GILEAD

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Idelalisib in Subjects Receiving Ruxolitinib as Therapy for Primary, Post-Polycythemia Vera, or Post-Essential Thrombocythemia Myelofibrosis with Progressive or Relapsed Disease	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	101254	
Clinical Trials.gov Identifier:	NCT02436135	
Indication:	Myelofibrosis	
Protocol ID:	GS-US-397-1245 (Previously GS-US-313-1245)	
Gilead Clinical Program Manager:	Name: Telephone:	PPD PPD
Gilead Medical Monitor:	Name: Telephone: Mobile: E-mail:	PPD PPD PPD PPD
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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 1b Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Idelalisib in Subjects Receiving Ruxolitinib as Therapy for Primary, Post-Polycythemia Vera, or Post-Essential Thrombocythemia Myelofibrosis with Progressive or Relapsed Disease
IND Number:	101254
Clinical Trials.gov Identifier:	NCT02436135
Study Centers Planned:	Two centers in the United States
Objectives:	The primary objectives of this study are as follows: • To evaluate the safety and tolerability of idelalisib through 28 days in subjects receiving ruxolitinib as therapy for intermediate to high risk primary myelofibrosis (PMF), post-polycythemia vera, or post-essential thrombocythemia myelofibrosis (post-PV MF or post-ET MF) with progressive or relapsed disease • To determine the pharmacokinetics (PK) of idelalisib and ruxolitinib, in subjects receiving ruxolitinib with PMF, post-PV MF, or post-ET MF with progressive or relapsed disease The secondary objectives of this study are as follows: • To evaluate the safety and tolerability of continuous daily administration of idelalisib beyond 28 days in subjects receiving ruxolitinib with PMF, post-PV MF, or post-ET MF • To evaluate the efficacy of idelalisib in subjects receiving ruxolitinib with PMF, post-PV MF, or post-ET MF by 2013 Revised International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European Leukemia Net (ELN) response criteria CCI [redacted]

Study Design:

This is a Phase 1b, open-label, dose escalation study. The planned number of subjects in each cohort is 6. There will be 4 cohorts (A, B, C, and D), which will be enrolled sequentially. Cohort A will be enrolled first.

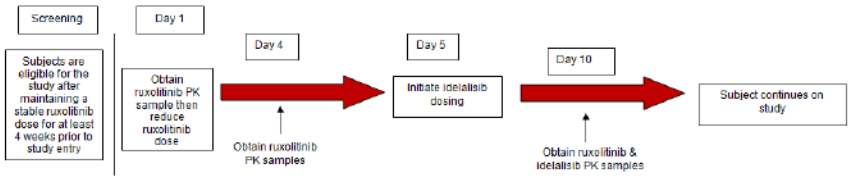
Idelalisib will be administered in subjects receiving ruxolitinib as therapy for PMF, post-PV MF, or post-ET MF and have been maintained on a stable dose of ruxolitinib for at least 4 weeks prior to study entry. On Day 1, subjects will have a PK sample drawn and then reduce the ruxolitinib dose as follows:

- Subjects on a stable ruxolitinib dose of greater than or equal to 10 mg twice daily, will have their ruxolitinib dose reduced by 50% (rounded up to the closest available tablet strength).
- Subjects on a stable ruxolitinib dose of 5 mg twice daily will have their ruxolitinib dose reduced to 5 mg once daily.

Idelalisib will be administered starting on Day 5.

PK samples will be obtained on Days 1, 4, and 10 as shown in the schema below:

Schema



The starting doses of idelalisib in Cohorts A, B, C, and D, are 50 mg once daily, 50 mg twice daily, 150 mg once daily, and 150 mg twice daily, respectively. Enrollment into the study will be on hold while the safety review team (SRT) evaluates the data prior to cohort expansion and dose escalation.

The first 3 subjects will be enrolled in Cohort A at 50 mg once daily idelalisib. After the third subject has completed Day 28 (4 weeks), the SRT will review the safety data. Enrollment will be on hold until the SRT determines the cohort can be expanded to enroll an additional 3 subjects. After the sixth subject in Cohort A completes Day 56 (8 weeks), the SRT will review the cumulative safety and PK data from all subjects in Cohort A. Enrollment will be on hold until the SRT determines Cohort B can be open to enrollment. If the SRT deems the combination of idelalisib with ruxolitinib safe and tolerable at the 50 mg once daily dose, Cohort B will be open to enrollment.

