



CLINICAL STUDY PROTOCOL

Study Title:	Open-label Study to Assess the Long-term Safety and Efficacy of Momelotinib in Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, Post-essential Thrombocythemia Myelofibrosis, Polycythemia Vera or Essential Thrombocythemia	
Sponsor:	Gilead Sciences, Inc.	
IND Number:	101155	
EudraCT Number:	2013-004476-36	
Indication:	Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, Post-essential Thrombocythemia Myelofibrosis, Polycythemia Vera, or Essential Thrombocythemia	
Protocol ID:	GS-US-352-1154	
Gilead Clinical Program Manager:	Name:	Ori Yellin
	Telephone:	+1 (650) 372-7643
Gilead Medical Monitor:	Name:	Jun Kawashima, MD
	Telephone:	+1 (650) 524-8930
	Fax:	+1 (650) 372-6730
Protocol Version/Date:	Original:	12 December 2013
	Amendment 1:	21 July 2014
	Amendment 2:	22 August 2014
	Amendment 3:	27 July 2015
	Amendment 4:	06 November 2017

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of Gilead Sciences, Inc., and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Gilead Sciences, Inc., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

TABLE OF CONTENTS

TABLE OF CONTENTS	2
LIST OF IN-TEXT TABLES	5
LIST OF IN-TEXT FIGURES	5
PROTOCOL SYNOPSIS	6
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS.....	11
1. INTRODUCTION	13
1.1. Background	13
1.2. Momelotinib (MMB)	13
1.2.1. General Information	13
1.2.2. Preclinical Pharmacology and Toxicology.....	14
1.2.3. Clinical Trials of Momelotinib.....	17
1.3. Rationale for This Study	18
1.3.1. Dose Justification	19
1.4. Compliance	20
1.5. Other Relevant Clinical Information.....	20
2. OBJECTIVES	21
3. STUDY DESIGN.....	22
3.1. Endpoints	22
3.2. Study Design	22
3.3. Study Treatments	22
3.4. Duration of Treatment.....	22
3.5. Discontinuation Criteria	22
3.6. Source Data	22
4. SUBJECT POPULATION.....	23
4.1. Number of Subjects and Subject Selection	23
4.2. Inclusion Criteria.....	23
4.3. Exclusion Criteria.....	23
5. INVESTIGATIONAL MEDICINAL PRODUCTS	25
5.1. Enrollment and Treatment Assignment.....	25
5.2. Description and Handling of MMB.....	25
5.2.1. Formulation	25
5.2.2. Packaging and Labeling	25
5.2.3. Storage and Handling	25
5.3. Dosage and Administration of MMB.....	25
5.3.1. Starting Dose	25
5.3.2. Dose Increase Based on Response	26
5.3.3. Dose Reductions and Rules for Interrupting MMB.....	27
5.3.4. Discontinuing or Interrupting Treatment.....	28
5.4. Concomitant Medications	28
5.4.1. Proscribed Medication.....	28
5.4.2. Restricted Medications.....	29
5.4.3. Breast Cancer Resistance Protein (BCRP) Substrates.....	29
5.4.4. Organic Anion-Transporting Polypeptide (OATP) Inhibitors.....	29
5.5. Accountability for MMB.....	30

6.	STUDY PROCEDURES	31
6.1.	Subject Enrollment and Treatment Assignment.....	31
6.2.	Study Procedure Description.....	31
6.2.1.	Obtain Written Informed Consent.....	31
6.2.2.	Recording Medical History.....	32
6.2.3.	Medication History.....	32
6.2.4.	Physical Examination and Symptom Assessment.....	32
6.2.5.	Vital Signs.....	32
6.2.6.	Electrocardiogram.....	32
6.2.7.	Ophthalmic Examination.....	32
6.2.8.	Laboratory Assessments.....	32
6.2.9.	Patient-reported Outcomes Assessments (PRO)	33
6.2.10.	Disease Assessment.....	34
6.3.	Pretreatment Assessment.....	34
6.3.1.	Screening Visit/Enrollment.....	34
6.4.	Treatment Assessments.....	35
6.4.1.	Months 1 and 2 (Cohorts 1 and 2 only).....	35
6.4.2.	Months 3 to Early Study Drug Discontinuation (ESDD) visits or End of Study	36
6.5.	Unscheduled visits.....	37
6.6.	Post-treatment Follow-up Assessments.....	37
6.7.	Assessments for Premature Discontinuation from Study.....	38
6.8.	Criteria for Discontinuation of Study Treatment.....	38
6.9.	End of Study.....	38
7.	ADVERSE EVENTS AND TOXICITY MANAGEMENT.....	39
7.1.	Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events.....	39
7.1.1.	Adverse Events.....	39
7.1.2.	Serious Adverse Events.....	39
7.2.	Assessment of Adverse Events and Serious Adverse Events.....	40
7.2.1.	Assessment of Causality for Study Drug and Procedures.....	40
7.2.2.	Assessment of Severity.....	41
7.3.	Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead.....	41
7.4.	Gilead Reporting Requirements.....	43
7.5.	Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events.....	43
7.6.	Toxicity Management.....	44
7.7.	Special Situations Reports.....	44
7.7.1.	Definitions of Special Situations.....	44
7.7.2.	Instructions for Reporting Special Situations.....	44
8.	STATISTICAL CONSIDERATIONS.....	46
8.1.	Analysis Objectives and Endpoints.....	46
8.1.1.	Analysis Objectives.....	46
8.1.2.	Primary Endpoints.....	46
8.1.3.	Secondary Endpoints.....	46
8.1.4.	Exploratory Endpoints.....	48
8.2.	Analysis Conventions.....	48
8.2.1.	Analysis Sets.....	48
8.3.	Data Handling Conventions.....	48
8.4.	Demographic Data and Baseline Characteristics.....	48
8.5.	Efficacy Analysis.....	49

8.5.1.	Time-to-Event Endpoints	49
8.5.2.	Categorical Endpoints	49
8.5.3.	Continuous Endpoints	49
8.6.	Safety Analysis.....	49
8.6.1.	Extent of Exposure	49
8.6.2.	Adverse Events.....	50
8.6.3.	Laboratory Evaluations	50
8.7.	Sample Size.....	51
9.	RESPONSIBILITIES.....	52
9.1.	Investigator Responsibilities	52
9.1.1.	Good Clinical Practice.....	52
9.1.2.	Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval.....	52
9.1.3.	Informed Consent.....	52
9.1.4.	Confidentiality.....	53
9.1.5.	Study Files and Retention of Records	53
9.1.6.	Case Report Forms	54
9.1.7.	Investigational Medicinal Product Accountability and Return.....	55
9.1.8.	Inspections.....	55
9.1.9.	Protocol Compliance	55
9.2.	Sponsor Responsibilities	55
9.2.1.	Protocol Modifications	55
9.2.2.	Study Report and Publications	56
9.3.	Joint Investigator/Sponsor Responsibilities	56
9.3.1.	Access to Information for Monitoring	56
9.3.2.	Access to Information for Auditing or Inspections	56
9.3.3.	Study Discontinuation	57
10.	REFERENCES	58
11.	APPENDICES	60
Appendix 1.	Investigator Signature Page.....	61
Appendix 2.	Study Procedures Table.....	62
Appendix 3.	International Working Group for Myelofibrosis Research and Treatment (IWG- MRT) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia	64
Appendix 4.	2013 European LeukemiaNet (ELN) and International Working Group for Myelofibrosis Response and Treatment (IWG-MRT) Consensus.....	66
Appendix 5.	Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations	68
Appendix 6.	ECOG status.....	71

LIST OF IN-TEXT TABLES

Table 1-1. Preliminary Data on the Relative Bioavailability of MMB Tablet vs Capsule..... 19
Table 5-1. Starting Dose of MMB Cohorts 1 and 2..... 26
Table 5-2. Dose Adjustments of MMB from a Once-daily to a Twice-daily Regimen 27
Table 5-3. Doses for Restarting MMB after Withholding Treatment for Toxicity 28
Table 6-1. Analytes..... 33
Table 7-1. Grading of Adverse Event Severity..... 41
Table 7-2. Grading of Hemoglobin Severity 43

LIST OF IN-TEXT FIGURES

Figure 6-1. Initial Study Procedures 31

PROTOCOL SYNOPSIS

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

Study Title: Open-label Study to Assess the Long-term Safety and Efficacy of Momelotinib in Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, Post-essential Thrombocythemia Myelofibrosis, Polycythemia Vera or Essential Thrombocythemia

IND Number: 101155

EudraCT Number: 2013-004476-36

Study Centers Planned: Approximately 35 centers in North America, Europe and Australia

Objectives: The primary objective of this study is to determine the long-term safety and tolerability of momelotinib (MMB) in 4 cohorts of subjects:

- Cohort 1: Subjects who are currently receiving MMB capsules in the CCL09101E study for primary myelofibrosis (PMF) and post-polycythemia vera/essential thrombocythemia myelofibrosis (post-PV/ET MF) whose disease has not progressed on study
- Cohort 2: Subjects who are currently receiving MMB capsules in the YM387-II-02 study for PMF and post-PV/ET MF whose disease has not progressed on study
- Cohort 3 was closed and all enrolled subjects were discontinued from this study due to limited efficacy of MMB in the treatment of PV and ET on GS-US-354-0101.
- Cohort 4: Subjects who are currently receiving MMB tablets in the GS-US-352-1672 study for PMF and post-PV/ET MF, who completed 24 weeks of treatment and have responded to treatment while on study, per investigator's discretion.

The secondary objective of this study is to determine the long-term efficacy of MMB in these 4 cohorts of subjects.

