus 30 days will be summarized. Data for the pretreatment will be included in data listings.

The baseline levels, and changes in biomarker levels over time from baseline level, will be evaluated. Descriptive statistics will be provided at each sampling time, and by response category for each clinical endpoint being considered for association with biomarkers, as appropriate. Exploratory graphics, such as side-by-side boxplots will also be generated.

Univariate and multivariate statistical techniques may be explored to evaluate the association of baseline biomarkers and changes in biomarkers with clinical outcomes as appropriate. Due to the exploratory nature of the end points, no formal hypothesis testing will be conducted.

Sample Size Calculation

This study will enroll approximately 40 subjects. Due to the exploratory nature, the study is not designed to detect a specific effect size. A sample size of 40 subjects is considered adequate for this exploratory study.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
AUC_{last}	AUC up to the last measurable concentration
BCRP	Breast cancer resistant protein
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/PBMC concentration of drug
C_{last}	last observed quantifiable concentration
CML	Chronic mylogenous leukemia
CR	complete remission
CRF	case report form(s)
CRO	contract (or clinical) research organization
CRP	C-Reactive Protein
CSR	Clinical Study Report
CT	computed tomography/computed axial tomography scan
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
Da	Dalton
DIPSS	Dynamic International Prognostic Scoring System
DSPH	Drug Safety and Public Health
ECG	electrocardiogram
eCRF	Electronic case report form(s)
EDC	Electronic data capture
eDiary	Electronic diary
EPO	Erythropoietin
ESDD	Early Study Drug Discontinuation
ET	Essential thrombocythemia
FDA	(United States) Food and Drug Administration
FSH	Follicle stimulating hormone

GLOSSARY OF ABBREVIATIONS AND DEFINITIONS OF TERMS (CONTINUED)

GCP	Good Clinical Practice (guidelines)
GD	Gestational Days
Gilead	Gilead Sciences, Inc.
GLP	Good Laboratory Practice (guidelines)
hCG	human chorionic gonadotropin
HDPE	high-density polyethylene
Hgb	hemoglobin
HIV	human immunodeficiency virus
HSPC	hematopoietic stem/progenitor cells
IB	investigator's brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IND	Investigational New Drug (Application)
IRB	institutional review board
IUD	intrauterine device
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
IWRS	interactive web response system
JAK	Janus kinase
LIC	Liver iron concentration
LLN	lower limit of the normal range
m	meter
MCV	Mean cell volume
medDRA	Medical dictionary for regulatory activities
MF	myelofibrosis
mg	milligram
MMB	momelotinib
MPL	megakaryocyte proliferative ligand
MPN	myeloproliferative neoplasm
MPNSAF TSS	Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score
MRI	magnetic resonance image
N	Number in population
n	Number in data
NOAEL	no observed adverse effect level
NOEL	No observed effect level
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic

GLOSSARY OF ABBREVIATIONS AND DEFINITIONS OF TERMS (CONTINUED)

PMF	primary myelofibrosis
PR	partial remission
PRO	patient-reported outcome
PV	polycythemia vera
QD	once daily
RBC	Red blood cell
SADR	Serious adverse drug reactions
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	standard operating procedure
STAT	Signal Transducer and Activator of Transcription
SUSAR	Suspected Unexpected Serious Adverse Reaction
t_{max}	The time (observed time point) of C_{max}
$t_{½}$	An estimate of the terminal elimination half-life of the drug
TYK	Tyrosine kinase
U	Units
ULN	upper limit of the normal range
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Myeloproliferative neoplasm (MPN) is classified by the World Health Organization (WHO) into eight categories that include polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, chronic eosinophilic leukemia, mast cell disease, and MPN unclassifiable {25836}. Clonal hematopoiesis is a shared feature of the MPNs, with CML characterized by the presence of the Philadelphia chromosome, the product of a reciprocal translocation between the long arms of chromosomes 9 and 22. This translocation results in the formation of the BCR-ABL1 oncogene, the molecular pathogenetic event of CML {25841}. Subsequently, a single acquired point mutation in the Janus kinase (JAK) 2 gene at codon 617, resulting in the substitution of valine for phenylalanine (JAK2V617F), was identified in patients with PV (~96%), ET (~50%), and myelofibrosis (~50%) {23864},{24753},{23911},{23913}. Positivity for the JAK2V617F mutation results in constitutive activation of the downstream Signal Transducer and Activator of Transcription (STAT), cytokine hypersensitivity, and formation of erythropoietin-independent erythroid colonies {25845}.

Since the discovery of the JAK2V617F mutation in patients with MPN, additional mutations have been identified including signaling mutations that activate the thrombopoietin receptor (MPL). Somatic mutations of CALR, the gene encoding calreticulin, have also been identified in patients with wild type JAK2, as well as mutations in epigenetic regulators of DNA methylation and chromatin structure {27663}.

Myelofibrosis is associated with a characteristic marrow stroma pattern, leukoerythroblastosis, and elevated levels of inflammatory cytokines. Patients may experience anemia, leukopenia or leukocytosis, thrombocytopenia or thrombocytosis, constitutional symptoms, and extramedullary hematopoiesis resulting in hepatosplenomegaly{27076}. In a proportion of patients, myelofibrosis may transform into acute leukemia {27070}. Treatment for PMF, and the phenotypically similar Post-PV/ET MF, are principally focused on symptom palliation, with allogeneic stem cell transplantation offering a potential cure for select patients {27077}.

Momelotinib (MMB) is a small molecule JAK1 and JAK2 inhibitor, with good selectivity over other JAK family kinases (JAK3, TYK2) and excellent selectivity over other tyrosine and serine/threonine kinases. In the phase 1/2 study of MMB which enrolled 166 subjects with PMF or Post-PV/ET MF (Study CCL09101), the rate of spleen response, defined as ≥ 50% reduction in palpable splenomegaly lasting ≥ 8 weeks for baseline splenomegaly ≥ 10 cm plus resolution of palpable splenomegaly lasting ≥ 8 weeks for baseline splenomegaly > 5 to < 10 cm, was 33%. Anemia response, defined as a transfusion-free interval of ≥ 12 weeks for baseline transfusion dependence, plus ≥ 2 g/dL rise in hemoglobin (Hgb) for baseline transfusion independence and Hgb < 10 g/dL, was 41%. Baseline transfusion dependence for Study CCL09101 was defined as ≥ 2 units (U) red blood cell (RBC) transfusion in the 30 days prior to first dose of MMB or identified as transfusion dependent in the medical history. In general, over the course of the study, the mean total symptom scores decreased from baseline. Most common Grade 3 or 4

treatment-related events reported by ≥ 2 subjects on study were thrombocytopenia (24%), lipase increased (4%), neutropenia (3%), and anemia (2%). Treatment-emergent peripheral neuropathy or sensory neuropathy adverse events were reported by 55 subjects (33%), with the neuropathy events categorized in 45 subjects (27%) as probably or possibly related to MMB.

1.2. Momelotinib (MMB)

1.2.1. General Information

MMB dihydrochloride (N (cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide, CYT387, GS-0387) is a novel, weakly basic, disubstituted pyrimidine compound with a molecular weight of 487.38 daltons (Da). The free base is poorly soluble in water. MMB is presented for clinical administration as a dihydrochloride monohydrate salt. The dihydrochloride monohydrate salt shows kinetic solubility in water at concentrations up to 60 mg/mL. MMB dihydrochloride is manufactured from a pyrimidine scaffold in a five-step process.

In cellular assays and in vitro, MMB was shown to be a potent and selective ATP-competitive small-molecule inhibitor of JAK1 and JAK2, and is active at low nanomolar concentrations. MMB demonstrates marked disease-modifying properties in ex vivo assays of human erythroid cells from PV patients and in a transgenic mouse model of myeloproliferative neoplasm. Kinase profiling of MMB indicates the compound is broadly selective for JAK1 and JAK2 over other kinase enzymes, including the closely related JAK3 and tyrosine kinase (TYK) 2. MMB displays potent in vitro inhibitory activity against cells dependent on JAK.

For further information on MMB, refer to the investigator's brochure (IB) for MMB.

1.2.2. Preclinical Pharmacology and Toxicology

1.2.2.1. Absorption, Distribution, Metabolism, and Elimination (ADME)

Equivalent mean maximal plasma concentrations of MMB (~700 ng/mL) and comparable elimination half-lives (~1h) were observed in both fed and fasted animals, consistent with previous data. There was however a notable prolongation in absorption in fed dogs with a delayed T_{max} (3h fed vs. 1h fasted). Furthermore, the AUC following dosing to feed dogs was approximately double that seen in fasted animal studies suggesting that MMB systemic availability is markedly improved when the compound is administered postprandially.

Consistent with the moderate to high bioavailability seen in nonclinical species, MMB shows high permeability in vitro across human Caco-2 cell monolayers with low efflux potential. These results indicate that MMB is likely to have high permeability across the intestinal mucosa in humans and high oral absorption in vivo.

Data from plasma protein binding studies using rat and human plasma indicate that MMB binds extensively to rat plasma proteins (~ 97%) and moderately to human plasma proteins (87% to 92%). The mean human blood-to-plasma ratio was determined to be approximately 1.1, suggesting similar distribution between the cellular and plasma fractions of blood. The rat blood-to-plasma ratio ranged from 0.6 to 0.8 indicating a lesser partitioning into blood cells.

The systemic clearance of MMB was low in rats and significantly higher in dogs. The steady state volume of distribution in both species substantially exceeded total body water. Following oral administration as the dihydrochloride salt, MMB showed high bioavailability in the rat (50%) and moderate bioavailability in the dog (20%). The pharmacokinetic (PK) parameters in both the rat and dog indicated that MMB was well absorbed. In the rat, less than 10% of an administered dose of MMB was recovered in the urine as parent compound suggesting that urinary excretion is a minor clearance route for the parent compound.