Enrollment and safety assessment by the SRT in Cohort B at 50 mg twice daily idelalisib will proceed as follows: The first 3 subjects will be enrolled. After the third subject has completed Day 28 (4 weeks), the SRT will review the cumulative safety data for Cohorts A and B. Enrollment will be on hold until the SRT determines Cohort B can be expanded to enroll an additional 3 subjects. After the sixth subject in Cohort B completes Day 28 (4 weeks), the SRT will review the cumulative safety data from all subjects in Cohorts A and B, and the cumulative PK data for Cohort B. Enrollment will be on hold until the SRT determines Cohort C can be open to enrollment. If the SRT deems the combination of idelalisib with ruxolitinib safe and tolerable at the 50 mg twice daily dose, Cohort C will be open to enrollment.

Enrollment and safety assessment by the SRT in Cohort C at 150 mg once daily idelalisib will proceed as follows: The first 3 subjects will be enrolled. After the third subject has completed Day 28 (4 weeks), the SRT will review the cumulative safety data for Cohorts A, B, and C. Enrollment will be on hold until the SRT determines Cohort C can be expanded to enroll an additional 3 subjects. After the sixth subject in Cohort C completes Day 28 (4 weeks), the SRT will review the cumulative safety data from all subjects in Cohorts, A, B, and C and the cumulative PK data for Cohort C. Enrollment will be on hold until the SRT determines Cohort D can be open to enrollment. If the SRT deems the combination of idelalisib with ruxolitinib safe and tolerable at the 150 mg once daily dose, Cohort D will be open to enrollment.

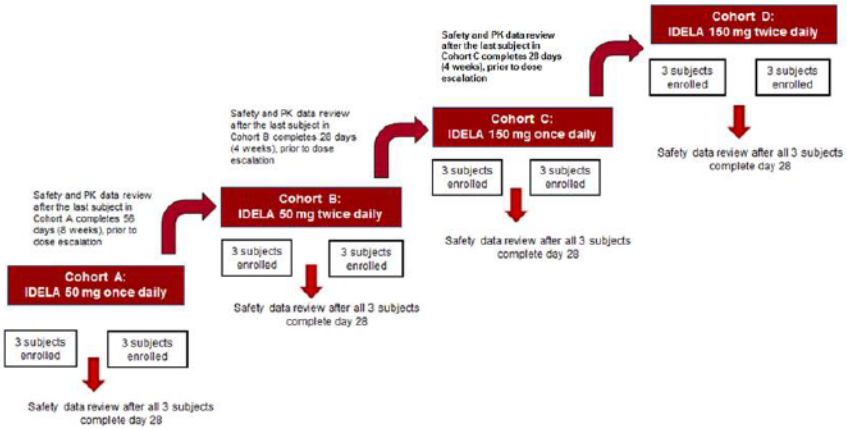
Enrollment and safety assessment by the SRT in Cohort D at 150 mg twice daily idelalisib will proceed as follows: The first 3 subjects will be enrolled. After the third subject has completed Day 28 (4 weeks), the SRT will review the cumulative safety data for Cohorts A, B, C, and D. Enrollment will be on hold until the SRT determines Cohort D can be expanded to enroll an additional 3 subjects. After the sixth subject in Cohort D completes Day 28 (4 weeks), the SRT will review the cumulative safety data from all subjects in Cohorts A, B, C, and D, and the cumulative PK data for Cohort D.

Additional cohorts are not planned after enrollment in Cohort D is complete. Subjects who do not receive $\geq$ 1 dose of idelalisib will be deemed unevaluable and replaced.

In subjects without demonstrable clinical benefit, dose escalation (to a higher dose cohort) may be permitted by the SRT after Cohort C (idelalisib 150 mg once daily) has been fully enrolled and the last subject has been on study drug for at least 28 days.