Study Design:	An open-label study for subjects with PMF, post-PV MF, post-ET MF, PV, or ET, who have tolerated and achieved stable disease or better with MMB treatment while enrolled in a previous MMB clinical trial. After screening, subjects in Cohorts 1 and 2 will discontinue the MMB capsule and initiate the tablet form of MMB according to Table 5-1 . Subjects in Cohort 4 will discontinue MMB tablets from the previous study and initiate MMB tablets in this study.
Number of Subjects Planned:	Based on the number of previously enrolled subjects in Cohorts 1,2, and 3 including the number of expected subjects in Cohort 4, up to 105 subjects maybe enrolled: Cohort 1: 30 subjects enrolled Cohort 2: 22 subjects enrolled Cohort 3: 13 subjects enrolled Cohort 4: 40 subjects expected
Target Population:	Four cohorts of subjects whose disease has not progressed on a previous study.
Duration of Treatment:	Subjects will continue on MMB for a duration of approximately 4 years from the start of this study or until study termination.
Diagnosis and Main Eligibility Criteria:	Inclusion Criteria <ul style="list-style-type: none">• Currently enrolled in study CCL09101E, or YM387-II-02, or successfully completed 24 weeks of study GS-US-352-1672.• Did not end treatment with MMB for any reason other than to enroll in this study• Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 at enrollment of this study• Negative serum or urine pregnancy test is required for female subjects (unless surgically sterile or greater than two years post-menopausal)• 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 5• Ability and agreement to attend protocol-specified visits at the study site• Any Grade 3 or 4 non-hematologic toxicity that the investigator considers related to previous MMB use must have resolved, reverted to Grade 1, or to baseline of the prior study prior to Day 1 of this study

- Able to comprehend and willing to sign the informed consent form

Exclusion Criteria

- Known hypersensitivity to MMB, its metabolites, or formulation excipients
- Incomplete recovery from major surgery prior to Day 1 of this study
- Presence of peripheral neuropathy \geq Common Terminology Criteria for Adverse Events CTCAE Grade 3
- Known positive status for human immunodeficiency virus (HIV)
Known chronic active or acute viral hepatitis A, B, or C infection

Study Procedures/ Frequency:

Procedures performed at a regular follow-up visit on subject's previous MMB study may be used to fulfill screening criteria and to establish any new medical history on this study.

At Day 1, the starting dose of MMB tablets will be determined per the criteria in protocol Section 5.3. All subjects will self-administer MMB tablets.

Subjects who have not undergone a bone marrow aspirate/biopsy within 12 months prior to Day 1 of this study will undergo a bone marrow biopsy. The bone marrow aspirate/biopsy will be repeated every 24 months and/or at the time of study withdrawal.

Study visits consisting of clinical, laboratory, and disease assessments will be completed every 3 months. Cohorts 1 and 2 will have 2 additional visits at Months 1 and 2. All study required laboratory assessments will be performed by Central laboratory and ECG assessments will be performed and interpreted by local departments. Following treatment, subjects will be followed for safety and disease status for a period of 30 days. Subjects who continue treatment with MMB in the extended access program following the end of this study are not required to complete the 30 day post-treatment follow-up assessments.

Test Product, Dose, and Mode of Administration:

MMB 100 mg, 150 mg, or 200 mg tablet orally self-administered once daily (QD).

Cohort 1 and Cohort 2 will be initiated on the tablet form of MMB according to the following table:

Previous Capsule Dose of MMB	Initial Tablet Dose of MMB
100 mg QD	100 mg QD
150 mg QD	100 mg QD
200 mg QD	150 mg QD
250 mg QD	150 mg QD
300 mg QD	200 mg QD
50 mg BID	100 mg QD
100 mg BID	150 mg QD
150 mg BID	200 mg QD
200 mg BID	200 mg QD

BID = twice a day; QD = once daily

Cohort 4 will continue the tablet form of MMB at the same dose they were receiving in study GS-US-352-1672.

Doses will be adjusted per Section 5.

Criteria for Evaluation:

Safety	The primary endpoint is safety. Safety will be evaluated by the incidence and severity of adverse events and clinical laboratory abnormalities, as defined by Common Terminology Criteria for CTCAE v4.03.
Efficacy	<p>Efficacy endpoints are considered secondary and will include:</p> <ul style="list-style-type: none"> • Overall survival (OS): defined as the interval from the first dose of MMB on the previous study until death from any cause • Progression-free survival (PFS): defined as the interval from the first dose of MMB on the previous study until the first documentation of definitive progressive disease or death from any cause • Leukemia free survival: defined as the interval from the first dose of MMB on the previous study until the first documented leukemic transformation or death from any cause • Rate of red blood cells (RBC) transfusion: defined as the average number of RBC units per subject month from the first dose of MMB in the previous study during the study period • Other cohort-specific endpoints
Pharmacokinetics:	None

Statistical Methods:

Analysis Methods

Full Analysis Set consists of all subjects who are enrolled into this study. This analysis set will be used in the analyses of subject characteristics, study drug treatment administration, safety and efficacy endpoints.

All study endpoints will be summarized by descriptive statistics. Descriptive summaries will be prepared to show sample size, mean, standard deviation (SD), 90% confidence intervals (CIs) on the mean, median, minimum and maximum for continuous variables and counts, percentages and 90% CIs on the percentage for categorical variables. Baseline data are defined as the data collected prior to dosing on the previous study. All time-to-event endpoints will be analyzed using the Kaplan-Meier method. The medians and 90% confidence intervals for medians of these endpoints will be provided if the medians can be estimated. Data will be analyzed according to the nominal visits.

AEs will be summarized by system organ class, high level term and preferred term. Clinical laboratory tests, vital signs, and their changes from baseline will be summarized descriptively.

Sample Size

No formal hypothesis testing is planned for this study. Up to 105 subjects who have previously participated in a Gilead clinical trial with MMB will be enrolled.

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
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
BCRP	breast cancer resistance protein
BID	twice a day
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CL _{cr}	creatinine clearance
C _{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CR	complete remission
CRF	case report form(s)
CRO	contract (or clinical) research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
DOR	duration of response
DSPH	Drug Safety and Public Health
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form(s)
ELN	European LeukemiaNet
EOT	end of treatment
ESDD	early study drug discontinuation
ET	essential thrombocythemia
EudraCT	European clinical trials database
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice (guidelines)
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product

IRB	institutional review board
IUD	intrauterine device
IWG	International Working Group
IWG-ELN	International Working Group-European LeukemiaNet
IWG-MRT	International Working Group for Myelofibrosis Response and Treatment
IXRS	interactive voice/web response system
LCM	left costal margin
M	month
mg	milligram
MMB	momelotinib
MPN	myeloproliferative neoplasm
MRI	magnetic resonance image
NOAEL	no observed adverse effect level
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PGIC	Patients' Global Impression of Change
PK	Pharmacokinetic
PMF	Primary Myelofibrosis
PR	partial remission
PRO	Patient-reported outcome
PV	polycythemia vera
QD	once daily
RBC	red blood cell
SAE	serious adverse event
SD	stable disease
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	An estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
US	United States
WBC	White blood cell

1. INTRODUCTION

1.1. Background

The myeloproliferative neoplasms (MPN), most notably polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) are a diverse but inter-related group of clonal disorders of pluripotent hematopoietic stem cells {[Tefferi 2008](#)}. The MPN share a range of biological, pathological, and clinical features including the relative overproduction of one or more cells of hematopoietic origin, growth factor independent colony formation in vitro, marrow hypercellularity, extramedullary hematopoiesis, spleno- and hepatomegaly, and thrombotic and/or hemorrhagic diatheses {[Tefferi 2005](#)}.

In early 2005, several research groups independently reported that a single acquired point mutation at codon 617 in JAK2 (V617F mutation), a cytoplasmic tyrosine kinase, was present in the majority of patients with the *BCR-ABL*-negative MPN (ie, PV, ET, and PMF) {[Baxter 2005](#)}, {[James 2005](#), [Kralovics 2005](#), [Levine 2005](#)}. Since then, additional JAK2 and thrombopoietin receptor (MPL) mutations have been described in PV and ET/PMF, respectively {[Pardanani 2007](#), [Pardanani 2006](#), [Pikman 2006](#), [Scott 2007](#)}. Studies have shown that these mutations cause cytokine independent activation of the JAK-STAT, PI3K, AKT, MAPK, and ERK pathways; all of which are implicated in erythropoietin (EPO) receptor signaling. The JAK2 V617F mutation leads to ongoing auto-phosphorylation of JAK2, which on binding to a cytokine receptor, promotes STAT recruitment and subsequent STAT phosphorylation {[James 2005](#)}. This mutation is the likely cause of the hypersensitivity to cytokines that characterizes hematopoietic progenitor cells (HPC) from each of the MPNs.

The occurrence of JAK2 mutations in the majority of patients with PV (almost 100%), ET (approximately 60%) or PMF (approximately 60%) has reinforced the putative oncogenic role of abnormal JAK-STAT signaling in these disorders {[Levine 2007](#)}. As a result, in less than 5 years from the first description of JAK2V617F {[Baxter 2005](#), [James 2005](#), [Kralovics 2005](#), [Levine 2005](#)}, small molecule JAK2 inhibitor drugs have been developed {[Pardanani 2008](#)} and approved {[DSM Pharmaceuticals Inc. 2011](#), [Novartis Pharma GmbH 2013](#)}. Results from these trials and subsequent approvals have demonstrated efficacy in amelioration of constitutional symptoms and reduction of splenomegaly {[Pardanani 2011](#)}.

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 molecular weight of 487.38 Da. The free base is poorly soluble in water. MMB is presented for clinical administration as a dihydrochloride monohydrate salt which 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.