The distribution of MMB into brain tissue was assessed in Swiss outbred mice following intravenous administration (5 mg/kg). The brain-to-plasma ratio for MMB was determined to be 0.075 and 0.215 at 5 and 60 minutes following MMB administration, respectively, suggesting low permeability of MMB across the blood brain barrier.

Metabolite profiling has identified major putative metabolites from in vitro and in vivo studies. Metabolite M19 (GS-642112) was present in greater amounts in both rat (both dose levels) and dog plasma pools, than in the human plasma pool. Metabolites M15, M17, and M20 were present in greater amounts in the rat plasma pool (both dose levels), than in the human or dog plasma pools. Metabolite M21 (GS-644603) was present in human plasma at higher levels than that observed in rat plasma (20 mg/kg or 80 mg/kg doses, respectively). Metabolite M21 was not observed in the dog plasma. M8 was not observed in either the rat or dog plasma pools.

The ability of the major drug-metabolizing cytochrome P40 (CYP450) enzymes (CYP1A2, 2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP3A5) to metabolize MMB was assessed with recombinant human CYP450 enzymes (Supersomes™) and human primary hepatocytes. MMB is primarily metabolized by multiple CYP enzymes, including CYP3A, CYP2C8 and CYP2C19, with aldehyde oxidase also participating in metabolism to form the major, active metabolite M21.

The potential of MMB to impair the metabolism of other agents by inhibition of major drug metabolizing enzymes has also been investigated. The half-maximal inhibitory concentration (IC_{50}) of MMB on the five CYP isoforms investigated (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was greater than 25 μM. MMB is therefore unlikely to mediate significant metabolic drug-drug interactions through inhibition of these isoforms in vivo. MMB was determined to have the potential to be an inhibitor of UGT1A1, a major human uridine diphosphate glucuronosyltransferase enzyme responsible for the glucuronidation of bilirubin, with an IC_{50} of 0.3 μM but it is not clinically relevant as no clinically significant elevation of indirect (unconjugated) bilirubin has been reported in the Phase 1/2 CCL09101 study.

The potential of MMB to inhibit major drug transporters was studied in cells in which the individual transporters were over expressed and determining were possible the MMB IC_{50} for the transport of probe substrates. MMB did not significantly inhibit P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP mediated transport of probe substrates at 15 μM. MMB was determined to be an inhibitor of BCRP with an IC_{50} of 2.9 μM.

1.2.2.2. Nonclinical Toxicology

Nonclinical safety pharmacology and toxicology studies have characterized the safety of MMB and included both repeat dose toxicology studies and in vitro genotoxicity studies. All pivotal toxicology studies, including the genotoxicity studies, were conducted in full compliance with good laboratory practice (GLP) regulations (21 CFR 58). The scope of the nonclinical safety evaluation is consistent with guidance issued by the International Conference on Harmonisation (ICH).

The potential for MMB to induce hemodynamic or electrocardiogram (ECG) effects was evaluated in male beagle dogs following a single oral dose of 5, 30 or 100 mg/kg. A marked decrease in mean arterial pressure and increase in heart rate was observed after a single dose of 100 mg/kg.

MMB was generally well-tolerated clinically when given to rats for 26 weeks at doses of 5 and 15 mg/kg/day. There were three unscheduled deaths in the 50 mg/kg/day group potentially related to MMB administration. By Week 26, 50 mg/kg/day group mean body weight in males was 23.6% lower than control and in females was 13.1% lower than control. A reversible, mild slowing of caudal and digital nerve conduction velocity, consistent with a mild, minimally progressive and reversible deficit in distal sensory velocities, was observed at 50 mg/kg/day. At all dose levels, decreases in leukocytes, lymphocytes, eosinophils, and/or basophils were indicative of bone marrow and lymphoid suppression (in spleen, lymph node, thymus, and/or gut associated lymphoid tissue [GALT]). The myelosuppression was considered adverse at 50 mg/kg/day. No histopathological correlate was observed. At 50 mg/kg/day, mild, reversible decreases in red cell mass (erythrocytes, hemoglobin, and hematocrit) in both sexes, with concurrent increases in reticulocytes and mean cell volume (MCV) indicating an appropriate regenerative response, were observed. These alterations were associated with reversible increases in total bilirubin and correlated microscopically with irreversible tissue pigment seen microscopically in the kidney, mesenteric lymph nodes, liver, and spleen, and with erythrocytosis/erythrophagocytosis in the mandibular and mesenteric lymph nodes. Dose related adverse findings due to GS-0387 administration included reversible minimal tubular degeneration/regeneration in the kidney at ≥ 15 mg/kg/day and mild decreased cellularity in bone marrow, and irreversible degeneration/atrophy in testes and oligospermia/germ cell debris in epididymides at 50 mg/kg/day. Due to the adverse changes in the kidneys at 15 mg/kg/day, the no observed adverse effect level was 5 mg/kg/day. Following 26 weeks at 5 mg/kg/day in male and female rats, the GS-0387 $AUC_{(0-24)}$ values were 33800 and 73100 ng*hr/mL, respectively, and the C_{max} values were 4020 and 7590 ng/mL, respectively.

Momelotinib was well-tolerated when given orally to dogs once daily for 39 weeks at doses up to 20 mg/kg/day. The majority of dogs at 50 mg/kg/day had periodic body weight loss, decreased food consumption, and/or excessive emesis/vomitus, and three males at this dose were given week-long dose holidays. One male at 50 mg/kg/day was euthanized in extremis on Day 175 with findings suggesting inanition played a role in the moribundity. Cataracts were observed in dogs at 50 mg/kg/day at termination and persisted through the recovery period. MMB-related microscopic findings were limited to the 50 mg/kg/day group and included minimal or mild

tubular epithelial cell vacuolation in the kidneys in both sexes and a minimal decrease in cellularity in the bone marrow, mild spermatid/spermatocyte degeneration in the testes, and a mild increase in germ cell debris in the epididymides in males. The no-observed adverse effect level was considered to be 20 mg/kg/day. Following 39 weeks at this dose, the GS-0387 $AUC_{(0\text{-}24)}$ value was 4620 ng*hr/mL, and the C_{max} value was 938 ng/mL.

The plasma AUC_{τ} in patients from Study CCL09101 at 300 mg capsule was 4.3 µg•h/mL. Therefore, the margin of exposure for the no-observed-adverse-effect-level (NOAEL) in the 90-day toxicity studies to the steady state AUC NOAEL is 22 in the rat and 0.8 in the dogs.

An in vitro bacterial reverse mutation assay (Ames test), an in vitro mammalian cell gene mutation assay (chromosomal aberration test), and an in vivo rat bone marrow micronucleus assay were conducted with MMB. No evidence of mutagenicity or clastogenicity was observed indicating a low potential for MMB to cause genotoxicity.

MMB was administered to adult male rats at 5, 25, and 100/68 mg/kg/day for 4 weeks prior to mating and throughout mating (~10 weeks total). Mortality, adverse clinical signs, reduced body weight gain, reduced fecundity and fertility, reduced testis and seminal vesicle weights and reduced sperm concentration and motility occurred in the group administered 100/68 mg/kg/day. Reduced body weight gain, reduced seminal vesicle weight and reduced sperm concentration and motility occurred in the group administered 25 mg/kg/day. Reduced body weight gain occurred in the group administered 5 mg/kg/day. The NOAEL for male fertility was 5 mg/kg/day. MMB was administered to adult female rats at 5, 25 or 100 (reduced to 68) mg/kg/day for 14 days prior to mating, throughout mating and through gestation day (GD) 7. Maternal toxicity occurred after oral administration of 100/68 mg/kg/day to adult female rats as evidenced by mortality and associated clinical signs, reduced mean body weight and food consumption, significantly reduced numbers of corpora lutea and mean number of estrous cycles, and reduced mean ovarian and vagina weight. Adverse effects on cesarean section parameters were observed at 25 and 100/68 mg/kg/day and included an increase in early resorptions, increased post-implantation loss and decreased number of live fetuses. Therefore, the no-observed-effect level (NOEL) for maternal toxicity and fertility was 25 mg/kg/day and the NOEL for early embryonic development was 5 mg/kg/day.

MMB when administered orally to pregnant rats during organogenesis (from GD 6-17) showed evidence of embryo-fetal toxicity. Adverse fetal effects were observed at 12 mg/kg/day. The 12 mg/kg/day group had increased early resorptions, percent post implantation loss, and reduced gravid uterus weight. The number of live fetuses and adjusted mean fetal weight were also reduced. Therefore, the NOAEL for maternal toxicity was 12 mg/kg/ day (GD 17 GS-0387 C_{max} and $AUC_{0\text{-}t}$ of 7.45 µg/mL and 75.8 µg•hr/mL, respectively). The NOAEL for embryo-fetal effects was 6 mg/kg/day (GD 17 GS-0387 C_{max} and $AUC_{0\text{-}t}$ of 3.58 µg/mL and 25.5 µg•hr/mL, respectively).

MMB produced maternal toxicity at 60 mg/kg/day when administered by oral gavage to rabbits from GD 7-20. Maternal toxicity was based on reductions in food consumption as well as associated clinical signs. Embryo-fetal effects (reduced adjusted mean fetal weight, delayed bone ossification, and an abortion) were considered secondary to maternal toxicity and not

GS-0387-01-related. Therefore, the NOAEL for maternal toxicity was 30 mg/kg/day which corresponded to GD 20 C_{max} and AUC_{0-t} values of 312 ng/mL and 543 ng•hr/mL and the NOAEL for embryo-fetal toxicity was 60 mg/kg/day which corresponded to GD 20 C_{max} and AUC_{0-t} values of 994 ng/mL and 4100 ng•hr/mL, respectively.

A more detailed summary of findings from the studies in rats and dogs is available in the investigator brochure IB) for MMB. Investigators should refer to this document prior to initiating therapy with MMB.

1.2.3. Clinical Trials of Momelotinib

Completed and Ongoing Clinical Trials

Please refer to the MMB IB for a listing of completed and ongoing MMB clinical trials.