The SRT will consider the following – the subject's compliance with therapy, tolerability of the combination of idelalisib and ruxolitinib, overall incidence and severity of adverse events (AEs) related to idelalisib or ruxolitinib, dose reduction for severe toxicity and dose modifications. Additionally, subjects must show a lack of response by volumetric imaging (three dimensional [3D] magnetic resonance imaging [MRI] or computed tomography [CT], if MRI is not feasible), or by palpation of the liver and/or spleen, after at least 12 weeks on study.

The SRT will consist of at least one investigator and the following Gilead Sciences, Inc. (Gilead) study team members: the medical monitor, representatives from Drug Safety and Public Health (DSPH), Clinical Operations, and Biostatistics. Others may be invited to participate as members of the SRT if additional expertise is desired. The medical monitor serves as the chair of the SRT.



Number of Subjects Planned:	Approximately 24
Target Population:	Subjects currently receiving ruxolitinib for treatment of PMF, post-PV MF, or post-ET MF and meet 2013 Revised IWG-MRT and ELN response criteria for progressive or relapsed disease.
Duration of Treatment:	The duration of treatment is 24 weeks. Subjects who complete the 24-week treatment period on idelalisib, and in the opinion of the investigator are deriving clinical benefit, can remain on the study for the extension period until disease progression. The overall duration of the trial is expected to be approximately 3 years.

Diagnosis and Eligibility Criteria:

Inclusion Criteria:

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

1) Age ≥ 18 years of age
2) Subjects must have been on a stable dose of ruxolitinib for at least 4 weeks prior to study entry
3) Subjects with PMF, post-PV MF, or post-ET MF classified as high risk or intermediate risk as defined by the Dynamic International Prognostic Scoring System (DIPSS) for Primary Myelofibrosis (Appendix 4) or DIPSS Plus, if cytogenetics are available (Appendix 5)
4) Subjects with PMF, post-PV MF, or post-ET MF who are receiving ruxolitinib and meet 2013 Revised IWG-MRT and ELN response criteria with progressive and relapsed disease, with modifications for progressive disease
    a) Progressive disease:
        - Appearance of a new splenomegaly that is palpable at least 5 cm below the left costal margin (LCM), or
        - A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm, or
        - A 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm, or
        - An increase in palpable splenomegaly from best ruxolitinib response of > 25% but < 50% in a subject who does not meet criteria for complete remission (CR), partial remission (PR), or clinical improvement (CI)
    b) Relapsed disease:
        - No longer meeting criteria for at least CI after achieving CR, PR, or CI, or
        - Loss of anemia response persisting for at least 1 month, or
        - Loss of spleen response persisting for at least 1 month
5) Life expectancy > 24 weeks in the opinion of the investigator
6) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2

7) Required screening laboratory values as shown in the following table:

Organ System	Parameter	Required Value
Hepatic	Serum total bilirubin	≤ 1.5 × ULN (unless elevated due to Gilbert's syndrome or hemolysis)
	Serum ALT	≤ 2.5 × ULN
	Serum AST	
Hematopoietic	ANC	≥ 1.0×10^9/L
	Peripheral blood blast or bone marrow blood blast count	< 20%
	Platelets	≥ 50×10^9/L
Renal	$_eC_{Cr}$[a]	≥ 30 mL/min
Pregnancy	β-hCG[b]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody, or positive HBc antibody and negative for HBV DNA by quantitative PCR
	HCV	Negative viral RNA (if HCV antibody is positive)
	CMV	Negative CMV PCR or pp65 antigen

a As calculated by the Cockcroft-Gault formula or measured
b For women of childbearing potential only
Abbreviations: HBc antibody=anti-hepatitis B core antibody

8) Female subjects of childbearing potential, willing to use a protocol-recommended method of contraception during heterosexual intercourse from signing of informed consent throughout the study treatment period and to 30 days from the last dose of idelalisib (see Appendix 10 for more information)

9) Male subjects having intercourse with females of childbearing potential, willing to use a protocol recommended method of contraception from Day 1 throughout the study treatment period and for 90 days following the last dose of idelalisib and to refrain from sperm donation from Day 1 throughout the study treatment period and for 90 days following the last dose of idelalisib (see Appendix 10 for more information)