MMB is a potent and selective small-molecule inhibitor of JAK1 and JAK2 in vitro enzyme and cellular assays, with marked disease-modifying properties in ex vivo assays of human erythroid cells from PV patients and in a transgenic mouse model of the MPN. In vitro enzyme assays demonstrated that MMB is an ATP-competitive inhibitor of JAK1 and JAK2 which is active at low nanomolar concentrations. Kinase profiling of MMB indicated that the compound is broadly selective for JAK1 and JAK2 over other kinase enzymes, including the closely related JAK3 and TYK2. MMB displays potent in vitro inhibitory activity against cells dependent on JAK2, including the JAK2V617F mutant which is associated with the etiology of PV and other MPNs.

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. Preclinical ADME and Pharmacokinetics (PK)

Equivalent mean maximal plasma concentrations of MMB (~ 700 ng/mL) and comparable elimination half-lives (~ 1 hour) 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 fed 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 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 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 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 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 CYP450 enzymes (CYP1A2, 2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5) to metabolize MMB was assessed with recombinant human CYP450 enzymes (Supersomes™). These in vitro studies demonstrated that MMB exhibits measurable metabolism by CYP3A4.

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 (IC₅₀) of MMB on the six CYP isoforms investigated (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was greater than 25 μM. IC₅₀ of MMB on CYP2B6 was 12.4 μM. No time dependent inhibition was observed for GS-0387 on CYP1A2 or CYP3A4. 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 IC₅₀ of 0.3 μM, but it is not clinically relevant as no clinically significant elevation of indirect (unconjugated) bilirubin has been reported in the PI/II clinical study.

The potential of major metabolites (M19 and M21) to impair the metabolism of other agents by inhibition of drug metabolizing enzymes has also been investigated. The IC₅₀ of MMB on the seven CYP isoforms investigated (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was greater than 25 μM. No time dependent inhibition was observed for M19 and M21 on CYP3A4. M19 and M21 did not show any activation of PXR.

The potential of MMB to inhibit the major drug transporters was studied in cells in which the individual transporters were over expressed and the MMB IC₅₀ for the transport of probe substrates was determined, where possible. 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 breast cancer resistance protein (BCRP) with an IC₅₀ 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. Mean arterial pressure was decreased at an oral dose of 30 and 100 mg/kg and heart rate was increased at 100 mg/kg.

Toxicological findings were principally related to the pharmacological action of the compound, as indicated by hematological and organ weight changes related to lymphatic and bone marrow tissues. A dose-dependent decrease in body weight gain, correlated with a dose-dependent decrease in food consumption, was observed in all studies and considered significant at high-dose levels in all studies except the 13-week dog study. Following very high exposure levels in the rat 28-day study, some off-target reversible toxicity was observed that included changes in the kidney, gastrointestinal tract, heart, and liver, of which none were observed in the rat 13-week study or the dog studies. Female reproductive changes were observed only at high doses in the rat 28-day study and were reversible. Dose-dependent testicular degeneration was observed in rats following 28 days or 13 weeks of repeated dosing. Recovery of testicular findings was dependent upon the cycle length of spermatogenesis with reversibility observed after a 10-week recovery period (13-week study) but not after a 28-day recovery period (28-day study). These changes were not observed above background levels in sexually mature dogs consistent with the role of JAK2 in maturation of the reproductive organs {Wu 2005}.

There were several effects observed that could not be readily attributed to JAK1/2 inhibition. This potential off-target toxicity was noted in the kidney, heart, and gastrointestinal tract of the rat, and gall bladder of the dog. All effects were reversible upon cessation of dosing.

In the 90-day oral rat toxicity study, based upon the significant loss of body weight at 80 mg/kg/day, the no observed adverse effect level (NOAEL) was determined as 20 mg/kg/day, with associated Day 91 AUC₀₋₂₄ values of 94,200 ng·h/mL in males and 102,000 ng h/mL in females. The C_{max} values in males and females on day 91 were 6720 and 7290 ng/mL, respectively.

In the 3-month dog study, the highest NOAEL was 60 mg/kg/day once daily. Associated AUC₀₋₁₂ values at the NOAEL on Day 91 were 4160 and 3220 ng·h/mL, respectively. The C_{max} values in males and females on day 91 were 1250 and 1150 ng/mL, respectively.

The plasma AUC_τ in subjects from Study CCL09101 at 300 mg capsule was 4.3 μg h/mL. Therefore, the margin of exposure for the 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.

Preliminary data from a dose range finding embryo-fetal developmental toxicity study in rats are available. MMB was orally administered to pregnant rats (7 to 8/group plus additional animals for TK evaluations) at 0 (vehicle), 4.3, 17, and 68 mg free base equivalents/kg/day

(5, 20, 80 mg/kg/day dihydrochloride salt) from gestation days 6 through 17. Based on the preliminary data, no maternal adverse effects and no embryo fetal adverse events (AEs) were observed at 4.3 mg/kg/day. Maternal toxicity was observed at 17 and 68 mg/kg/day. At these maternally toxic doses, MMB administration resulted in embryo fetal effects (increase in post implantation loss resulting in a reduced number of viable fetuses). No viable fetuses were obtained at 68 mg/kg/day. At 17 mg/kg/day, there was an increase in the percentage of litters with absent innominate artery. The toxicokinetic data is not yet available from this study. Based on the data from non-pregnant female rats, the mean systemic exposure (AUC_{0-24}) at the NOAEL is 4-fold higher than the systemic exposure observed in patients administered 300 mg MMB, the maximum recommended dose (MRD). The exposure of MMB in non-pregnant rats at 17 mg/kg/day, the current minimum effect level, is approximately 23 fold higher than the MRD.

The metabolism of MMB could result in the release of cyanide via metabolite CYC-11384. While theoretically possible, the in vitro metabolite profiling studies indicate minimal conversion to CYC-11384 (and the consequent liberation of aminoacetonitrile and cyanide). In addition, during the first 9 cycles of MMB treatment in the CCL09101 study, elevations above the population-based reference ranges which reflect ordinary dietary, occupational and environmental exposure to cyanide were observed in 11 subjects (7%). In the majority of these cases, values were borderline elevations above the reference range and in no case did thiocyanate values ever approach the toxic range. In addition, available data from the extension portion of the study (CCL09101E), which includes observation to a maximum of 30 months of dosing, continue to demonstrate an absence of significant thiocyanate elevations, with only one additional subject with a minor elevation above the reference range.

The lack of significant drug-induced thiocyanate generation is further strengthened by preliminary thiocyanate data collected to 6 months of dosing in the ongoing study YM387-II-02, where subjects are treated with higher daily MMB doses in a twice daily dosing regimen. These results are consistent with current observations from the core study with only 1 of 42 subjects (2%) experiencing a minimal elevation above the reference range.

Together, these clinical findings in a comparatively large number of MF subjects indicate that any drug-induced thiocyanate generation over the extended MMB dosing period is relatively insignificant in comparison with exogenous environmental cyanide exposure and based on the currently available data does not appear to compromise the very favorable clinical activity and chronic tolerability of the compound.

A more detailed summary of findings from the nonclinical studies is available in the current 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.

1.3. Rationale for This Study

MMB displays potent in vitro inhibitory activity against cells dependent on JAK2, including the JAK2V617F mutant which is associated with the etiology of PV and the other MPNs. It has been shown to potently inhibit JAK2 signaling and the formation of JAK2V617F mutant myeloid colonies in a dose-responsive manner (IC_{50} = 0.3 μ M and 1 to 2 μ M, respectively), suggesting potential activity for the compound in these disease settings.

MMB demonstrated activity in vivo in JAK2-dependent models. In a study investigating the effects of twice daily administered MMB (25 and 50 mg/kg) in a transgenic mouse model of the JAK2-mediated human MPN there was significant reduction of leukocyte count into the normal range within 1 week of dosing and reduction of erythrocytosis after 6 weeks of dosing. After 56 days of dosing, the average spleen size was significantly reduced in a dose-dependent manner, extra-medullary hematopoiesis was reduced, and normal erythrocytosis was being re-established in the bone marrow compartment.

Based on the analysis of clinical study CCL09101 and its extension study CCL09101E, with a data cutoff date of April 2013, subjects continued to obtain clinical benefit from treatment with MMB with duration of follow-up on-study ranging from 15 to 34 twenty-eight-day cycles. Clinical benefit was demonstrated by durable decreases in spleen size, anemia response, and improved symptoms. Fifty seven (32.4%) of the spleen evaluable subjects achieved a spleen response with a median duration of response of 323.5 days.

Another benefit of MMB was an improvement in anemia related outcomes with a decrease in the rate of transfusion dependence and increased hemoglobin. Forty-three (60%) of the transfusion dependent subjects achieved a transfusion independence response per International Working Group for Myelofibrosis Response and Treatment (IWG-MRT) criteria that lasted at least 12 weeks (Gale criteria) {[Gale 2011](#)}. Eight of the transfusion independent, but anemic subjects (20%) achieved a hemoglobin increase of at least 2 g/dL with a minimum duration of at least 8 weeks. The maximum duration of anemia response has approached 3 years.

MMB administration appears to have been well tolerated overall and with prolonged administration in the extension study. Most of the treatment-emergent AEs were reported as Grade 1 or mild. The most commonly reported treatment-emergent AEs were thrombocytopenia, diarrhea, anemia, dizziness, peripheral neuropathy, and abnormalities in liver/pancreas-related lab values, and elevated uric acid lab values. As of April 2013, 28 deaths (16 during the 9 month core and 12 during the extension) were reported; however, none of these deaths were reported as treatment-related.

At the initial dose escalation phase of the YM387-II-02 study, although no dose limiting toxicities were observed, 250 mg twice daily (BID) was not well tolerated and 200 mg BID was the dose level chosen for the dose confirmation phase. Preliminary results of the YM387-II-02 study, as of a data cut off of 3 September 2013, demonstrated similar safety, tolerability, and efficacy to the once daily dosing (n = 61). Clinical splenic responses in this study have been evaluated by physical examination demonstrating a 66.0% spleen response rate by 2006 IWG-MRT (n = 50 with spleen > 5 cm at baseline) which lasted at least 8 weeks.