1.2.4. Special Risk

Clinical development of the JAK2 inhibitor fedratinib (SAR302503) in myelofibrosis (MF) was halted due to reported cases of Wernicke's encephalopathy. One case of suspected Wernicke's encephalopathy has been reported with MMB. Preliminary nonclinical data have suggested that some JAK inhibitors, eg, fedratinib and AZD-1480, have the potential to inhibit the transporter-mediated uptake of thiamine from the intestine while others, including MMB, show no effect (data on file). In order to understand the thiamine status of subjects with MF, thiamine level will be collected from all subjects at regular intervals across all MMB studies, with supplementation of thiamine as clinically indicated in the medical judgment of the treating physician.

1.3. Rationale for This Study

Targeted inhibitors of JAK2 including MMB and ruxolitinib have demonstrated significant clinical activity in MF. Both drugs have been shown to provide substantial improvement in symptomatic splenomegaly and constitutional symptoms. Ruxolitinib treatment does not typically lead to improvement in anemia, while patients on MMB were noted to experience improvement in anemia per International Working Group-Myelofibrosis Research and Treatment (IWG-MRT) criteria. A mechanistic explanation for this differential anemia response has not been elucidated. A phase 3 study comparing the efficacy of MMB versus ruxolitinib is currently ongoing, but specific biomarker studies to explore predictors and mechanisms of response were not able to be feasibly incorporated in the study design.

Anemia is a well-established prognostic factor in MF: 38% of patients have a Hgb level of <10 g/dL and 24% required RBC transfusions at initial diagnosis {27673}. Additionally, the prevalence of anemia increases during the course of the disease. Erythropoietin, the hormone that regulates RBC production, signals through JAK2. Therefore, a JAK2 inhibitor should reduce erythropoiesis, and aggravated anemia was not unexpected for ruxolitinib. Patients treated with MMB, however, experienced an improvement in anemia, with 53% of patients having a positive anemia response. To investigate the mechanism of this anemia benefit, markers of iron

metabolism will be evaluated in this study. Red blood cell transfusions, required by many MF patients, relieve anemia symptoms, but exacerbate iron storage. Markers of iron storage (eg, ferritin), markers of available iron (eg, serum iron and transferrin saturation), Liver Iron Concentration MRI (LIC MRI), and markers of erythropoiesis will be evaluated throughout this study, along with standard markers of inflammation. Furthermore, levels of the hormone hepcidin will also be tested. Hepcidin is considered to be the master regulator of iron homeostasis in the body, and responds to iron availability, inflammatory signals and other inputs {34378}. Increased hepcidin is associated with reduced dietary iron absorption and reduced iron availability, and is a poor prognostic factor for MF {34379}. It is expected that markers of iron metabolism will help elucidate the MMB mechanism of anemia benefit as patients traverse from requiring transfusion to becoming transfusion-independent.

Several important issues regarding the use of MMB in MF remain unresolved. Momelotinib, like ruxolitinib, inhibits both JAK1 and JAK2, and thus the relative role of JAK1 versus JAK2 inhibition in providing clinical benefit in MF is uncertain. Anti-inflammatory effects mediated by JAK1 inhibition may be critical. Furthermore, the degree to which MMB is able to "hit the target" in the cells that matter, the $CD34^+$ hematopoietic stem/progenitor cells (HSPC) that are thought to initiate and drive the disease, remains uncertain. Though several investigators have examined the effects of ex vivo treatment of primary patient cells with JAK inhibitors, to date there have been no comprehensive studies examining the in vivo effects of JAK inhibitors on signaling in the HSPC compartment. This is largely related to the technical nuances of examining signaling in relatively rare cells (HSPC) within complex, heterogeneous mixtures of cells, eg, blood or bone marrow. Conventional biochemical techniques are inadequate to address this important question.

Mass cytometry is a novel technology that merges aspects of flow cytometry with mass spectrometry, thereby enabling the simultaneous measurement of > 30 parameters at the single cell level {34561}. Using such an approach, up to 15-20 intracellular markers can be evaluated in distinct cell subsets across the entire hematopoietic continuum, including HSPC as well as myeloid and lymphoid lineage subsets. This technology has been implemented in several recent studies {34603} {34562} {34563} {34638} {34604}.

In addition to querying the effect of MMB on signaling in $CD34^+$ cells, this technique will also allow investigation of how signaling in this and other blood cell subsets changes in response to MMB treatment. Integrating mass cytometry data with expression profiling of blood cells before and during MMB treatment will enable better understanding of the biological basis of response to MMB.

1.4. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To determine the transfusion independence response rate for transfusion dependent MF subjects treated with MMB

The secondary objectives of this study are:

- To evaluate baseline levels and changes in markers of iron metabolism in transfusion dependent MF subjects treated with MMB
- To assess inhibition of JAK1/2 in transfusion dependent MF subjects treated with MMB
- To evaluate MMB PK in transfusion dependent MF subjects
- To evaluate changes in circulating cytokine and inflammatory markers in transfusion dependent MF subjects treated with MMB

3. STUDY DESIGN

3.1. Endpoint

The endpoints of this study are described in Section 8.

3.2. Study Design

This is a single-arm, open-label study of MMB in subjects with PMF or Post-PV/ET MF who are transfusion dependent. Subjects will receive MMB for 24 weeks (± 7 days) on study.

After completion of the 24 week (± 7 days) treatment phase visit procedures, subjects who respond to treatment, at the investigator's discretion, will have the option of maintenance therapy with MMB on Study GS-US-352-1154 at the MMB dose they tolerated and/or derived clinical benefit from during the 24-week treatment period.

3.3. Study Treatments

The study drug in is MMB, supplied by Gilead. The formulation and packaging of MMB are further described in Section 5.

3.4. Duration of Treatment

The duration of study treatment is 24 weeks (± 7 days). Subjects will continue study treatment until disease progression, unacceptable toxicity, consent withdrawal, or subject's refusal of treatment.

3.5. Discontinuation Criteria

The study may be discontinued at any time based on periodic reviews of safety and efficacy data by Gilead.

Subject discontinuation criteria are described in Section 6.8.

3.6. Source Data

Patient reported outcomes data that are collected on paper will be considered source data.

Subject identification number captured by the interactive web response system (IWRS) is considered source data.

3.7. Biomarker Testing

3.7.1. Biomarker Samples to Address the Study Objectives:

The following biological specimens will be collected in this study and used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with MMB response including efficacy and/or adverse events, to increase knowledge and understanding of the biology of MF and related diseases, and may support development of possible companion diagnostics. The specific analyses will include, but will not be limited to, the biomarkers and assays listed in Table 3-1.

Because biomarker science is a rapidly evolving area of investigation, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of our knowledge. Specimens will be collected from all subjects.

Table 3-1. Biomarker Specimens and Tests to Address Study Objectives

Study Objective	Biomarker Test
Blood	
To evaluate the mechanism of anemia response of MMB, the tests to be performed may include but are not limited to:	Iron studies, eg, serum iron level, total iron binding capacity, ferritin, non-transferrin bound iron, transferrin saturation, soluble transferrin receptor Hepcidin, a peptide hormone that regulates iron metabolism and which demonstrates daily fluctuations in levels. Testing for hepcidin requires strict adherence to time-of-day requirements as described in Section 5.3.1 Complete blood count, reticulocyte count
To evaluate pharmacodynamics response to MMB, the tests to be performed may include but are not limited to:	Flow cytometric analysis of phosphorylated STAT3 Exploratory pharmacodynamics test
To evaluate the effect of MMB on inflammation, the tests to be performed include but are not limited to:	Circulating cytokines and inflammatory markers (eg, interleukin-8 [IL-8], interleukin-2 receptor [IL-2R[, interleukin 6 [IL-6], interferon gamma [IFN-γ], etc)
To evaluate how MMB treatment influences survival and proliferative signaling in blood cells, including $CD34^+$ cells, tests may include, but are not limited to:	Mass cytometry to interrogate multiple signaling pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and RAS/MAPK Standard flow cytometry immunophenotyping, to investigate how MMB treatment influences the relative percentages of the blood cell subsets Evaluation of gene expression patterns (RNA) and DNA mutations may be performed.
To evaluate mutation status (eg, JAK2V617F, CALR), and whether allele burden changes with MMB treatment. Tests may include, but are not limited to:	Molecular determination of JAK2V617F mutation Molecular determination of other mutations that may be associated with MF (eg, CALR, MPL, TET2).
Bone Marrow Biopsy	
To evaluate fibrosis, RBC development, markers of MMB mechanism and stored iron, and whether MMB treatment influences these, the tests may include, but are not limited to:	Trichrome, silver, Prussion blue, glycophorin, CD71 stains Evaluation of gene expression patterns (RNA) and DNA mutations may be performed
Liver Iron Concentration MRI	
To evaluate iron storage in the liver (performed in conjunction with spleen MRI)	
Buccal Swab	
To provide normal genomic baseline for molecular studies.	

3.7.2. Storage of Samples for Future Research

All biomarker specimens and samples collected during the study will be stored for future research. These unused subject samples are instrumental for continued research to increase the knowledge of the biology of MF and related diseases, and about the mechanism of MMB action. Most importantly, the stored unused samples will enable future experiments to build upon the strong scientific understanding that will be gained from the testing that is part of this study, providing significantly greater breadth and depth of knowledge. As new information about MF becomes available, tests such as investigation into newly identified immune cell subsets or determination of circulating levels of a newly identified cytokine correlated with MF may be undertaken. This new information will benefit from the deep characterization of the subject samples that will be performed in the current study.

The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of sample storage for future research. In the event of a subject's death or loss of competence, the subject's specimens and data will continue to be used as part of the future research.

The specimens collected for future research, including body fluids, solid tissues, and derivatives thereof (eg, RNA, proteins, peptides), will be destroyed no later than 15 years after the end of study. The specimen storage period will be in accordance with the internal review board (IRB)-approved Informed Consent Form and applicable laws (eg, health authority requirements).