10) In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current myelofibrosis disease status, medical condition, the potential benefits and risks of alternative treatments for myelofibrosis

11) Willing and able to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions, including mandatory prophylaxis for Pneumocystis jiroveci pneumonia (PJP)

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

Exclusion Criteria:

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

1) Subjects on a stable ruxolitinib dose of 5 mg once daily

2) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation

3) Ongoing drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver

4) Ongoing drug-induced pneumonitis

5) Ongoing inflammatory bowel disease

6) Ongoing alcohol or drug addiction

7) Cytomegalovirus (CMV): Ongoing infection, treatment, or prophylaxis within the past 28 days

8) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled bacterial, fungal, or viral infection (or active or chronic bleeding event within 4 weeks prior to first dose of investigational medicinal product (IMP) that would limit compliance with study requirements as judged by the treating physician

9) History of a concurrent or second malignancy except for adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma *in situ*, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for $\geq$ 1 year, adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for $\geq$ 5 years

10) Participation in an ongoing investigational drug or device trial or use within 6 weeks of chemotherapy (with exception made for hydroxyurea, see Section 5.4.6), investigational agent, immunomodulating therapy, biologic therapy or radiation therapy. Erythropoietin stimulating agents (ESA) are allowed as long as a subject has been on a stable dose for a minimum of 12 weeks for the treatment of anemia.
11) Symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or unstable cardiac arrhythmia requiring medication
12) Known hypersensitivity to the study IMP, the metabolites, or formulation excipients
13) Unwilling or unable to take oral medication
14) Unresolved non-hematologic toxicities from prior therapies that are > Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 (with the exception of alopecia [Grade 1 or 2 permitted])
15) Pregnant or lactating females

Study Procedures/ Frequency:

Treatment

Subjects will reduce their ruxolitinib dose on Day 1 by 50% as described in Study Design.

Idelalisib will be administered orally (PO) beginning on Day 5 at 50 mg once daily (Cohort A), 50 mg twice daily (Cohort B), 150 mg once daily (Cohort C), and 150 mg twice daily (Cohort D). The once daily dose will be taken in the morning. Ideally, doses taken twice daily should be at approximately 12-hour intervals (eg, at 7 AM and at 7 PM). Both ruxolitinib and idelalisib should be taken at the same time, and in the clinic when visits are scheduled.

Visits and Evaluations

After the 28-day screening period, study visits are scheduled on Day 1 and Day 4 during Week 1, every week from Weeks 2 to 4 and every 2 weeks thereafter up to Week 24. Subjects who are continuing study after Week 24 will have study visits scheduled every 4 weeks.

On Days 1 to 4 on study initiation, only ruxolitinib will be administered. Blood samples for PK will be collected on Days 1 and 4 relative to the morning dose of ruxolitinib. On Day 5, idelalisib administration will be initiated and idelalisib and ruxolitinib will be dosed together. PK blood samples will be collected on Day 10 relative to the morning dose of idelalisib and ruxolitinib.