Magnetic resonance imaging (MRI) evaluation of spleen response was also obtained at 6 months in the 58 subjects who had not undergone a previous splenectomy, demonstrating a 46.6% spleen response ($\geq 35\%$ reduction in spleen volume by MRI). Of the 28 subjects who were transfusion dependent at baseline, 28.6% (n = 8) achieved a 12-week transfusion independent response.

The encouraging nonclinical data coupled with the common occurrence of JAK2 pathway aberrations in patients with MPN and a known contribution of the JAK2V617F mutation to various phenotypes of these disorders render the JAK2 pathway an attractive and relevant target for drug development in other related MPNs such as PV and ET.

The purpose of this extension study is to continue to collect long-term safety, tolerability, and efficacy data from subjects with MPNs who have received a clinical benefit from treatment with MMB on a Phase 2 clinical trial.

1.3.1. Dose Justification

The starting MMB dose for each subject in this study will correspond to the dose which the subject tolerated and which provided clinical benefit in their parent study. The maximum dose of 200 mg was selected based on PK results from Study GS-US-352-0102, which compared the relative bioavailability of the tablet vs capsule. Dose reductions will be allowed on this study if clinically indicated (Section 5.3.3).

PK results from Study GS-US-352-0102 indicate the 200 mg tablet results in equivalent exposure (AUC and C_{max}) as the 300 mg capsule as shown in Table 1-1.

Table 1-1. Preliminary Data on the Relative Bioavailability of MMB Tablet vs Capsule

PK Parameters	200 mg Tablet: Mean (standard deviation)	300 mg Capsule: Mean (standard deviation)	GMR [%] (90% CI)
C_{max} (ng/mL)	324 (188)	356 (196)	92.0 (79.0, 107)
AUC_{inf} (h·ng/mL)	2570 (1670)	2670 (1990)	102 (87.7, 118)
AUC_{last} (h·ng/mL)	2340 (1510)	2440 (1740)	101 (86.8, 116)

The reduced MMB tablet doses of 150 mg and 100 mg represent 25% and 50% dose reductions, respectively, compared to the starting tablet dose of 200 mg which provided equivalent exposures to the MMB 300 mg capsule. Based on the PK results from Study GS-US-352-0102, 150 mg and 100 mg tablets resulted in ~70% and ~50% of MMB exposures (AUC_{inf} and C_{max}) compared to the 300 mg capsule. These reduced tablet doses of MMB are still expected to provide efficacy based on previous dose-response analyses, where robust spleen response was observed at average daily MMB capsule dose of $\geq \sim 150$ mg.

1.4. Compliance

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

1.5. Other Relevant Clinical Information

A recent clinical trial of the JAK2 inhibitor fedratinib (SAR302503) in myelofibrosis was halted due to reported cases of Wernicke's encephalopathy. There has been one case of suspected Wernicke's encephalopathy reported in clinical trials with MMB in subjects with myelofibrosis. Peripheral neuropathy has also been reported as an adverse event. Based on these data, thiamine status will be monitored throughout the duration of the study treatment.

2. OBJECTIVES

The primary objective of this study is to determine the long-term safety and tolerability of MMB in 4 cohorts of subjects:

- Cohort 1: Subjects who are currently receiving MMB capsules in the CCL09101E study for PMF and post-PV/ET MF without documented progressive disease
- Cohort 2: Subjects who are currently receiving MMB capsules in the YM387-II-02 study for PMF and post-PV/ET MF without documented progressive disease
- Cohort 3 was closed and all enrolled subjects were discontinued from this study due to limited efficacy of MMB in the treatment of PV and ET on GS-US-354-0101.
- Cohort 4: Subjects who are currently receiving MMB tablets in the GS-US-352-1672 study for PMF and post-PV/ET MF, who completed 24 weeks of treatment and have responded to treatment, per investigators discretion.

The secondary objective of this study is to determine the long-term efficacy of MMB in these 4 cohorts of subjects.

3. STUDY DESIGN

3.1. Endpoints

The endpoints for this study are described in Section 8.

3.2. Study Design

This is an open-label study for subjects with MF, post-PV/ET MF, PV or ET, who have tolerated MMB and their corresponding disease has not progressed per 2006 IWG-MRT for MF ([Appendix 3](#)) or 2013 IWG-ELN and IWG-MRT criteria for PV/ET ([Appendix 4](#)) while enrolled in the previous study. After screening, subjects in Cohorts 1 and 2 will discontinue the MMB capsule and initiate the tablet form of MMB. Subjects in Cohort 4 will discontinue MMB tablets from the previous study and initiate MMB tablets in this study at the same dose they were receiving in the previous study. Dose adjustments may be made according to Section 5.3.

3.3. Study Treatments

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

3.4. Duration of Treatment

Subjects may participate in this study for approximately 4 years or until study termination.

3.5. Discontinuation Criteria

The study may be discontinued at any time based on periodic reviews of safety 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 voice/web response system (IXRS) is considered source.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Based on the number of enrolled subjects to date in Cohorts 1, 2, and 3, including the number of expected subjects in Cohort 4, up to 105 subjects (30 from Cohort 1, 22 from Cohort 2, 13 from Cohort 3, and approximately 40 from Cohort 4) may participate in this trial.

4.2. Inclusion Criteria

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

- Currently enrolled in study CCL09101E, YM387-II-02, or successfully completed 24 weeks of study GS-US-352-1672.
- Did not end treatment with MMB for any reason other than to enroll in this study
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 at enrollment of this study
- Negative serum or urine pregnancy test is required for female subjects (unless surgically sterile or greater than two years post-menopausal)
- 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 5](#)
- Ability and agreement to attend to protocol-specified visits at the study site
- Any Grade 3 or 4 non-hematologic toxicity that the investigator considers related to previous MMB use must have resolved, reverted to Grade 1, or returned to baseline on the prior study prior to Day 1 of this study
- Able to comprehend and willing to sign informed consent form

4.3. Exclusion Criteria

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

- Known hypersensitivity to MMB, its metabolites, or formulation excipients
- Incomplete recovery from major surgery prior to Day 1 of this study

- Presence of peripheral neuropathy \geq Common Terminology Criteria for Adverse Events (CTCAE) Grade 3
- Known positive status for human immunodeficiency virus (HIV)
- Known chronic active or acute viral hepatitis A, B, or C infection

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment and Treatment Assignment

Subjects will be enrolled via IXRS based on their dose on the previous study.

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 100 mg tablets are round-shaped, film-coated, brown tablets, MMB 150mg are round or triangle-shaped, film-coated, brown tablets, and MMB 200 mg tablets, 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.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

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

Until dispensed to the subjects, all MMB bottles should be stored in a securely locked area, accessible only to authorized site personnel. To ensure stability and proper identification, the drug products should be stored in the containers in which they are supplied.

5.3. Dosage and Administration of MMB

5.3.1. Starting Dose

Subjects will self-administer MMB tablets at 100 mg, 150 mg, or 200 mg orally once-daily.

Cohorts 1 and 2 will initiate the tablet form of MMB according to [Table 5-1](#).

Table 5-1. Starting Dose of MMB Cohorts 1 and 2

Dose of Capsule	Initial Dose of Tablet
100 mg QD	100 mg QD
150 mg QD	100 mg QD
200 mg QD	150 mg QD
250 mg QD	150 mg QD
300 mg QD	200 mg QD
50 mg BID	100 mg QD
100 mg BID	150 mg QD
150 mg BID	200 mg QD
200 mg BID	200 mg QD

BID = twice a day; QD = once daily

For Cohorts 1 and 2 the starting dose will be assigned by first determining the tablet dose corresponding to the capsule dose the subject was receiving prior to drug interruption using [Table 5-1](#). The reduced dose can then be determined using [Table 5-3](#).

Cohort 4 will continue the tablet form dose of MMB they were previously receiving in study GS-US-352-1672. If a toxicity requiring drug interruption during participation in GS-US-352-1672 persists for longer than a total of 30 days from the last MMB administration to Day 1 of this study, subjects will not be eligible to participate on study in Cohort 4 and will be considered screen failures. Subjects in screening on a drug hold < 30 days whom the investigator believes that the toxicity has resolved and that they can join Cohort 4 must seek consultation with the study Medical Monitor.

5.3.2. Dose Increase Based on Response

Cohorts 1 and 2

If, per the investigator's judgment, there is evidence of insufficient efficacy that does not meet the criteria of 2006 IWG-MRT for Progressive Disease ([Appendix 3](#)), and platelet, and neutrophil counts are adequate, the MMB dose may be increased in 50 mg increments once-daily to a maximum of 200 mg or 300 mg per day depending on the dosing schedule a subject was on in the prior study, in accordance with the following criteria. The MMB dose may not be increased after it is reduced due to a Grade 3 or 4 toxicity that the investigator considers related to MMB or after a switch to twice-daily dosing (if applicable- Cohorts 1 and 2 only). The MMB dose may not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks.

Insufficient efficacy and adequate platelet and neutrophil counts are described as follows:

- Insufficient efficacy: Insufficient efficacy is defined as an increase in palpable spleen length from the lower of baseline spleen length of the previous study (Study CCL09101 or YM387-II-02), or nadir of spleen length while on treatment during the previous study (Study CCL09101 or YM387-II-02) or the current study (Study GS-US-352-1154), but has not met the criteria for progressive disease. Refer to [Appendix 3](#) for IWG-MRT treatment response criteria.
- Adequate platelet and neutrophil :
 - Platelet count $\geq 25 \times 10^9/L$
 - Absolute neutrophil count (ANC) $\geq 0.75 \times 10^9/L$

Subjects, in Cohorts 1 and 2 only, who were receiving a twice-daily regimen of MMB in the 30 days immediately prior to enrollment in this study will be permitted to resume a twice-daily regimen per [Table 5-2](#) if they meet the above criteria for insufficient efficacy and adequate platelet and neutrophil counts. These subjects may only resume a twice-daily regimen if they are receiving 200 mg once daily or if they were reduced to 150 mg once daily after receiving 200 mg once daily in this study. For subjects resuming twice-daily dosing at 100 mg twice daily, dose increase to 150 mg twice daily is not permitted.