3.7.3. Biomarker Samples for Genomic Research

The genomic sample (buccal swab) will be used to provide a normal baseline for each subject. This is required to correctly identify and validate disease-related somatic mutations in the planned molecular studies.

In addition to the study-specific Informed Consent Form to be signed by each subject participating in the study, a separate specific signature will be required to document a subject’s agreement to participate in genomic research. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the genomic research. Subjects who decline to participate will not participate in the study. Subjects have the right to withdraw their consent for genomic research and study participation at any time and for any reason. If a patient wishes to withdraw consent, the investigator must inform the Sponsor.

In the event of a subject's death or loss of competence, the subject's specimens and data will continue to be used as part of the genomic testing.

The specimens consented for genomic research, including body fluids, solid tissues, and derivatives thereof (eg, DNA, proteins, peptides), will be destroyed no later than 15 years after the end of the study. The specimen storage period will be in accordance with the IRB -approved Informed Consent Form and applicable laws (eg, health authority requirements).

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 40 subjects will participate in this study.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1) Age ≥ 18 years old
2) Diagnosis of PMF or Post PV/ET-MF
3) Requires myelofibrosis therapy, in the opinion of the investigator
4) High risk OR intermediate-2 risk defined by dynamic international prognostic scoring system (DIPSS) OR intermediate-1 risk defined by DIPSS and associated with symptomatic splenomegaly and/or hepatomegaly
5) Transfusion dependent at baseline, defined as ≥ 4U RBC transfusion in the 8 weeks prior to first dose of MMB
6) Acceptable organ function as evidenced by the following:
   a) Platelet Count ≥ 50 x 10^9/L
   b) Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≤ 3 x upper limit of normal (ULN) or AST or ALT ≤ 5 x ULN if liver is involved by disease process as judged by the investigator
   c) Serum creatinine ≤ 2.0 mg/dL or calculated creatinine clearance of ≥ 60mL/min
   d) Direct bilirubin ≤ 2.0 x ULN
7) Peripheral blood blast count < 20%
8) Life expectancy of > 24 weeks
9) A negative serum pregnancy test for female subjects (unless surgically sterile or greater than two years postmenopausal)
10) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3
11) Lactating females must agree to discontinue nursing before MMB administration
12) Able to understand and willing to sign the informed consent form

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Prior splenectomy

2) Splenic irradiation within 3 months prior to the first dose of MMB

3) Prior treatment with MMB

4) Known positive status of human immunodeficiency virus (HIV)

5) Chronic active or acute viral hepatitis A, B, or C infection (testing required for hepatitis B and C), or hepatitis B or C carrier

6) Use of strong CYP3A4 inducer within 2 weeks prior to the first dose of MMB

7) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician

8) History of a prior diagnosis of any malignancy other than PMF or Post PV/ET-MF except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate specific antigen for >1 year prior to randomization, or any other cancer that has been in complete remission without treatment for ≥ 5 years prior to randomization

9) Treatment with a JAK inhibitor within 21 days of the planned first dose of MMB

10) Documented myocardial infarction or unstable/uncontrolled cardiac disease (eg, unstable angina, congestive heart failure [New York Heart Association > Class III]) within 6 months of randomization

11) Presence of peripheral neuropathy ≥ CTCAE Grade 2

12) Unwilling or unable to undergo a MRI per requirements in Section 6.2.11.2

13) Unwilling to consent to genomics sampling

14) Pregnant or breast-feeding

15) Known hypersensitivity to the study investigational medicinal products, the metabolites, or formulation excipients

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment and Treatment Assignment

Subjects will be enrolled via IWRS. All subjects will receive a starting dose of MMB 200 mg in a single tablet, taken orally once-daily.

5.2. Description and Handling of MMB

5.2.1. Formulation

MMB is supplied as GS-0387-01(dihydrochloride monohydrate) and is available as 100 mg, 150 mg, and 200 mg strength (as free base equivalent) tablets. The tablets contain excipients, microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, silicon dioxide, magnesium stearate, propyl gallate, polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide and red iron oxide. MMB tablets, 100 mg, are round-shaped, film-coated, brown tablets. MMB tablets, 150 mg, are round or triangle-shaped, film-coated, brown tablets. MMB tablets 200 mg, are capsule-shaped, film-coated, brown tablets.

5.2.2. Packaging and Labeling

MMB tablets are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, a silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child resistant screw cap with an induction-sealed, aluminum faced liner.

All MMB bottles will be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA) and/or other local regulations as applicable.

5.2.3. Storage and Handling

MMB should be stored at controlled room temperature of 25ºC (77ºF); excursions are permitted between 15ºC and 30ºC (59ºF and 86ºF).

Until dispensed to the subjects, all MMB bottles should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, the drug products should not be stored in a container other than the container in which they were supplied.

5.3. Dosage and Administration of MMB

5.3.1. Starting Dose

The starting dose of MMB for all subjects will be 200 mg in a single tablet. MMB will be orally self-administered once daily in the morning, and thereafter at approximately the same time each day. Subjects will be observed for 4 hours after the first MMB dose.

On the day of study visits, dosing should occur at the site. On the day of study visits requiring hepcidin sampling, MMB dosing must occur between 8 am and 10 am to accommodate the diurnal variation of hepcidin level.

5.3.2. Discontinuing or Interrupting MMB Treatment

When discontinuing treatment with MMB, dosing of MMB may be tapered at the investigator's discretion. For subjects on the 200 mg or 150 mg once-daily dose, it is recommended that the MMB dose be reduced to 100 mg once daily for 1 week prior to stopping treatment. Treatment may be stopped immediately for subjects receiving the 100 mg once-daily dose.

5.3.3. MMB Dose Adjustments and Dose Interruption

Treatment may be interrupted for up to 28 days, inclusive of taper, and restarted per the sections below. Platelet count must be $\geq 50 \times 10^9$/L prior to restarting treatment, regardless of the reason for treatment interruption. If toxicity persists beyond 28 days, treatment may be restarted upon sponsor approval.

5.3.4. Dose Adjustments for Thrombocytopenia

Platelet counts will be monitored throughout the study and the dose of MMB adjusted based on the degree of thrombocytopenia as per Table 5-1.

Table 5-1. MMB Dose Reductions for Subjects with Thrombocytopenia

Dose prior to reduction	**200 mg QD**	**150 mg QD**	**100 mg QD**
Platelet count	**Reduce to the dose below**		
$\geq 50 \times 10^9$/L	No dose adjustment required		
$\geq 25 \times 10^9$/L to $< 50 \times 10^9$/L If platelet count $\geq 100 \times 10^9$/L at study entry	150 mg QD	100 mg QD	Interrupt treatment
$\geq 25 \times 10^9$/L to $< 50 \times 10^9$/L If platelet count $< 100 \times 10^9$/L at study entry	No dose adjustment required		
$< 25 \times 10^9$/L	Interrupt treatment		

After dose interruption for thrombocytopenia, treatment may be restarted as per Table 5-2 if platelet count is $\geq 50 \times 10^9$/L in the absence of platelet transfusion for at least 5 days.

Table 5-2. Doses for Restarting MMB after Withholding Treatment for Toxicity

Dose at time of toxicity	Restarting dose level
200 mg QD	150 mg QD
150 mg QD	100 mg QD
100 mg QD	100 mg QD

5.3.5. Dose Adjustments for Neutropenia

If the absolute neutrophil count (ANC) is < 0.5 x 10^9/L, treatment will be interrupted. After recovery of the ANC to ≥ 0.75 x 10^9/L, MMB may be restarted per Table 5-2.

5.3.6. Dose Adjustments for Non-hematologic Toxicities

In the event of a new or recurrent Grade 3 or 4 non-hematologic toxicity that the investigator considers related to MMB, dosing will be interrupted for a maximum of 28 days, inclusive of taper, until the toxicity resolves or returns to baseline. Upon resolution of the new or recurrent Grade 3 or 4 non-hematologic toxicity MMB treatment may be restarted as per Table 5-2. If the toxicity persists beyond 28 days, treatment may be restarted only upon sponsor approval.

If a Grade 3 or 4 non-hematologic toxicity that the investigator considers related to MMB and had led to treatment interruption at the 100 mg once-daily dose recurs after restarting MMB at 100 mg once-daily, treatment will be permanently discontinued.

5.3.7. Dose Adjustments Based on Response

If efficacy is insufficient, subjects may increase the dose of MMB after dose reduction, provided there is no new or recurrent:

- Grade 3 or 4 non-hematologic toxicity related to MMB, and/or
- Platelet count < 50 x 10^9/L, and/or
- ANC < 0.75 x 10^9/L

The dose may not be increased during the first 4 weeks of therapy or within 4 weeks of a dose reduction. Where a dose increase is permitted, the dose may not be increased more frequently than every 2 weeks. The MMB dose may be increased by 50 mg per dose adjustment to a maximum of 200 mg per day.

Insufficient efficacy is defined as:

- Failure to achieve a reduction from pretreatment baseline in either palpable spleen length of ≥ 50% or spleen volume of ≥ 35% as measured by MRI

5.3.8. Dose Adjustments for Other Toxicities

In the event of a toxicity not covered in Sections 5.3.4, 5.3.5 or 5.3.6 that the investigator considers related to MMB, the investigator may interrupt dosing at their discretion for a maximum of 28 days. Following interruption, treatment may be restarted at the same dose level. If the investigator believes a dose reduction is warranted, treatment may be restarted at a reduced dose level per Table 5-2 with sponsor approval. If treatment interruption persists beyond 28 days, treatment may be restarted only upon sponsor approval.