	Safety and laboratory assessments will be conducted at study visits as defined in Section 6 and Appendix 2. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF, Appendix 8) will be completed by subjects weekly for the first 24 weeks then monthly for subjects on study beyond Week 24. Three dimensional (3D) MRI (or CT, if MRI is not feasible) of the liver and spleen will be evaluated at screening, Weeks 12 and 24. Idelalisib dosing will continue in the absence of disease progression or toxicity warranting discontinuation of therapy, as long as there is evidence of clinical benefit as judged by the investigator. Volumetric imaging of the liver by 3D MRI (or CT, if MRI not feasible) performed as standard of care prior to signing the ICF, and within 8 weeks of enrollment, may be used to fulfill the screening requirement.
Test Product, Dose, and Mode of Administration:	The dose of idelalisib for this study will be administered PO at 50 mg once daily (Cohort A), 50 mg twice daily (Cohort B), 150 mg once daily (Cohort C), or 150 mg twice daily (Cohort D). The dose will be decreased to Dose Level – 1, as defined in Table 5-1, if the subject has a toxicity requiring dose adjustment. No dose reduction is permitted in Cohort A. In Cohorts B, C, and D the dose may be increased back to the starting dose if the toxicity has resolved to ≤ Grade 1 or the subject's baseline, at the discretion of the investigator. In Cohort A the starting dose may be resumed if the toxicity has resolved to ≤ Grade 1 or the subject's baseline, at the discretion of the investigator.
Criteria for Evaluation:	<u>Primary Endpoints</u> • Overall safety profile of idelalisib and ruxolitinib after 28 days of exposure characterized by the type, frequency, severity, timing, and relationship to idelalisib of adverse events (AE), abnormal laboratory tests, drug discontinuations due to AE and serious adverse events (SAE). Toxicity will be assessed by grading of AE according to the CTCAE V4.03 • Pharmacokinetic parameters of ruxolitinib (and metabolite[s], as applicable) and idelalisib and/or its primary metabolite, GS-563117 (C_{max}, T_{max}, AUC, and C_{trough})

Secondary Endpoints

- Overall safety profile of idelalisib and ruxolitinib continuous daily administration beyond 28 days of exposure characterized by the type, frequency, severity, timing, and relationship to idelalisib of any AE, abnormal laboratory tests, drug discontinuations due to AE and SAE. Toxicity will be assessed by grading of AE according to the CTCAE V4.03
- Rate of overall response as defined by 2013 Revised IWG-MRT and ELN response criteria (Appendix 6), ie, CR, PR, or CI (the achievement of anemia, spleen, or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia)

CCI [redacted]

Pharmacokinetics:	Plasma concentration of ruxolitinib (and metabolite[s], as applicable) and idelalisib and/or its primary metabolite, GS-563117, will be measured. Blood samples for assessing ruxolitinib PK will be collected relative to the morning dose of ruxolitinib, on Day 1 predose, and Day 4 predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post dose after these subjects are enrolled into the study prior to the initiation of idelalisib treatment. On Day 5, idelalisib administration will be initiated, and idelalisib and ruxolitinib will be dosed together. Blood samples will be collected on Day 10, relative to the morning dose of idelalisib and ruxolitinib, predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post dose to assess ruxolitinib, idelalisib and corresponding metabolite PK. Beginning Day 15 and throughout the study as outlined in Section 6 and Appendix 2, PK samples will continue to be collected predose and 1.5 hours postdose.
Statistical Methods:	Analysis Methods The intent-to-treat (ITT) analysis set consists of all subjects who receive ≥ 1 dose of idelalisib. It will be used in the analyses of subject characteristics, study drug (idelalisib) treatment administration, safety and efficacy endpoints. Subject characteristics and study results will be described and summarized. Descriptive summaries will be prepared to show sample size, mean, standard deviation (StD), 95% confidence intervals (CIs) on the mean, median, minimum, and maximum for continuous variables and counts, percentages and 95% CIs on the percentage for categorical variables. Interim safety summaries for SRT will be shown by each cohort and all cohorts together. Response rates will be presented with corresponding exact 95% CIs. Subjects who have missing baseline or on-study response assessment will be counted as non-responders. PFS and duration of response (DOR) 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 95% CIs. Percent change from baseline at Weeks 12 and 24 and best change from baseline for spleen, liver, and TSS will be presented with corresponding median, standard deviation, minimum, and maximum.

Sample Size

As this is a Phase 1b study with a primary objective of assessing safety, the sample size is not based on formal power calculations. The sample size of approximately 6 subjects per dose cohort in Cohorts A, B, C, and D is considered adequate for an initial assessment of safety and tolerability for subsequent evaluations.