Cohort 4

Cohort 4 subjects may not dose increase.

Table 5-2. Dose Adjustments of MMB from a Once-daily to a Twice-daily Regimen

Dose at time of Adjustment	Adjusted Dose Regimen
100 mg QD	Not permitted
150 mg QD	100 mg BID
200 mg QD	150 mg BID

5.3.3. Dose Reductions and Rules for Interrupting MMB

Grade 3 or 4 Drug-related Non-hematologic Toxicities

In the event of a Grade 3 or 4 non-hematologic toxicity that the investigator considers related to MMB, dosing will be interrupted for a maximum of 30 days, inclusive of taper, until the toxicity resolves or returns to levels at enrollment. Additionally, dosing will be interrupted for any bleeding event of a Grade ≥ 2 or neuropathy Grade ≥ 3 . Treatment may be restarted within 30 days per [Table 5-3](#) (MMB). If the toxicity persists beyond 30 days, treatment may be restarted contingent on sponsor approval.

For any toxicity that does not meet the above criteria and the investigator considers related to MMB and is clinically significant, MMB may be interrupted for a maximum of 30 days until the toxicity resolves \leq Grade 1 or baseline, or permanently reduced as per [Table 5-3](#).

Table 5-3. 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*
150 mg BID	100 mg BID
100 mg BID	Permanently Discontinue treatment

QD = once daily, BID=twice daily

* If Grade 3 or 4 toxicity recurs after restarting MMB, treatment will be permanently discontinued.

Other Toxicities

Treatment may be interrupted at the investigator's discretion for up to 30 days, inclusive of taper, for any other toxicity. If the toxicity persists beyond 30 days, treatment may be restarted upon sponsor approval. Treatment may be restarted at the dose the subject was taking prior to interruption or at a reduced dose per [Table 5-3](#), at the investigator's discretion.

5.3.4. Discontinuing or Interrupting Treatment

When discontinuing or interrupting treatment, MMB may be reduced to 100 mg once daily for 1 week prior to stopping treatment, at the choice of the investigator. Treatment may be re-started at 100 mg once daily for subjects receiving 100 mg once daily, however if the same Grade 3 or 4 MMB-related toxicity recurs at the 100 mg once daily dose, MMB will be permanently discontinued.

5.4. Concomitant Medications

5.4.1. Proscribed Medication

The following are proscribed unless sponsor approval is obtained:

- Chemotherapy
- Immunomodulators
- Systemic corticosteroids (local topical, otic, nasal, ophthalmic, or inhaled corticosteroids are permitted)
- Hydroxyurea

- Anagrelide
- Androgen for the treatment of myelofibrosis
- Interferon
- JAK inhibitors other than the MMB administered in this trial
- Experimental therapy other than the MMB administered in this trial
- Erythropoiesis stimulating agents
- Granulocyte Colony Stimulating Factor (G-CSF) unless administered for the treatment of neutropenic fever
- Thrombopoietins
- Any other investigational treatment or procedure

5.4.2. Restricted Medications

CYP3A4 Inhibitors/Inducers

- 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

5.4.3. 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, where appropriate, dose modification or alternative medications as clinically appropriate may 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 Investigator Brochure 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.
- Record the date, subject number, and the MMB bottle number dispensed.
- Record the date, quantity of used and unused MMB returned, along with the initials of the person recording the information.

The methods of MMB return and destruction are described in Section [9.1.7](#).

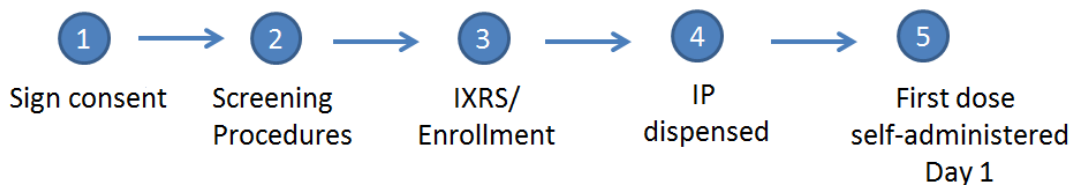
6. STUDY PROCEDURES

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. Additional information is provided in the study procedures manual.

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

The initial study procedures to be conducted for each subject enrolled in the study are presented in [Figure 6-1](#).

Figure 6-1. Initial Study Procedures



- Steps 1 through 5 may occur on the same or different days, but must occur sequentially
- The maximum amount of time allowed from step 1 to step 5 is 30 days
- Results from laboratory assessments and procedures performed up to 30 days prior to step 5 (eg, results from procedures performed during the previous study or as part of the subject's routine care (if documentation is available) may be utilized for determining eligibility)

6.1. Subject Enrollment and Treatment Assignment

A subject will be considered enrolled once enrolled in IXRS. It is the responsibility of the investigator to ensure that each subject is eligible for the study before enrollment. Details regarding treatment assignment and dosing are in [Section 5.3](#).

6.2. Study Procedure Description

6.2.1. Obtain Written Informed Consent

All subjects must personally sign and date the institutional review board / independent ethics committee (IRB/IEC) approved informed consent form before any study procedures are performed ([Section 9.1.3](#)).

6.2.2. Recording Medical History

Medical history from the previous study will not be reported in the electronic case report form (eCRFs) for this study. Any ongoing AE from the previous study at the time of enrollment in this study will be considered medical history on this study and should be reported in the eCRFs and followed to resolution.

6.2.3. Medication History

A current list of ongoing medications will be obtained prior to enrollment and recorded on the eCRF.

6.2.4. Physical Examination and Symptom Assessment

At all study visits, the physical examination will be an interim examination to monitor for any changes and will include vital signs, weight, clinical signs, 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. Weight should be collected with the subject standing without shoes.

6.2.5. Vital Signs

Vital signs will include pulse, systolic and diastolic blood pressure, and body temperature. They should be collected per institutional guidelines.

6.2.6. Electrocardiogram

A single 12-lead ECG will be collected at each applicable study visit per guidelines. ECGs will be read locally and the results will be reported in the eCRFs. The investigator will review all ECGs and retain the tracing with the source documents. Following completion of a thorough QT study and a review of cardiovascular-related events, ECG monitoring may be discontinued in this study.

6.2.7. Ophthalmic Examination

An eye exam will be performed to assess for cataracts and visual acuity. All assessments will be performed in accordance with standard practice.

6.2.8. Laboratory Assessments

All samples collected in this study for laboratory assessments will be sent to the central laboratory with the exception of urine pregnancy test which will be completed at the site. Screening laboratory samples should be obtained within 30 days prior to the first dose of MMB taken on this study. Local laboratory CBC assessments may be collected for dose adjustments throughout the study.

The central laboratory will be responsible for chemistry, CBC, coagulation, urinalysis, and serum pregnancy testing per Table 6-1. 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 to the central laboratory.

Table 6-1. Analytes

Chemistry	Urinalysis	Hematology and Coagulation	Other Analytes
Albumin			
Alkaline phosphatase			
ALT			
AST			
Amylase		RBC	
Bicarbonate	Color and appearance	Hemoglobin	
BUN	Specific gravity	Hematocrit	
Calcium	pH	Platelets	
Chloride	Occult blood	WBC	
Creatinine ^a	Protein	Differential	
GGT	Glucose	Neutrophils	
Glucose	Bilirubin	Bands/stabs	Serum beta hCG ^b
LDH	Leukocyte esterase	Eosinophils	Thiamine status
Lipase	Ketones	Basophils	
Magnesium	Nitrite	Lymphocytes	
Phosphorus	Urobilinogen	Monocytes	
Potassium	Microscopic ^c	% blasts	
Sodium	Urine beta hCG ^b	ANC	
Total bilirubin		PT (INR)	
Direct bilirubin		PTT	
Total protein			
Uric acid			

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = gamma-glutamyl transpeptidase; LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell; hCG=human chorionic gonadotropin
 Note: Additional components, abnormal, and/or atypical cells will also be reported if present

- a Estimated creatinine clearance/glomerular filtration rate will be calculated based on the Cockcroft-Gault formula
- b If applicable and either urine or serum HCG is acceptable
- c Reflex testing based on other abnormalities

6.2.9. Patient-reported Outcomes Assessments (PRO)

PRO assessments completed at study visits should be completed prior to any other visit assessments on the visit day.

The Patients’ Global Impression of Change (PGIC) will be used to assess patient reported outcome.

The PGIC is a single-item questionnaire to assess change in patient status over time. The questionnaire will be completed at each visit.

6.2.10. Disease Assessment

6.2.10.1. Treatment Response Assessment

Cohorts 1, 2, and 4

Treatment response for Cohorts 1, 2, and 4 will be assessed using the 2006 IWG criteria for treatment response in myelofibrosis ([Appendix 3](#)). The criteria classify treatment response based on laboratory (eg, bone marrow histology, hematology), physical examination (eg, splenomegaly), and symptoms assessments. Spleen and liver assessments will not require radiographic confirmation.

6.2.10.2. Bone Marrow Aspirate and Biopsy

Bone marrow aspirate/biopsy samples will be assessed by a local hematopathologist for grading of bone marrow fibrosis. Unstained slides should be made available to the sponsor for central review, if requested. Grading of bone marrow fibrosis will include assessments of reticulin (eg silver stain) and collagen fibrosis (eg, trichrome stain). Results from assessment of bone marrow aspirate/biopsy samples obtained as part of the subject's routine medical care may be used if the documentation is available.