5.4. Prior and Concomitant Medications

5.4.1. Restricted Medications

- Anti-hypertensive therapy should not be taken on the day of the first MMB dose until 4 hours after MMB administration
- Strong CYP3A4 inducers (eg, carbamazepine, phenytoin, St. John's Wort) may decrease MMB exposure and should be excluded
- Moderate inducers of CYP3A/2C8/2C19 may decrease MMB exposure and alternative medications should be considered if clinically appropriate when co-administered with MMB

5.4.2. Proscribed Medications

The following medications are proscribed during the treatment phase:

- Experimental therapy other than MMB administered in this trial
- Myelofibrosis therapy other than MMB administered in this trial

5.4.3. Breast Cancer Resistance Protein (BCRP) Substrates

In vitro, MMB was determined to be an inhibitor of BCRP. Results from a clinical drug-drug interaction study suggested that multiple doses of MMB at 200 mg increased the exposure (C_{max} and AUC) of rosuvastatin (a BCRP substrate) by approximately 3 fold. Plasma exposures of BCRP substrates may increase when administered with MMB. As such, when appropriate, dose modification or alternative medications as clinically appropriate should be considered when co-administered with MMB.

5.4.4. Organic Anion-Transporting Polypeptide (OATP) Inhibitors

MMB was determined to be a substrate of OATP1B1 and OATP1B3. A single dose of rifampin (potent inhibitor of OATP1B1 and OATP1B3) increased MMB C_{max} by ~40% and AUC_{inf} by ~56%. Care should be exercised when MMB is co-administered with OATP inhibitors.

Refer to the IB of MMB for more details. Refer to prescribing information of co-administered drugs prior to administration.

5.5. Accountability for MMB

The investigator is responsible for ensuring adequate accountability of all used and unused MMB. This includes acknowledgement of receipt of each shipment of MMB (quantity and condition). All used and unused MMB dispensed to subjects must be returned to the site.

MMB accountability records will be provided to each study site to:

- Record the date received and quantity of MMB bottles
- Record the date, subject number, subject initials, the MMB kit number dispensed
- Record the date, quantity of used and unused MMB returned, along with the initials of the person recording the information.

5.5.1. MMB Return or Disposal

The methods of MMB return and destruction are described in Section 9.1.7.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

A subject will be considered enrolled once enrolled in IWRS. It is the responsibility of the investigator to ensure that each subject is eligible for the study before enrolling the subject. Details regarding treatment assignment are in section 5.1.

6.2. Study Procedure Descriptions

The sections below describe the individual study procedures outlined in subsequent sections and the schedule of assessments (Appendix 2).

6.2.1. Informed Consent

All subjects must personally sign and date the IRB approved informed consent form before any study procedures are performed (Section 9.1.3).

6.2.2. Medical History

A complete medical and surgical history will be obtained prior to enrollment and recorded on the eCRF. The medical history will include 3 months of transfusion history (Section 6.2.11.3) prior to screening, and JAK2V617F mutation status, if documented.

6.2.3. Medication History

A history of medications taken within the 3 months prior to screening and during the screening period will be obtained prior to enrollment and recorded on the eCRF.

6.2.4. Physical Examination and Myelofibrosis Symptom Assessment

At screening, a complete physical examination will be performed including height, weight, clinical signs and symptoms, and palpable spleen length, measured with a ruler. The physical exam will include assessment of splenomegaly and hepatomegaly. Breast, genital, and rectal examinations are not required at any study visit unless warranted in the opinion of the investigator. Height and weight should be collected per standard practice. Physical examination findings during the screening period will either be reported as medical history or adverse events (AEs) based on the requirements in Section 7.

At subsequent study visits, the physical examination will be an interim examination to monitor for any changes and will also include weight and assessment of myelofibrosis symptoms.

6.2.5. Vital Signs

Vital signs will include pulse, systolic and diastolic blood pressure, and body temperature. Vital signs should be collected per standard practice.

6.2.6. Ophthalmic Examinations

Eye examinations will be performed to assess for cataract and visual acuity. All assessments will be performed in accordance with local standard practice.

6.2.7. Laboratory Assessments

All samples for laboratory assessments will be sent to the central laboratory with the exception of urine pregnancy tests which will be completed at the site, if applicable. Local laboratory complete blood count (CBC) assessments may be collected as required for dose adjustments throughout the study. Local laboratory assessments resulting in a dose change will be reported on the eCRF.

The central laboratory will be responsible for chemistry, CBC with differential, urinalysis, hepatitis serology, and serum pregnancy testing per Table 6-1 and storage or shipping of other study samples. Other tests listed in Table 6-1 will be performed by Gilead or a designated laboratory. Any samples collected per the Schedule of Assessments (Appendix 2) may be analyzed for any tests necessary to ensure subject safety. Specific instructions for processing, labeling, and shipping samples will be provided in a central laboratory manual. The date and time of sample collection will be reported.

Table 6-1. Analytes

Chemistry	Urinalysis	CBC and Coagulation	Other Analytes
Albumin	Color and appearance	RBC	Serum beta hCG
Alkaline phosphatase	Specific gravity	Hemoglobin	Hepatitis B surface antigen
ALT	pH	Hematocrit	Hepatitis B surface antibody
AST	Occult blood	Platelets	Hepatitis B core antibody
Amylase	Protein	WBC	Hepatitis C antibody
Bicarbonate	Glucose	Differential	MMB PK
BUN	Bilirubin	Reticulocyte Count	C-reactive protein
Calcium	Leukocyte esterase	% Hgb-Reticulocytes	Erythropoietin
Chloride	Ketones	Neutrophils	Hepcidin
Creatinine	Nitrite	Bands/stabs	Thiamine
Direct bilirubin	Urobilinogen	Eosinophils	Pharmacodynamics and exploratory biomarkers
GGT	Microscopic[a]	Basophils	
Glucose		Lymphocytes	
Iron		Monocytes	
Iron binding capacity		% blasts	
Ferritin		Absolute neutrophil count	
LDH		PT (INR)[b]	
Lipase		PTT[b]	
Magnesium			
Non-transferrin bound iron			
Phosphorus			
Potassium			
Sodium			
Total bilirubin			
Total protein			
Transferrin saturation			
Soluble transferrin receptor			
Uric acid			

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma glutamyl transpeptidase; LDH = lactate dehydrogenase; PT (INR)= Prothrombin time; PTT= partial thromboplastin time; RBC = red blood cell; WBC = white blood cell

a If applicable

b Baseline and Week 24 only

6.2.8. Biomarker Samples

Biomarker analysis will be performed on subject samples including: blood, Liver Iron Concentration (LIC) MRI, bone marrow biopsy, and buccal swab as indicated below. Refer to sections 6.3-6.5 and Appendix 2 for details regarding the biomarker sampling schedules.

6.2.8.1. Blood Samples for Biomarker Analysis

Blood samples will be collected and transferred to the central laboratory for analysis as whole blood, serum or plasma.

6.2.8.2. Liver Iron Concentration MRI (LIC MRI)

This anemia-related test will be performed in conjunction with spleen MRI to determine the amount of iron stored in the liver.

MRIs will be performed at local imaging centers and sent to a central imaging laboratory for assessment of liver iron concentration. The central imaging laboratory will provide instructions for collection and transfer of the LIC MRI. Repeat MRI scans may be required if the original scan is not accepted by the central imaging laboratory, which may occur if the scan is of poor quality. Computed tomography (CT) scans may not be performed.

The central imaging laboratory will assess liver iron concentration as described in the Independent Review Charter.

6.2.8.3. Bone marrow biopsy

The bone marrow biopsy, and if possible, bone marrow aspirate, should be processed according to the laboratory manual and shipped to the central lab embedded in paraffin blocks unless a block or unstained tissue slides are already available within 90 days of the Screening visit.

Bone marrow samples may also be assessed for cytogenetic abnormalities at Baseline (not required if previously completed within 90 days of the Screening visit and the required data are available for reporting to the eCRF). Cytogenetic assessments may be repeated for subjects with abnormalities at Baseline for assessment of cytogenetic response.

6.2.8.4. Buccal Swab

The buccal swab will be performed to provide a normal genome sample as a baseline to enable identification of somatic molecular changes related to disease. The sample should be collected at the Baseline visit, but may be collected at any time during the study.

6.2.9. Pharmacokinetics

Pharmacokinetics blood samples will be collected predose and at 2, 4, and 6 hours postdose at specified visits as instructed in sections 6.3-6.5.

6.2.10. Patient-reported Outcomes Assessments (PRO)

6.2.10.1. Modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPNSAF TSS) version 2

The modified MPNSAF TSS version 2 is an 8 item questionnaire developed to assess symptom burden and quality of life in patients with MPN. The total symptom score is assessed over time to evaluate changes in MPN-related symptoms. The questionnaire is completed daily on an electronic diary (eDiary) device.

6.2.10.2. Patient Global Impression of Change (PGIC)

The PGIC is a single question to assess the patient's impression of change in myelofibrosis symptoms since the start of study treatment. The Patient Global Impression of Change (PGIC) scale assessed patients' perceptions of change in their myelofibrosis symptoms over time. The PGIC has been widely used to evaluate a patient's overall sense of whether a treatment has been beneficial. In this study, subjects complete the PGIC on paper at the Week 24 visit.

6.2.11. Disease Assessments

6.2.11.1. Dynamic International Prognostic Scoring System (DIPSS)

The DIPSS for myelofibrosis will be assessed at screening to determine a subject's study eligibility. The DIPSS score is assessed using a combination of the subject's age, constitutional symptoms, and hematologic parameters. The DIPSS score corresponds to a risk group: low, intermediate-1, intermediate-2, or high {24006} (Appendix 4).

6.2.11.2. Spleen MRI

MRIs will be performed at local imaging centers and sent to a central imaging laboratory for assessment of spleen volume. The central imaging laboratory will provide instructions for collection and transfer of the spleen MRI. The spleen MRI will be performed in conjunction with the LIC MRI. Repeat MRI scans may be required if the original scan is not accepted by the central imaging laboratory, which may occur if the scan is of poor quality. CT scans may not be performed.

The central imaging laboratory will assess spleen volume as described in the Independent Review Charter.