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

3D	Three Dimensional
AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
ATP	Adenosine Triphosphate
AUC	Area Under the Serum Concentration Over Time Curve
β-hCG	Beta Human Chorionic Gonadotropin
BAT	Best Available Therapy
BCRP	Breast Cancer Resistance Protein
BID	Twice Daily
CFR	Code of Federal Regulations
CI	Clinical Improvement
CIs	Confidence Intervals
CLL	Chronic Lymphocytic Leukemia
CMV	Cytomegalovirus
C_{max}	Maximum Drug Concentration
C_{trough}	Trough plasma concentration
CR	Complete Remission
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450 Enzyme
DIPSS	Dynamic International Working Group Prognostic Scoring System
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
DSPH	Drug Safety and Public Health
EC_{90}	Drug concentration at 90% of maximal effect
ECG	Electrocardiogram
eC_{cr}	Estimated Creatinine Clearance
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
ELN	European Leukemia Net
EOS	End of Study
ESA	Erythropoietin Stimulating Agents
ESR	Erythrocyte Sedimentation Rate
ET	Essential Thrombocythemia
EU	European Union
FL	Follicular Lymphoma

FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GGT	Gamma-Glutamyltransferase
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
HBc	Hepatitis B Core
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HD	Hodgkin Disease
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
IB	Investigator's Brochure
IC_{50}	Concentration that results in 50% inhibition
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-6	Interleukin 6
IMP	Investigational Medicinal Product
iNHL	Indolent non-Hodgkin Lymphoma
IUD	Intrauterine Device
IRB	Institutional Review Board
ITT	Intent To Treat
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK2	Janus Kinase 2
LCM	Left Costal Margin
MDR1	Human P-glycoprotein
MF	Myelofibrosis
MPN	Myeloproliferative Neoplasm
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment For
MRI	Magnetic Resonance Imaging
pAkt	Phosphorylated AKT
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PE	Physical Examination

PFS	Progression Free Survival
PI3K	Phosphotidylinositol-3-kinase
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
PJP	Pneumocystis jiroveci pneumonia
PK	Pharmacokinetics
PMF	Primary Myelofibrosis
PO	Oral Administration
Post-ET MF	Post-Essential Thrombocythemia Myelofibrosis
Post-PV MF	Post-PolycythemiaVera Myelofibrosis
PR	Partial Remission
PRO	Patient-reported Outcomes
PT	Preferred Term
PV	Polycythemia Vera
QT	Electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
RBC	Red Blood Cell Count
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
SOP	Standard Operating Procedure
SRT	Safety Review Team
StD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
T_{max}	The time (observed time point) of C_{max}
TSS	Total Symptom Score
TTR	Time To Response
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Count

1. INTRODUCTION

1.1. Background

1.1.1. Background on Myelofibrosis

The chronic myeloproliferative neoplasms (MPNs)— polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF)— are acquired marrow disorders characterized by excessive production of mature myeloid cells. Major morbidity from these conditions result from thrombo-hemorrhagic complications (arterial and venous thrombosis, major bleeding) and transformation to acute leukemia.

Myelofibrosis originates from acquired mutations that alter the hematopoietic stem cell and produce alterations in the kinase-mediated signaling processes, resulting in clonal myeloproliferation, bone marrow fibrosis, and abnormal cytokine expression {Tefferi et al 2011}. Primary myelofibrosis is a rare disease with an incidence of 0.4 to 1.3 per 100,000 people in Europe, Australia, and the U.S. Myelofibrosis can also occur in patients with PV (10-20% of subjects after 10-20 years) and ET (2-3% of subjects), in which case it is called post-polycythemia vera (post-PV MF) or post-essential thrombocythemia myelofibrosis (post-ET MF). The primary pathogenic mechanism in PMF is the unchecked proliferation of a hematopoietic stem cell clone that leads to ineffective erythropoiesis, atypical megakaryocytic hyperplasia, and an increase in the ratio of immature granulocytes to total granulocytes. This clonal myeloproliferation is characteristically accompanied by bone marrow fibrosis and extramedullary hematopoiesis in the spleen, liver, and other organs. Characteristic features of extramedullary hematopoiesis on a blood smear include teardrop-shaped red cells, nucleated red cells, and myeloid immaturity. Typical clinical features include marked splenomegaly, progressive anemia, and constitutional symptoms.