6.2.10.3. Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance status is an investigator assessment of the impact of the disease on the subject's activities of daily living. It is assessed on a 6-point scale as described in [Appendix 6 {Oken 1982}](#).

6.2.10.4. Transfusion Recording

Subjects in all cohorts will record transfusion events in a diary throughout the study. The diary will include instructions for the transfusion clinic to provide the date, type (eg, whole blood, packed cells), and number of units of the transfusion. Transfusion events which occur prior to Day 1 of this study will be reported on the appropriate eCRF page for the previous study. Transfusion events which occur after administration of the first dose of MMB on this study will be reported on the transfusion eCRF for this study. The hemoglobin value at the time of the transfusion will be reported on the eCRF as an observational component of the study.

6.3. Pretreatment Assessment

6.3.1. Screening Visit/Enrollment

The screening date will be defined as the date the subject signs the informed consent form (ICF). Results from procedures performed within 30 days prior to Day 1 may be used to determine eligibility for this study and receiving drug. The maximum time allowed between consenting and the first dose of MMB on this study is 30 days. The following will be performed or documented at screening:

- Informed consent
- PGIC

- Current medications
- Physical examination and symptoms assessment
- Vital signs
- Single 12-lead ECG
- ECOG performance status
- Bone marrow aspirate/biopsy (not required if previously completed within 12 months of first dose of MMB on this study and the data are available for reporting to the eCRF)
- Laboratory assessments and blood sampling
 - Chemistry
 - Thiamine status
 - Complete Blood Count (CBC) and differential
 - Coagulation
 - Urinalysis
 - Serum or urine pregnancy test, if applicable
- Transfusion recording

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will discontinue the MMB received for their previous study and start their assigned dose of MMB tablets for this study.

If the MMB received per the previous study is held due to toxicity during the screening period the subject may delay screening for up to 30 days from the End of Treatment (EOT) visit on their previous study as long as all enrollment criteria are met.

6.4. Treatment Assessments

6.4.1. Months 1 and 2 (Cohorts 1 and 2 only)

As all subjects in Cohorts 1 and 2 are transitioning from MMB capsules to tablets and some subjects are transitioning from twice-a-day to once-daily dosing, 2 additional study visits at Months 1 and 2, within a window of ± 7 days, will evaluate dose adjustments based on tolerance and response. The following will be completed at these visits:

- Physical examination and symptoms assessment
- Vital signs

- Single 12-lead ECG
- Laboratory assessments and blood sampling
 - Chemistry
 - Thiamine status (Repeat if sample was not able to be analyzed during Screening/Enrollment visit)
 - CBC and differential
- Transfusion recording
- Response assessment
- AEs and concomitant medications
- MMB accountability and dispensing

6.4.2. Months 3 to Early Study Drug Discontinuation (ESDD) visits or End of Study

On-study visits during this period will occur every 3 months within a window of ± 7 days. The following procedures will be completed at each visit, unless otherwise specified.

- PGIC
- Physical examination and symptoms assessment
- Vital signs
- Single 12-lead ECG
- Laboratory assessments and blood sampling
 - Chemistry
 - Thiamine status
 - CBC and differential
 - Coagulation
 - Urinalysis
 - Urine pregnancy test

- ECOG performance status
- Transfusion recording
- Response assessment
- Bone marrow aspirate/biopsy (Months 24 and 48 only)
- Ophthalmic Examination (Month 6, 12 and annually thereafter and at the Month 48/ESDD visit if not done within the previous 6 months)
- AEs and concomitant medications
- MMB accountability and dispensing

6.5. Unscheduled visits

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

6.6. Post-treatment Follow-up Assessments

A safety follow-up visit is required for subjects at approximately 30 days after ending treatment. Subjects who continue treatment with MMB in the extended access program following the end of this study are not required to complete the 30 day post-treatment 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:

- PGIC
- Physical examination and symptoms assessment
- Vital signs
- Single 12-lead ECG
- ECOG performance status
- Laboratory assessments
 - Chemistry
 - Thiamine Status
 - CBC and differential

- Coagulation
- Urinalysis
- Urine pregnancy test
- Transfusion recording
- AEs and Concomitant medications

6.7. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.6). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

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
- 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 5](#)
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

6.9. End of Study

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. End of study for a subject is defined as the date of the last study-related procedure or protocol-defined follow-up contact.

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 pharmaceutical 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 AE and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the first dose of MMB on the previous study, are considered medical history. If they occurred during the previous study, prior to the first dose of MMB on this study, but have not resolved, they are considered medical history on this study
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) or serious adverse drug reaction (SADR) 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 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 by the investigator will not be considered SAEs:

Cohorts 1, 2, and 4:

- Progression of MF (including leukemia)
- Death related to progression of MF (per IWG criteria)
- Death related to MF (not meeting IWG criteria for disease progression)

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 Study Drug 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 AE has an etiology other than the MMB. 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 (IMP).

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE 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 AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures, (eg, venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the 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. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in [Section 7.1.2](#).

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

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 CRF/eCRF database.

All AEs resulting from protocol-associated procedures must be reported to the CRF/eCRF database as instructed, starting from the time the subject first consents to participate in the study and throughout the duration of the study.

All AEs, regardless of cause or relationship, that occur from the first dose of MMB in this study until 30 days after the last administration must be reported to the eCRF database as instructed.

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.

All AEs should be followed up until resolution if possible. If by the last day on study (including the off-study medication follow-up period) the AE has not resolved, then the AE will be followed up until the investigator and/or Gilead Sciences determine that the subject's condition is stable. However, Gilead Sciences may request that certain AEs be followed until resolution.

Investigators are not obligated to actively seek SAEs after the post-treatment follow-up period or 30 days after the last dose of MMB (whichever is later). 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 or to the designated CRO.

- All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.
- SAEs will be reported using an electronic SAE (eSAE) system. Gilead will provide training and account information.

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 SAE reporting form and submit within 24 hours as described above.

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 CRF/eCRF database within the timelines outlined in the CRF/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, SADR, 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 IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the IRB or IEC 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. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to MMB interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE Version 4.03 except for anemia (hemoglobin) which will be graded using the CTCAE Version 3.0 as defined in [Table 7-2](#).

Table 7-2. Grading of Hemoglobin Severity

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

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.6. Toxicity Management

Dosing requirements for certain toxicities are specified in Section 5.3.4. The investigator may contact the medical monitor to review toxicities that are not directly discussed in the protocol. Laboratory abnormalities (eg, thiamine deficiency) 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, lack of effect reports, and pregnancy reports regardless of an associated AE. Also includes reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints and reports arising from occupational exposure.

A pregnancy report is used to report any pregnancy following maternal or paternal exposure to the medicinal product.

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 or 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 all pregnancies that are identified after the subject first consents to participate in the study (ie, signs the informed consent) and throughout the study, including the post study drug follow-up period, to the Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Refer to Section 7.3 and the CRF/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 7.1.1 and 7.1.2. 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 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. 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 or 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.

Refer to [Appendix 5](#) for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations.

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 the designated CRO or Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve MMB, but do not apply to concomitant medications. Except for situations that result in AEs, special situations involving concomitant medications will not be reported. Any inappropriate use of medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF/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 long term safety and tolerability of momelotinib (MMB) in 4 cohorts of subjects:

- Cohort 1: Subjects who are currently receiving MMB capsules in the CCL09101E study for PMF and post-PV/ET MF without documented progressive disease
- Cohort 2: Subjects who are currently receiving MMB capsules in the YM387-II-02 study for PMF and post-PV/ET MF without documented progressive disease
- Cohort 3 was closed and all enrolled subjects were discontinued from this study due to limited efficacy of MMB in the treatment of PV and ET on GS-US-354-0101.
- Cohort 4: Subjects who are currently receiving MMB tablets in the GS-US-352-1672 study for PMF and post-PV/ET MF without documented progressive disease.

The secondary objective of this study is to determine the long-term efficacy of MMB in these 4 cohorts of subjects.

8.1.2. Primary Endpoints

The primary endpoint is safety. Safety will be evaluated by the incidence and severity of adverse events and clinical laboratory abnormalities, as defined by CTCAE v4.03.

8.1.3. Secondary Endpoints

The secondary endpoints are all efficacy-related endpoints and no analyses/summaries of efficacy endpoints will be performed for Cohort 3 subjects as Cohort 3 was closed and all enrolled subjects were discontinued from this study due to limited efficacy of MMB in the treatment of PV and ET on study GS-US-354-0101.