6.2.11.3. Transfusion Recording

Subjects will record transfusion events in a diary during the screening period and throughout the study. The diary will include instructions for the transfusion clinic to provide the date, type (eg, whole blood, platelets, packed cells), and number of units of the transfusion. Transfusion events will be reported on the eCRF. The hemoglobin or platelet value at the time of the transfusion will be reported on the eCRF as an observational component of the study.

6.3. Pretreatment Assessments

6.3.1. Screening Visit

The Screening visit date will be defined as the date the subject signs the informed consent form. Subjects will complete screening and baseline assessments within 28 days after signing the informed consent form to determine eligibility for participation in the study. Subjects who do not enroll within the 28 day window will be screen failed. The following assessments will be performed and documented at the screening visit (-28 to -21 days prior to first dose of MMB):

- Informed consent
- Medical history (includes prior 3 months of transfusion history)
- Medication history
- Physical examination
- Myelofibrosis symptoms assessment
- Vital signs
- Disease Status
  - DIPSS
- Distribution of eDiary with instructions for collection of daily modified MPNSAF TSS. Subjects will be issued a hand-held device and will complete the MPNSAF TSS questionnaire each night during screening through to the Week 24 visit.
- Laboratory assessments:
  - Chemistry
  - Complete blood count (CBC) with differential, reticulocyte count (including hemoglobin-containing reticulocytes)
  - Viral hepatitis B and C testing
  - Serum pregnancy test, if applicable
  - C-Reactive Protein (CRP)
  - Urinalysis

- Biomarker Sampling:
  - Iron studies
  - Cytokines/chemokines
  - $CD34^+$ cell count
  - Gene expression
  - Immunophenotype (flow cytometry)

From the time of obtaining informed consent through the first administration of MMB, all serious adverse events (SAEs), as well as any non-serious AEs related to protocol-mandated procedures must be recorded on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 for additional details.

Laboratory assessments may be repeated 1 time during the screening period for confirmation prior to registering the subject as a screen failure. Subjects failing to meet eligibility or complete the initial screening will be registered as a screen failure and permitted to rescreen 1 time. Rescreening requirements will be the same as the screening requirements. Assessments from the first screening attempt that fall within the specified timeframes (eg, bone marrow aspirate/biopsy within 90 days of screening visit) do not need to be repeated.

6.3.2. Baseline Assessments

The following baseline assessments will be completed within 7 days (±2 days) prior to first dose of MMB, except for the ophthalmic examination which may be completed at any time during the screening period prior to first dose of MMB.

Laboratory assessments and biomarker samplings must be completed ≥ 7 days after a RBC transfusion.

- Physical exam
- Myelofibrosis symptoms assessment
- Vital signs
- Transfusion recording
- Ophthalmic examination
- Laboratory assessments:
  - CBC with differential, reticulocyte count (including hemoglobin-containing reticulocytes)

  - Thiamine status
  - Erythropoietin (EPO)
  - CRP
  - Urine pregnancy test
- Biomarker Sampling:
  - Iron Studies
  - Hepcidin (between 8-10 am, and 6 hours later)
  - Exploratory signaling (mass cytometry)
  - JAK2V617F allele burden, and other mutation tests
  - Buccal swab
  - Bone marrow biopsy and if possible aspirate (not required if previously completed within 90 [+14] days of the Screening visit, and formalin-fixed paraffin embedded [FFPE] block or tissue slides plus the data are available)
- Spleen & LIC MRI (per Section 6.2.11)
- AEs and concomitant medications

6.4. Enrollment

Enrollment may be completed following confirmation of subject eligibility and completion of the above screening and baseline procedures. The IWRS will assign medication at the time of enrollment. The site will train the subject on the dosing schedule for MMB at the time of dispensing. The first dose of MMB may occur within 5 days following enrollment in IWRS.

6.4.1. Enrollment Assessments

The following enrollment assessments will be completed on the day of first dose of MMB:

- Modified MPNSAF TSS (completed daily)
- Physical examination
- Myelofibrosis symptoms assessment
- Vital signs

- Transfusion recording
- Biomarker sampling:
  - Pharmacodynamics (predose, 2, 4, 6 hours postdose)
  - Pharmcokinetics (predose, 2, 4, 6 hours postdose)
  - Exploratory pharmacodynamics sample (predose, 2 hours postdose)
  - Hepcidin (predose, 6 hours postdose)
  - Cytokines/chemokines (predose, 6 hours postdose)
  - $CD34^{+}$ cell count (predose)
  - Gene expression (predose)
  - Immunophenotype (predose)
- AEs and concomitant medications
- MMB dosing

6.5. Treatment Assessments

Each on-study visit will be scheduled based on the date of enrollment in IWRS. Visits will follow the schedule of assessments in Appendix 2.

6.5.1. Week 2

The Week 2 visit may be completed within a window of ± 3 days. The following procedures will be completed at the Week 2 visit, unless otherwise specified:

- Modified MPNSAF TSS (completed daily)
- Physical examination
- Myelofibrosis symptoms assessment
- Transfusion recording
- Laboratory assessments (all predose):
  - CBC with differential, reticulocyte count (including hemoglobin-containing reticulocytes)
  - CRP

- Biomarker Sampling:
  - Hepcidin (predose, 6 hrs postdose)
  - Iron Studies
- AEs and concomitant medications

6.5.2. Week 4, 8, 12, 16 and Week 20

On-study visits during this period may be completed within a window of ± 3 days. The following procedures will be completed at each visit, unless otherwise specified:

- Modified MPNSAF TSS (completed daily)
- Physical examination
- Myelofibrosis symptoms assessment
- Vital signs
- Transfusion recording
- Laboratory Assessments:
  - CBC with differential ,reticulocyte count (including hemoglobin-containing reticulocytes) (All visits, predose)
  - Chemistry (Week 12 only, predose)
  - Thiamine status (Week 12 only, predose)
  - Erythropoietin (Weeks 8, 20, predose)
  - CRP (Week 12 only, predose)
  - Urinalysis
- Biomarker Sampling:
  - Hepcidin (All visits, predose, 6 hours postdose)
  - Iron Studies(all visits, predose)
  - Cytokines/chemokines (All visits, predose)

  - CD34^{+} cell count (Week 12, 20 predose)
  - Immunophenotype (flow cytometry) (Weeks 12, 20, predose)
  - Gene expression (Weeks 12, 20, predose)
  - Exploratory signaling (mass cytometry) (Weeks 4, 12, predose)
  - Pharmacodynamics (Week 4 predose, 2, 4, 6 hours postdose)
  - Pharmacokinetics (Week 4 predose, 2, 4, 6 hours postdose)
- Urine pregnancy test (all visits; if applicable)
- AEs and concomitant medications
- MMB accountability and dispensing

6.5.3. Week 24

Subjects will complete the Week 24 visit within a window of ± 7 days. Subjects will continue MMB treatment until completion of this visit. The following procedures will be completed:

- Modified MPNSAF TSS (completed daily; the eDiary will be collected at this visit)
- PGIC Questionnaire
- Physical examination
- Myelofibrosis symptoms assessment
- Vital signs
- Transfusion recording
- Laboratory assessments:
  - Chemistry (predose)
  - CBC with differential, reticulocyte count (including hemoglobin-containing reticulocytes) (predose)
  - Thiamine status (predose)
  - CRP (predose)
  - Urinalysis

- Biomarker Sampling:
  - Hepcidin (predose, 6 hours postdose)
  - Exploratory signaling (mass cytometry) (predose)
  - Iron Studies (predose)
  - Cytokines/chemokines (predose)
  - JAK2V617F allele burden, and other mutation tests
  - Pharmacodynamics (predose, 2, 4, 6 hours postdose)
  - Pharmacokinetics (predose, 2, 4, 6 hours postdose)
  - Bone marrow biopsy/aspirate
- Urine pregnancy test (if applicable)
- Ophthalmic examinations
- Spleen & LIC MRI (per Section 6.2.11)
- AEs and concomitant medications
- MMB accountability

6.6. Unscheduled visits

Unscheduled visits may occur at any time during the study. Vital signs, laboratory assessments, physical examination and MMB dispensation may be conducted at these visits.

6.7. Post-treatment Assessments

6.7.1. Early Study Drug Discontinuation

Subjects discontinuing study MMB prior to the Week 24 visit will complete the Early Study Drug Discontinuation (ESDD) visit and will not be eligible to receive MMB maintenance treatment. The following procedures will be completed within 7 days of early MMB discontinuation:

- Modified MPNSAF TSS (completed daily, the eDiary will be collected at this visit)
- Physical examination
- Myelofibrosis symptoms assessment
- Vital signs

- Spleen and LIC MRI
- Ophthalmic examinations (not required if completed within 12 weeks prior to ESDD)
- Laboratory assessments:
  - Chemistry
  - CBC with differential, reticulocyte count (including hemoglobin-containing reticulocytes)
  - CRP
  - Urinalysis
- Urine pregnancy test (if applicable)
- Biomarker Sampling:
  - JAK2V617F allele burden, and other mutation tests
- Transfusion recording
- AEs and concomitant medications
- MMB accountability (if required)

6.7.2. 30-Day Follow-up Assessments

The following procedures will be completed 30 days after the subject's last dose of MMB, within a window of ±7 days. Subjects completing the Week 24 visit and entering maintenance treatment on study GS-US-352-1154 will not complete the 30-Day Follow Up visit:

- Physical examination
- Myelofibrosis symptoms assessment
- Vital signs
- Laboratory assessments:
  - Chemistry
  - CBC with differential, reticulocyte count (including hemoglobin-containing reticulocytes)
  - Urinalysis

- Transfusion recording
- AEs and concomitant medications

6.8. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator.
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Disease progression
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 3
- Discontinuation of the study at the request of Gilead, a regulatory agency or an IRB

6.9. End of Study

End of Study for a subject is defined as the date of the last study-related procedure or the date of death for an on-study subject. All treatment-emergent AEs and laboratory abnormalities present at the end of study are to be followed until resolution or the event is determined to be irreversible by the investigator.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history case report form (CRF).