Unfortunately, current treatments for MF are palliative and do not alter the natural disease course. The only potential cure for MF is allogeneic stem cell transplant, the availability of which is limited by age and donor restrictions. In 2005, a mutation in the *JAK2* cytoplasmic tyrosine kinase (*JAK2*V617F) was identified that leads to constitutive activation of *JAK2* and unabated JAK-STAT signaling, resulting in the unrestrained cellular proliferation characteristics of MPNs. This prompted the development of *JAK2* inhibitors for myelofibrosis, the most challenging of the MPNs.

Although very effective in reducing spleen size and mitigating symptoms, JAK inhibitors have thus far not shown the ability to improve leukemia-free survival, reverse disease-defining features such as bone marrow fibrosis, nor substantially reduce *JAK2*V617F mutation burden. The biologic basis for these suboptimal responses has not been established but is likely attributable to *JAK2* dependent and independent mechanisms. To date, resistance mutations within *JAK2* have not been identified as a basis for acquired resistance to JAK inhibitors in the clinical setting. However, persistent JAK-STAT signaling mediated by the heterodimerization between *JAK2* with the related kinases JAK1 or TYK2 was recently described as a mechanism of "disease persistence" in presence of chronic inactivation of *JAK2* {Koppikar et al 2012}.

This phenomenon of persistence of the JAK-STAT activity was observed in vivo in MPN murine models, and in primary samples of patients treated with the *JAK2* inhibitor ruxolitinib, recently approved by the Food and Drug Administration (FDA) in November 2011 for the treatment of MF.

1.1.2. Rationale for Inhibition of PI3K/AKT Pathway in Myelofibrosis

Phosphatidylinositol 3-Kinase (PI3K)/AKT is a signaling pathway that plays a crucial role in cell growth, proliferation, and survival, and there has been increasing evidence that abnormal up-regulation of PI3K/AKT is relevant to MPN pathophysiology.

Because the PI3K/AKT pathway is prominently activated in *JAK2*V617 and MPLW515L induced MPNs, Khan and colleagues evaluated the activity of MK-2206 a selective AKT inhibitor in *JAK2*V617F expressing cell lines {Kahn et al 2013, Khan et al 2011}. These investigators found that inhibition of AKT potently suppressed growth of these cells by inducing cell cycle arrest and apoptosis. Exposure of *JAK2*V617F $CD34^+$ peripheral cells from MF patients to MK-2206 suppressed colony formation from these progenitor cells. The expansion of megakaryocytes (CFU-MKs) from murine bone marrow cells transduced with MPL W515L was abrogated in the presence of the AKT inhibitor MK-2206 suggesting a requirement for the PI3K/AKT pathway in aberrant megakaryocyte expansion, a feature of MF.

Synergistic inhibition of proliferation, induction of apoptosis and inhibition of colony formation from MPN hematopoietic progenitors were recently demonstrated in multiple publications using JAK inhibitors combined with PI3K inhibitors, mTOR inhibitors, a kinase downstream of PI3K, or a dual PI3K-mTOR inhibitor {Bogani et al 2013, Choong et al 2012, Fiskus et al 2013}. Choong and colleagues extensively explored the combination of two JAK inhibitors (ruxolitinib and SAR302503) with a panel of 15 inhibitors targeting additional signaling pathways in cell lines engineered to overexpress WT *JAK2*, *JAK2*V617F, TPOR W515L and WT TPOR. Among the 15 inhibitors tested, only the PI3K inhibitors (ZSTK474, GDC0941 and BEZ235) synergized to inhibit the cell proliferation and survival of the cells engineered to mimic the genetic lesions observed in MPN. Combination of ruxolitinib and GDC0941 was further shown to reduce CFU-E and BFU-E colony formation from hematopoietic progenitors isolated from a mouse model of MPN and from two PV patients. BEZ235, a dual PI3KmTOR inhibitor induced cell cycle arrest and apoptosis in *JAK2*V617F expressing human cell lines and in cells derived from MPN patient {Fiskus et al 2013}. Combination of BEZ235 with SAR302503 a JAK inhibitor, synergistically decreased viability in *JAK2*V617F expressing cell lines and $CD34^+$ progenitor cells from MF patients. Normal $CD34^+$ progenitor cells appeared less sensitive to the combined inhibition of the *JAK2* and the PI3K pathway. The generation of erythropoietin-dependent colonies from PV patients was also synergistically inhibited by the combination of mTOR inhibitors with the JAK inhibitors ruxolitinib and AZD1480 {Bogani et al 2013}. These in vitro data indicate that inhibition of PI3K or of the downstream effector kinases AKT or mTOR are active against MPN cells and their combination with JAK inhibitors produced synergism. The PI3K inhibitors GDC0941 and BEZ235 inhibit all Class I PI3K isoforms. The Class I PI3K is composed of a regulatory subunit and a catalytic subunit (designated p110α, p110β, p110δ, or p110γ) endowed with kinase activity. The catalytic subunit