Secondary endpoints are:

- **Overall survival (OS):** defined as the interval from the first dose of MMB on the previous study until death from any cause
- **Progression-free survival (PFS):** defined as the interval from the first dose of MMB on the previous study until the first documentation of definitive progressive disease or death due to any cause
 - **Progressive Disease (Cohorts 1 and 2)** defined as ([Appendix 3](#)):
 - Leukemic transformation confirmed by a bone marrow blast count of $\geq 20\%$, OR

- Peripheral blood blast count of $\geq 20\%$ associated with an absolute blast count of $\geq 1 \times 10^9 /L$ that lasts for a at least 8 weeks, OR
- Progressive splenomegaly defined as:
 - Appearance of new splenomegaly that is palpable > 5 cm below the left costal margin (LCM), OR
 - A $\geq 100\%$ increase in palpable spleen length below LCM, for baseline palpable splenomegaly of previous study that measured >5 and <10 cm below LCM, OR
 - A $\geq 50\%$ increase in palpable spleen length below LCM, for baseline splenomegaly of previous study that measured ≥ 10 cm below LCM
- **Leukemia-free survival:** defined as the interval from the first dose of MMB on the previous study until the first documented leukemic transformation or death from any cause
- **Rate of RBC transfusion:** defined as the average number of RBC units per subject month from the first dose of MMB on the previous study during the study period

Other secondary endpoints specific to Cohorts 1 and 2:

- **Duration of splenic response:** defined as the interval from the first onset of splenic response (in the previous study or this study) to the earliest date of loss of splenic response which persists for at least 4 weeks or death from any cause. Splenic response is defined as $> 50\%$ reduction in palpable splenomegaly of a spleen that is ≥ 10 cm below the LCM at baseline or a spleen that is palpable at > 5 cm below the LCM at baseline becomes not palpable.
- **Duration of transfusion independence response:** defined as the interval from the first onset date of transfusion independence (in the previous study or this study) to the earliest onset date of transfusion dependence or death from any cause, among those subjects who are transfusion dependent at baseline. Transfusion independence is defined as absence of RBC transfusions for ≥ 12 weeks.
- **Duration of anemia response:** defined as the interval from the first onset of anemia response (in the previous study or this study) to the earliest date of loss of anemia response which persists for at least 4 weeks or death from any cause. Anemia response is defined as $\geq 2g/dL$ increase in hemoglobin for baseline transfusion independent subjects with baseline hemoglobin level of $< 10g/dL$, or becoming transfusion independent for those who were transfusion dependent at baseline for ≥ 12 weeks.

Secondary endpoints specific to Cohort 4 are:

- **Transfusion response rate:** defined as becoming not transfusion dependent for ≥ 12 weeks at any time from the first dose of MMB on the previous study until end of this study.

8.1.4. Exploratory Endpoints

Exploratory endpoints are:

- Change in hemoglobin level over time
- Change in patient global impression of change (PGIC) over time

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Full Analysis Set

The Full Analysis Set consists of all subjects who are enrolled into this study. The Full Analysis Set will be used for demographic and baseline characteristics, medical and disease history, study treatment administration and compliance, and efficacy and safety analyses.

8.3. Data Handling Conventions

Unless otherwise specified, data will be summarized and analyzed by each cohort separately. Within each cohort, data will be summarized by the initial dose in the parent study (CCL09101 for Cohort 1).

In general, the baseline value used in each analysis will be the baseline defined in the previous study. 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.

Unless otherwise specified, all analyses will be 2-sided at the 0.1 level of significance.

The following censoring conventions will be applied for time-to-event endpoints:

- Duration of response: Data from subjects who remain response will be censored at the date of last visit.
- Progression-free survival: Data from surviving, non-progressing subjects will be censored at the last adequate response assessment date prior to the initiation of myelofibrosis (Cohorts 1, 2, and 4) treatment other than MMB or the last time that lack of definitive progression was objectively documented.
- Overall survival: Data from surviving subjects will be censored at the date of last contact.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized using standard descriptive methods. Demographic summaries will include sex, race/ethnicity, and age.

8.5. Efficacy Analysis

There is no primary efficacy endpoint in this study. Safety summaries will be generated to evaluate the primary objective. There will be no efficacy analyses for Cohort 3 subjects as Cohort 3 was closed and all enrolled subjects were discontinued from this study.

8.5.1. Time-to-Event Endpoints

Progression-free survival, duration of response, leukemia-free survival and overall survival will be described in the appropriate analysis set using Kaplan-Meier methods. The survival functions will be plotted and median survival times will be presented with corresponding 90% CIs.

8.5.2. Categorical Endpoints

Categorical endpoints will be described. Response rates will be presented with corresponding exact 90% CIs.

Rate of RBC transfusion will be summarized descriptively.

8.5.3. Continuous Endpoints

Continuous endpoints will be summarized descriptively over time. Both changes from baseline to each subsequent time point and best overall on-study changes will be evaluated. Means and standard errors will be presented.

8.6. Safety Analysis

All safety data collected on or after the date that MMB was first dispensed in the previous study up to the date of last dose of MMB plus 30 days will be summarized. Events occurred on or after the first dose date of MMB in the current study may also be summarized separately.

8.6.1. Extent of Exposure

A subject's extent of exposure to MMB data will be generated from the MMB administration data. Exposure data will be summarized.

Descriptive information will be provided by cohort 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, and the number and timing of prescribed dose modification and interruptions.

Compliance will be described 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 in the previous study to 30 days after the last dose of MMB.

AEs will be classified using Medical Dictionary for Regulatory Activities (MedDRA) (<http://www.meddramsso.com>) with descriptions by System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT). 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 the MMB will be categorized as related or unrelated.

Treatment-emergent AEs will be summarized. 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 PT (or SOC) is counted only once for that PT (or SOC) using the worst severity grade. AE descriptions will be presented by decreasing frequency for a given SOC, HLT and PT. 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 in the previous study 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 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. Sample Size

No formal hypothesis testing is planned for this study. Up to 105 subjects who have previously participated in a Gilead clinical trial with MMB will be enrolled.

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), 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. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of GCP, 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)/Independent Ethics Committee (IEC) 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 (for studies conducted in the United States) or IEC (for studies conducted outside of the United States). The investigator will not begin any study subject activities until approval from the IRB or IEC 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 or IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial 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-/ IEC-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 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 date of birth (where allowed), 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, IRB/IEC, 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 IB, this protocol, CRF/eCRF, the IP, 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/IEC 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 AEs and other safety parameters (start and end date, and 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. 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 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 Medicinal Product Accountability and Return

Gilead recommends that used and unused IMP supplies (MMB is the IMP for this study) 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 IMP disposal procedures and provide appropriate instruction for destruction of unused IMP 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 IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

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

The study monitor will review IMP 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 IECs, 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 or IEC in accordance with local requirements and receive documented 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. 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 CRF/eCRF.

The monitor is responsible for routine review of the CRF/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 CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.2. 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.

9.3.3. 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), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

- Barosi G, Mesa R, Finazzi G, Harrison C, Kiladjian JJ, Lengfelder E, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. *Blood* 2013;121 (23):4778-81.
- Baxter EJ, Scott LM, Campbell PJ, East C, Fourouclas N, Swanton S, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet* 2005;365 (9464):1054-61.
- DSM Pharmaceuticals Inc. JAKAFI™ (ruxolitinib) tablets, for oral use. US Prescribing Information. Greenville, NC. Revised November. 2011:
- Gale RP, Barosi G, Barbui T, Cervantes F, Dohner K, Dupriez B, et al. What are RBC-transfusion-dependence and -independence? *Leuk Res* 2011;35 (1):8-11.
- James C, Ugo V, Le Couedic JP, Staerk J, Delhommeau F, Lacout C, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. *Nature* 2005;434 (7037):1144-8.
- Kralovics R, Passamonti F, Buser AS, Teo SS, Tiedt R, Passweg JR, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. *N Engl J Med* 2005;352 (17):1779-90.
- Levine RL, Pardanani A, Tefferi A, Gilliland DG. Role of JAK2 in the pathogenesis and therapy of myeloproliferative disorders. *Nature reviews. Cancer* 2007;7 (9):673-83.
- Levine RL, Wadleigh M, Cools J, Ebert BL, Wernig G, Huntly BJ, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer cell* 2005;7 (4):387-97.
- Novartis Pharma GmbH. Jakavi 5 mg tablets. EU SmPC. Nuremberg Germany. Revised April. 2013:
- Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5 (6):649-55.
- Pardanani A. JAK2 inhibitor therapy in myeloproliferative disorders: rationale, preclinical studies and ongoing clinical trials. *Leukemia* 2008;22 (1):23-30.
- Pardanani A, Gotlib JR, Jamieson C, Cortes JE, Talpaz M, Stone RM, et al. Safety and efficacy of TG101348, a selective JAK2 inhibitor, in myelofibrosis. *J Clin Oncol* 2011;29 (7):789-96.

- Pardanani A, Lasho TL, Finke C, Hanson CA, Tefferi A. Prevalence and clinicopathologic correlates of JAK2 exon 12 mutations in JAK2V617F-negative polycythemia vera. *Leukemia* 2007;21 (9):1960-3.
- Pardanani AD, Levine RL, Lasho T, Pikman Y, Mesa RA, Wadleigh M, et al. MPL515 mutations in myeloproliferative and other myeloid disorders: a study of 1182 patients. *Blood* 2006;108 (10):3472-6.
- Pikman Y, Lee BH, Mercher T, McDowell E, Ebert BL, Gozo M, et al. MPLW515L is a novel somatic activating mutation in myelofibrosis with myeloid metaplasia. *PLoS Med* 2006;3 (7):e270.
- Scott LM, Tong W, Levine RL, Scott MA, Beer PA, Stratton MR, et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. *N Engl J Med* 2007;356 (5):459-68.
- Tefferi A. Myeloproliferative Disorders: Essential Thrombocythemia and Primary Myelofibrosis [Abstract 177]. *Myeloproliferative Disorders* 2008:1280.
- Tefferi A, Barbui T. bcr/abl-negative, classic myeloproliferative disorders: diagnosis and treatment. *Mayo Clin Proc* 2005;80 (9):1220-32.
- Tefferi A, Barosi G, Mesa RA, Cervantes F, Deeg HJ, Reilly JT, et al. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). *Blood* 2006;108 (5):1497-503.
- Wu J, Jester WF, Jr., Orth JM. Short-type PB-cadherin promotes survival of gonocytes and activates JAK-STAT signalling. *Developmental biology* 2005;284 (2):437-50.