7.1.2. Serious Adverse Events

A serious adverse event (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.2.1. Protocol-Specific Serious Adverse Event Instructions

To maintain the integrity of the study, the following events that are assessed as unrelated to MMB will not be considered as SAEs:

- Progression of myelofibrosis
- Death related to progression of myelofibrosis

However, events of progression of myelofibrosis and death due to progression of myelofibrosis that are assessed by the investigator to be related to MMB will be considered as SAE and will be reported to regulatory agencies by Gilead accordingly.

All events of progression of myelofibrosis and death related to progression of myelofibrosis, regardless of investigator assessment of relationship to MMB, will be reported in the eCRFs and, as appropriate, in the final clinical study report (CSR) and in any relevant aggregate safety reports.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to MMB interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (eg, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for MMB and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to MMB therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than MMB treatment. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.

- **Yes:** The adverse event occurred as a result of protocol procedures (eg, venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1.

Table 7-1. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention.
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affect clinical status, and may require medical intervention.
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life.
Grade 5	Fatal	Sign or symptom results in death.

The distinction between the seriousness and the severity of an AE should be noted. Severity is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to initiation of MMB:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form eCRF: all SAEs and adverse events related to protocol-mandated procedures.

7.3.1. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of MMB must be reported to the eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

7.3.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of MMB, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of MMB, he/she should promptly document and report the event to Gilead DSPH.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

7.3.2.1. Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours as described above to Gilead DSPH: email Safety_FC@gilead.com; or fax +1 (650) 522-5477.

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with MMB. The investigator should notify the IRB of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs (Section 7.1.3). When laboratory abnormalities are recorded as AEs or SAEs, severity should be recorded and graded according to the CTCAE Version 4.03 except for anemia (hemoglobin, Hgb) which will be graded using the CTCAE Version 3.0 as defined in Table 7-2.

Table 7-2. Grading of Anemia (Hgb) Severity

Grade (CTCAE 3.0)				
1	**2**	**3**	**4**	**5**
<LLN – 10.0 g/dL <LLN – 6.2 mmol/L <LLN – 100 g/L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L	Death

7.6. Toxicity Management

Dosing requirements for certain toxicities are specified in Section 5.3 and 5.3.3. The investigator may contact the medical monitor to review toxicities that are not directly discussed in the protocol. Laboratory abnormalities (eg, below normal thiamine level) identified at Screening/Baseline and during study participation should be treated at the investigator's discretion.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post MMB treatment follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in sections 7.3 and 7.4. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to or Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, email Safety_FC@gilead.com or fax +1 (650) 522-5477.

Refer to Appendix 3 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve MMB and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications do not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To determine the transfusion independence response rate for transfusion dependent MF subjects treated with MMB

8.1.2. Primary Endpoint

The primary endpoint is:

- Transfusion independence response rate by Week 24, defined as becoming transfusion independent for ≥ 12 weeks at any time on study. A subject is considered as transfusion independent on study if no RBC transfusion occurs in any 12 weeks during the 24-week treatment period.

8.1.3. Secondary Endpoints

Secondary endpoints are:

- Transfusion response rate by Week 24, defined as becoming not transfusion dependent for ≥ 8 weeks at any time on study
- Baseline and change in marker of anemia (eg, hepcidin, ferritin)
- Change in pharmacodynamics biomarker pSTAT3
- Splenic response rate at Week 24, defined as ≥ 35% reduction in spleen volume from baseline as measured by MRI
- Response rate in TSS at Week 24, defined as achieving a ≥ 50% reduction from baseline in TSS as measured by the modified MPNSAF TSS diary
- Pharmacokinetics parameters (C_{max}, C_{last}, C_{tau} and AUC_{last}, if available) for MMB
- Change in circulating cytokine and inflammatory markers (eg, IL-6, IL-8, IFN gamma, TNF alpha)

8.1.4. Exploratory Endpoints

The exploratory endpoints are:

- Baseline and change in markers of orthogonal or parallel signaling pathways (eg, RAS/MAPK, PI3K/AKT)
- Baseline and change in gene expression profiles in whole blood and change in somatic mutations in whole blood, if applicable.
- Baseline and change in immune subsets in whole blood
- Change in exploratory pharmacodynamics markers of signaling mediated by JAK1 and/or JAK2 (eg, pSTAT1, pSTAT5, and pSTAT6)

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Safety Analysis Set

The Safety Analysis Set includes all subjects who receive ≥ 1 dose of MMB. Since this study is a non-randomized study, Safety Analysis Set will be used for subject's characteristics, efficacy and safety endpoints, and study treatment administration.

8.2.1.2. Biomarker Analysis Set

The Biomarker Analysis Set consists of all subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest. The Biomarker Analysis Set will be used for biomarkers and the correlation analyses between biomarkers and efficacy clinical endpoints.

8.2.1.3. Pharmacokinetics (PK) Analysis Set

The PK Analysis Set consists of all subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.3. Data Handling Conventions

By-subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation (StD), 90% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 90% CIs on the percentage. Unless otherwise indicated, 90% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2 sided. Data will be described and summarized by relevant dose level, analysis set, and time point. As

appropriate, changes from baseline to each subsequent time point will be described and summarized by dose level. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized by dose level. Graphical techniques (eg, waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative.

The baseline value will be the last (most recent) pre-treatment value. Data from all sites will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

8.4. Demographic Data and Baseline Characteristics

Subject demographic and baseline characteristics will be listed and summarized for the Safety Analysis Set. Imbalances in subject characteristics may be compared using the Wilcoxon rank-sum test for continuous variables and the Fisher's exact test for categorical variables.

8.5. Efficacy Analysis

Transfusion independence response rate, transfusion response rate, splenic response rate and response rate in TSS will be presented with corresponding 2-sided 90% exact CIs using the binomial distribution. Subjects who do not have sufficient baseline or on-study assessment to characterize the response will be counted as non-responders.

8.6. Safety Analysis

All safety data collected on or after the date that MMB was first dispensed up to the date of last dose of MMB plus 30 days will be summarized. Data for the pretreatment will be included in data listings.

8.6.1. Extent of Exposure

Descriptive information will be provided by dose level regarding the number of doses of MMB prescribed, the total number of doses taken, the percent of expected doses taken, the number of days of MMB treatment, and the number and timing of prescribed dose modification and interruptions.

Compliance will be described by dose level in terms of the proportion of MMB actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed modification and interruptions).

8.6.2. Adverse Events

All AEs will be listed. The focus of AE summarization will be on treatment-emergent AEs. A treatment-emergent AE is defined as an AE that occurs or worsens in the period from the first dose of MMB to 30 days after the last dose of MMB.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA http://www.meddramsso.com) with descriptions by System Organ Class (SOC), High Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term. The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.03, whenever possible. If a CTCAE criterion does not exist for a specific type of AE, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the AE: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the AE to MMB will be categorized as related or unrelated.

Treatment-emergent AEs will be summarized by dose level. Summary tables will be presented to show the number of subjects reporting treatment-emergent AEs by severity grade and corresponding percentages. A subject who reports multiple treatment-emergent AEs within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade. AE descriptions will be presented by decreasing frequency for a given System Organ Class and Preferred Term. Separate listings and summaries will be prepared for the following types of treatment emergent AEs:

- Study-drug-related AEs
- AEs that are Grade ≥ 3 in severity
- AEs leading to MMB interruption and/or dose modification
- AEs leading to MMB discontinuation
- SAEs

8.6.3. Laboratory Evaluations

All laboratory data will be listed. Summaries of laboratory data will be based on observed data. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by >1 grade in the period from the first dose of MMB to 30 days after the last dose of MMB. If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade >1 in severity) will be considered treatment emergent.

Hematological, serum biochemistry, and urine data will be programmatically graded according to CTCAE severity grade, when applicable. For parameters for which a CTCAE scale does not exist, reference ranges from the central laboratory will be used to determine programmatically if a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc.

Hematological and serum biochemistry and their changes from baseline will be summarized by dose level, by visit. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (eg, during the study or from baseline to a particular visit).

Shift tables for hematology and serum biochemistry will also be presented by showing change in CTCAE severity grade from baseline to the worst grade post-baseline. For parameters for which a CTCAE scale does not exist, shift tables will be presented showing change in results from baseline to the worst grade post baseline. Separate listings and summaries will be prepared for laboratory abnormalities that are Grade ≥ 3 in severity.

8.7. Pharmacokinetics Analysis

The concentration data of MMB and its major metabolite GS-644603 will be summarized by nominal sampling time using descriptive statistics. PK parameters (C_{max}, C_{last}, C_{tau}, and AUC_{last}, if available), will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, coefficient of variation (%) standard deviation, median, minimum, and maximum). Plasma concentrations over time will be plotted in semi logarithmic and linear formats as mean ± standard deviation, and median (Q1, Q3) if applicable. Exposure-response relationship may also be evaluated.

8.8. Biomarker Analysis

The baseline levels, and changes in biomarker levels over time from baseline level, will be evaluated. Descriptive statistics will be provided at each sampling time, and by response category for each clinical endpoint being considered for association with biomarkers, as appropriate. Exploratory graphics, such as side-by-side boxplots will also be generated.

Univariate and multivariate statistical techniques may be explored to evaluate the association of baseline biomarkers and changes in biomarkers with clinical outcomes as appropriate. Due to the exploratory nature of the end points, no formal hypothesis testing will be conducted.

8.9. Sample Size

This study will enroll approximately 40 subjects. Due to the exploratory nature, the study is not designed to detect a specific effect size. A sample size of 40 subjects is considered adequate for the exploratory study. Given a sample size of 40 subjects in the study, Table 8-1 shows the exact 90% CIs using the binomial distribution for a given transfusion independence response rates ranging from 0.10 to 0.5.

Table 8-1. Exact 90% CIs for various response rates

No. of Responders	Response Rate	Exact 90% CI (N=40)
4	0.10	(0.035, 0.214)
6	0.15	(0.067, 0.274)
8	0.20	(0.104, 0.332)
10	0.25	(0.142, 0.387)
12	0.3	(0.183, 0.440)
14	0.35	(0.226, 0.492)
16	0.4	(0.269, 0.542)
18	0.45	(0.315, 0.591)
20	0.5	(0.361, 0.639)

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB. The investigator will not begin any study subject activities until approval has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or local requirements.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, eCRF, MMB, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;

- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of MMB, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. The eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification within the electronic data capture (EDC) system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site

coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Product Accountability and Return

Gilead recommends that used and unused MMB supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's disposal procedures and provide appropriate instruction for destruction of unused MMB supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused MMB supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If MMB is destroyed on site, the investigator must maintain accurate records for all MMB destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the MMB supplies. Upon study completion, copies of the accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review MMB supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRBs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB in accordance with local requirements and receive documented IRB approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form, OR
- The study has been completed at all study sites for at least 2 years

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (eg, central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), and IRBs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 2, Open-label, Translational Biology Study of Momelotinib in Transfusion-Dependent Subjects with Primary Myelofibrosis (PMF) or Post-polycythemia Vera or Post-essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)

GS-US-352-1672 Original 18 May 2015

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

Helen Collins
Name (Printed)
Author

Signature

18 May 2015
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

Assessment	Screening (-28 to -21 Days)	Baseline (-7 +/- 2 Days)	Enrollment	Week 2 (+/- 3 days)	Week 4 (+/- 3 days)	Week 8 (+/- 3 days)	Week 12 (+/- 3 days)	Week 16 (+/- 3 days)	Week 20 (+/- 3 days)	Week 24 (+/- 7 days)	Early Study Drug Discontinuation	30 Day Follow-Up
Informed consent	X											
Medication and medical history	X											
Transfusion Recording	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam and myelofibrosis symptoms assessment	X	X	X	X	X	X	X	X	X	X	X	X
DIPSS Assessment	X											
Vital Signs	X	X	X		X	X	X	X	X	X	X	X
AEs, Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Ophthalmic examination		X								X	X	
MMB accountability and dispensing[g]			X		X	X	X	X	X	X	X	
MMB dosing at site			X	X	X	X	X	X	X	X		
Patient Reported Outcomes												
Modified MPNSAF TSS	←---------- Daily ----------→										X	
PGIC										X	X	

Assessment	Screening (-28 to -21 Days)	Baseline (-7 +/- 2 Days)	Enrollment	Week 2 (+/- 3 days)	Week 4 (+/- 3 days)	Week 8 (+/- 3 days)	Week 12 (+/- 3 days)	Week 16 (+/- 3 days)	Week 20 (+/- 3 days)	Week 24 (+/- 7 days)	Early Study Drug Discontinuation	30 Day Follow-Up
Laboratory Assessments												
Viral Hepatitis B and C	X											
Chemistry	X						X			X	X	X
CBC with differential, reticulocyte count	X	X		X	X	X	X	X	X	X	X	X
Thiamine status		X					X			X		
Erythropoietin		X				X			X			
C-Reactive Protein (CRP)	X	X		X			X			X	X	
Urinalysis	X				X	X	X	X	X	X	X	X
Serum pregnancy test[a]	X											
Urine pregnancy test		X			X	X	X	X	X	X	X	
Biomarker Samples												
Bone marrow biopsy & aspirate		X								X		
Buccal Swab		X										
Spleen & LIC MRI		X								X	X	
Iron Studies	X	X		X	X	X	X	X	X	X		
Hepcidin		X	X	X	X	X	X	X	X	X		

Assessment	Screening (-28 to -21 Days)	Baseline (-7 +/- 2 Days)	Enrollment	Week 2 (+/- 3 days)	Week 4 (+/- 3 days)	Week 8 (+/- 3 days)	Week 12 (+/- 3 days)	Week 16 (+/- 3 days)	Week 20 (+/- 3 days)	Week 24 (+/- 7 days)	Early Study Drug Discontinuation	30 Day Follow-Up
JAK2V617F allele burden and other mutation tests		X								X	X	
Pharmacodynamics[c,d]			X[d]		X					X		
Pharmacokinetics[e]			X		X					X		
Cytokines/chemokines	X		X[f]		X	X	X	X	X	X		
Exploratory signaling (mass cytometry)		X			X		X			X		
$CD34^+$ Cell Count	X		X				X		X			
Gene expression	X		X				X		X			
Immunophenotype (flow cytometry)	X		X				X		X			

a For female subject post-menopausal for less than two years, if FSH < 40 mIU/ mL a serum pregnancy test will be required

b Hepcidin sample collection will occur at the following times: Baseline Visit:, between 8 am-and 10 am, 6 hours later; Enrollment, Weeks 4, 8, 12, 16, 20, and 24 predose (between 8 am and 10 am) and 6 hours postdose

c Pharmacodynamics biomarker sample collection will occur at the following times: predose, 2, 4, and 6 hours postdose at Enrollment, then Weeks 4 and 24.

d Additional exploratory pharmacodynamics sample collection will occur at the following times: predose, and 2 hours postdose at Enrollment only.

e PK sample collection at the following times: predose, 2, 4, and 6 hours postdose at Enrollment, then Weeks 4 and 24.

f Cytokine sample collection times at enrollment: predose, 6 hours postdose. All other time points: predose only.

g MMB accountability ONLY at Week 24 and ESDD visits

Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1. Pregnancy and Contraception Requirements for Males and Females of Childbearing Potential

The risks of treatment with momelotinib (MMB) during pregnancy have not been evaluated. Data available at this time suggest that this drug does not have a drug-drug interaction (DDI) with hormones used for contraception. Please refer to the latest version of the investigator's brochure for additional information.

2. Definition of Female of Childbearing Potential

For the purposes of this study, a female subject of childbearing potential is a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a pubertal female who has not yet started menstruating. A woman who has had a tubal sterilization is considered to be of childbearing potential.

A female subject may be considered menopausal in either of the following conditions:

- Surgical menopause: Appropriate medical documentation of prior complete bilateral oophorectomy (ie, surgical removal of the ovaries and occurring at the age at which the procedure was performed)

- Spontaneous menopause: Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency by a certified health care provider. The worldwide mean age of spontaneous menopause is 49.24 (SD 1.73) years

- A hormonal deficiency should be properly documented in the case of suspected spontaneous menopause as follows:

- If age ≥54 years and with the absence of normal menses: serum follicle stimulating hormone (FSH) level elevated to within the postmenopausal range based on the laboratory reference range where the hormonal assay is performed

- If age <54 years and with the absence of normal menses: negative serum or urine human chorionic gonadotropin (hCG) with concurrently elevated serum FSH level in the postmenopausal range, depressed estradiol (E2) level in the postmenopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed

3. Contraceptive Requirements

Male subjects and female subjects of childbearing potential who engage in intercourse must agree to utilize protocol specified methods of contraception from the screening/enrollment visit throughout the study period and, for male subjects for 90 days following the last dose of MMB, and for female subjects of childbearing potential, for 30 days following the last dose of MMB.

Female study subjects who are not heterosexually active must provide periodic confirmation of continued abstinence from heterosexual intercourse and regular pregnancy testing while taking MMB. The investigator will counsel subjects on the protocol specified method(s) for avoiding pregnancy in case the subject chooses to engage in heterosexual intercourse. See Appendix Table 1 for the protocol specified contraceptive methods.

If tubal sterilization is via the Essure procedure, verification of tubal blockage by hysterosalpingogram (HSP) must be performed approximately 3 months after microinsertion. Prior to verification, Essure is not considered a reliable form of contraception and the contraception methods described below must be used.

Female subjects who utilize hormonal contraceptives as one of their birth control methods must have used the same method for at least 3 months before study dosing.

Female subjects of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to receiving the first dose of MMB. Lactating females must discontinue nursing before MMB administration.

Appendix Table 1. Protocol Specified Contraceptive Methods

<table>
<tr><th rowspan="2">Methods to Use by Themselves</th><th colspan="2">Combination Methods</th></tr>
<tr><th>Hormone Methods
(choose one and use with a barrier method)</th><th>Barrier Methods
(choose one and use with a hormone method)</th></tr>
<tr><td rowspan="2">Intrauterine Devices (IUDs)
• Copper T 380A IUD
• LNg 20 IUD

Tubal Sterilization</td><td>Estrogen and Progesterone
• Oral contraceptives
• Transdermal patch
• Vaginal ring
Progesterone
• Injection
• Implant</td><td>• Diaphragm with spermicide
OR
Cervical cap with spermicide
• Male condom (with or without spermicide)</td></tr>
<tr><td colspan="2">Partner’s vasectomy must be used with a hormone or barrier method.</td></tr>
</table>

The investigator will counsel all subjects on the most effective method(s) for avoiding pregnancy during the study.

4. Additional Requirements for Male Subjects

Male subjects must agree to use condoms during heterosexual intercourse and avoid sperm donation while enrolled in the study and for at least 90 days after administration of the last dose of MMB.

5. Procedures to be Followed in the Event of Pregnancy

Subjects should be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last MMB dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue MMB immediately. The investigator should report all pregnancies to the CRO Safety Department using the pregnancy report form within 24 hours of becoming aware of the pregn*a*ncy. The investigator should counsel the subject regarding the possible effects of prior MMB exposure on the fetus and the need to inform the study site of the outcome of the pregnancy. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.

Appendix 4. Dynamic International Prognostic Scoring System (DIPSS) for Primary Myelofibrosis

Prognostic variable	Value		
	0	**1**	**2**
Age	≤ 65	> 65	
WBC	≤ 25	> 25	
Hgb	≥ 10		< 10
Peripheral blast	< 1	≥ 1	
Constitutional symptoms	No	Yes	

The risk category is obtained by adding up the values of each prognostic variable.

Risk categories are defined as:
Low: 0
Intermediate-1: 1 or 2
Intermediate-2: 3 or 4
High: > 4

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