11. APPENDICES

- Appendix 1. Investigator Signature Page
- Appendix 2. Study Procedures Table
- Appendix 3. International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia
- Appendix 4. 2013 European LeukemiaNet (ELN) and International Working Group for Myelofibrosis Response and Treatment (IWG-MRT) Consensus
- Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations
- Appendix 6. ECOG status

Appendix 1. Investigator Signature Page

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

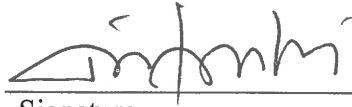
STUDY ACKNOWLEDGEMENT

Open-label Study to Assess the Long-term Safety and Efficacy of Momelotinib in Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, Post-essential Thrombocythemia Myelofibrosis, Polycythemia Vera or Essential Thrombocythemia

GS-US-352-1154, Amendment 4, 06 November 2017

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

JUN KAWASHIMA
Name (Printed)
Author


Signature

13 Nov 2017
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

	Screening/ enrollment	Months 1&2 (Cohorts 1 & 2 only)	3 M	6 M	9 M	12 M	15 M	18 M	21 M	24 M	27 M	30 M	33 M	36 M	39 M	42 M	45 M	48 M+/Q3 Months/ ESDD	Post-treatment Follow up ^b	
Informed Consent	X																			
General and Safety Assessments																				
Medication History	X																			
Physical Examination and Symptoms Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Examination				X		X				X				X				X ^a		
Response Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease Assessments																				
PGIC	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transfusion Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																				
Bone Marrow Aspirate/Biopsy	X ^b									X								X ^g		
Serum / Urine Pregnancy Test ^c	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thiamine status	X	X ^f	X ^f	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC and Differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening/ enrollment	Months 1&2 (Cohorts 1 & 2 only)		3 M	6 M	9 M	12 M	15 M	18 M	21 M	24 M	27 M	30 M	33 M	36 M	39 M	42 M	45 M	48 M+/Q3 Months/ ESDD	Post-treatment Follow up ^h
Coagulation	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product																				
MMB Accountability and Dispensing	X ^d	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ^e	

- a EOT/Early Withdrawal if not done within the previous 6 months
- b Bone Marrow biopsy at screening if not performed within 12 months of Day 1.
- c For women of childbearing age only. Serum or urine testing at screening only. Urine pregnancy test for other visits.
- d Dispensing only
- e Accountability only at ESDD visit or final study visit
- f Thiamine levels may be repeated if sample was not able to be analyzed during Screening/Enrollment Visit
- g Bone marrow biopsy to be performed at month 48 only, not required for Q3 Months visits or ESDD visit
- h Subjects who continue treatment with MMB in the extended access program following the end of the study are not required to complete the 30 day post-treatment follow-up assessments.

Appendix 3. International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia

Complete remission (CR)	<ul style="list-style-type: none"> i. Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly. ii. Peripheral blood count remission defined as hemoglobin level at least 110 g/L, platelet count at least $100 \times 10^9/L$, and absolute neutrophil count (ANC) at least $1.0 \times 10^9/L$. In addition, all 3 blood counts should be no higher than the upper normal limit. ^a iii. Normal leukocyte differential including disappearance of nucleated red blood cells, blasts, and immature myeloid cells in the peripheral smear, in the absence of splenectomy. iv. Bone marrow histologic remission defined as the presence of age-adjusted normocellularity, no more than 5% myeloblasts, and an osteomyelofibrosis grade no higher than 1. ^b
Partial remission (PR)	Requires all of the above criteria for CR except the requirement for bone marrow histologic remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill criteria for CR.
Clinical improvement (CI)	<p>Requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment (CI response is validated only if it lasts for no fewer than 8 weeks):</p> <ul style="list-style-type: none"> i. A minimum 20-g/L increase in hemoglobin level or becoming transfusion independent (applicable only for subjects with baseline hemoglobin level of less than 100 g/L). ii. Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable. ^c iii. A minimum 100% increase in platelet count and an absolute platelet count of at least $50\,000 \times 10^9/L$ (applicable only for subjects with baseline platelet count below $50 \times 10^9/L$). iv. A minimum 100% increase in ANC and an ANC of at least $0.5 \times 10^9/L$ (applicable only for subjects with baseline ANC below $1 \times 10^9/L$).
Progressive disease (PD)	<p>Requires 1 of the following: ^d</p> <ul style="list-style-type: none"> i. Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at greater than 5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of greater than 10 cm. ii. Leukemic transformation confirmed by a bone marrow blast count of at least 20%. iii. An increase in peripheral blood blast percentage of at least 20% that lasts for at least 8 weeks.
Stable disease (SD)	None of the above.
Relapse (Loss of CR, PR, or CI)	Subject with CR or PR is considered to have undergone relapse when he or she no longer fulfills the criteria for even CI.

- a Because of subjectivity in peripheral blood smear interpretation, CR does not require absence of morphologic abnormalities of red cells, platelets, and neutrophils
- b In patients with CR, a complete cytogenetic response is defined as failure to detect a cytogenetic abnormality in cases with a pre-existing abnormality. A partial cytogenetic response is defined as 50% or greater reduction in abnormal metaphases. In both cases, at least 20 bone marrow- or peripheral blood-derived metaphases should be analyzed. A major molecular response is defined as the absence of a specific disease-associated mutation in peripheral blood granulocytes of previously positive cases. In the absence of a cytogenetic/molecular marker, monitoring for treatment-induced inhibition of endogenous myeloid colony formation is encouraged. Finally, baseline and posttreatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process
- c In splenectomized patients, palpable hepatomegaly is substituted with the same measurements
- d It is acknowledged that worsening cytopenia might represent progressive disease, but its inclusion as a formal criterion was avoided because of the difficulty distinguishing disease-associated from drug-induced myelosuppression. However, a decrease in hemoglobin level of 20 g/L or more, a 100% increase in transfusion requirement, and new development of transfusion dependency, each lasting for more than 3 months after the discontinuation of protocol therapy, can be considered disease progression
- e Progressive splenomegaly only applies to those subjects who were on IP treatment for at least 7 days prior without dose interruption during those prior 7 days

{Tefferi 2006}

Appendix 4. 2013 European LeukemiaNet (ELN) and International Working Group for Myelofibrosis Response and Treatment (IWG-MRT) Consensus

Response Criteria for ET	
Complete Remission	
A	Durable ^c resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement, ^a AND
B	Durable ^c peripheral blood count remission, defined as: platelet count $\leq 400 \times 10^9/L$, WBC count $< 10 \times 10^9/L$, absence of leukoerythroblastosis, AND
C	Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND
D	Bone marrow histological remission defined as disappearance of megakaryocyte hyperplasia and absence of $>$ grade 1 reticulin fibrosis.
Partial Remission	
A	Durable ^c resolution of disease-related signs including palpable hepatosplenomegaly, and large symptoms improvement, AND
B	Durable ^c peripheral blood count remission, defined as: platelet count $\leq 400 \times 10^9/L$, WBC count $< 10 \times 10^9/L$, absence of leukoerythroblastosis, AND
C	Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND
D	Without bone marrow histological remission, defined as the persistence of megakaryocyte hyperplasia.
No Response	
A	Any response that does not satisfy partial remission
Progressive Disease	
A	Transformation into PV, post-ET myelofibrosis, myelodysplastic syndrome or acute leukemia

Response Criteria for PV

Complete Remission

A	Durable [‡] resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement [‡] AND
B	Durable [‡] peripheral blood count remission, defined as Ht lower than 45% without phlebotomies; platelet count $\leq 400 \times 10^9/L$, WBC count $< 10 \times 10^9/L$, AND
C	Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND
D	Bone marrow histological remission defined as the presence of age-adjusted normocellularity and disappearance of trilinear hyperplasia, and absence of $>$ grade 1 reticulin fibrosis

Partial Remission

A	Durable [‡] resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement [‡] AND
B	Durable [‡] peripheral blood count remission, defined as Ht lower than 45% without phlebotomies; platelet count $\leq 400 \times 10^9/L$, WBC count $< 10 \times 10^9/L$, AND
C	Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND
D	Without bone marrow histological remission defined as persistence of trilinear hyperplasia.

No Response

A	Any response that does not satisfy partial remission
---	--

Progressive Disease

A	Transformation into PV, post-ET myelofibrosis, myelodysplastic syndrome or acute leukemia [‡]
---	--

{Barosi 2013}

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations

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

The risks of treatment with 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; female subjects for 30 days and male subjects for 90 days following the last dose of study drug. Female study subjects who are not heterosexually active must

provide periodic confirmation of continued abstinence from heterosexual intercourse and regular pregnancy testing while taking IMP. The investigator will counsel subjects on the protocol specified method(s) for avoiding pregnancy in case the subject chooses to engage in heterosexual intercourse.

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 at baseline (Day 1) prior to receiving the first dose of study drug. Lactating females must discontinue nursing before IMP administration.

Appendix Table 1. Protocol Specified Contraceptive Methods

Single Methods	Combination Methods
<p>Intrauterine Devices (IUDs)</p> <ul style="list-style-type: none"> • Copper T 380A IUD • LNG 20 IUD <p>Progesterone</p> <ul style="list-style-type: none"> • Implant • Injection <p>Tubal Sterilization</p> <p>Vasectomy with Documented Azoospermia 3 months After the Procedure</p>	<p>Estrogen and Progesterone plus Barrier</p> <ul style="list-style-type: none"> • Combined oral contraceptives plus barrier <ul style="list-style-type: none"> • Transdermal patch plus barrier • Vaginal ring plus barrier <p>Two Barrier Methods</p> <ul style="list-style-type: none"> • Diaphragm/spermicide plus condom

Acceptable barrier methods include diaphragm (with spermicide) and the male condom.

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 IMP.

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 study drug dose. If a subject does become pregnant or suspects that she may have become pregnant while in this study, the investigator, in consultation with the medical monitor, will decide whether the benefit of continuation of the study outweighs any potential risk to the pregnant subject or her offspring. The investigator should counsel the subject regarding the possible effects of study drug exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section [7.7.2.1](#).

Appendix 6. ECOG status

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

{Oken 1982}