of the heterodimer defines the 4 Class I PI3K isoforms: PI3Kα, PIKβ, PI3Kδ, and PI3Kγ. Idelalisib is an oral selective small molecule adenosine triphosphate (ATP) competitive inhibitor of the PI3Kδ isoform whose expression is restricted to hematopoietic cells. The PI3Kδ isoform was identified as the predominant isoform expressed in $CD34^+$ cells from MF patients (Gilead, data on file). Idelalisib inhibited the PI3K/AKT pathway, with a dose-dependent decrease of p-AKT and p-S6 ribosomal protein, downstream pharmacodynamic markers of this pathway. Inhibition was observed in $CD34^+$ peripheral cells from both ruxolitinib-naïve and chronic ruxolitinib-treated patients. Idelalisib alone and in combination with ruxolitinib inhibited the survival and induced apoptosis as assessed by Annexin V staining in MF-derived progenitor cells {Meadows et al 2013}. Based on PI3K/AKT involvement in MF, the expression of PI3K δ isoform in MF progenitor cells, the potent and selective inhibition of the PI3Kδ isoform achieved by idelalisib, and the ability of idelalisib to inhibit AKT signaling and survival of MF $CD34^+$ progenitor cells {Meadows et al 2013} (Gilead data on file), we propose a Phase 1b trial of idelalisib in combination with ruxolitinib in subjects with PMF, post-PV MF or post-ET MF and who meet the criteria of progressive or relapsed disease as defined in the inclusion criteria, and based on the 2013 Revised International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) response criteria particularly given the lack of useful, disease-modifying agents in these ruxolitinib treated patients {Cervantes et al 2009}.

1.2. Idelalisib

1.2.1. General Information

Idelalisib was approved in the US on July 23, 2014 and in the European Union (EU) on September 18, 2014. Refer to local labeling for the approved indication statements and dosing recommendations.

Idelalisib is a potent competitive inhibitor of the ATP binding site of the PI3K p110δ catalytic domain, which has been shown to be prominently expressed in cells of hematopoietic origin {Lannutti et al 2011, Okkenhaug et al 2003a, Vanhaesebroeck et al 2005}. Inhibition of PI3Kδ has been shown to modulate cellular functions including motility, proliferation, survival, and recruitment of additional intracellular signaling enzymes through the B-cell receptor (BCR), cytokine, chemokine and integrin receptors.

1.2.1.1. Role of Phosphatidylinositol 3-Kinases in Tumor Pathogenesis

Class I PI3Ks are a family of intracellular signaling proteins that are essential components of migratory, proliferative, survival, and differentiation pathways in many cell types, including those of hematopoietic origin {Okkenhaug et al 2002, Okkenhaug et al 2003a, Okkenhaug et al 2003b}. These enzymes consist of a regulatory subunit (designated p50, p55, p85, or p101) and a catalytic subunit (designated p110α, p110β, p110γ, or p110δ). Upon PI3K activation, p110 generates the key lipid second messenger phosphatidylinositol (3,4,5)-trisphosphate (PIP3) through phosphorylation of the 3 position of the inositol head group of phospholipids present in the cell membrane. PIP3 acts as a binding site for recruitment and activation of numerous intracellular signaling enzymes. The most important of these is the serine/threonine kinase, AKT,

which mediates a positive pleotropic effect on cell survival, proliferation, growth, and metabolism {Engelman et al 2006} acting through mTOR signaling {Hay 2005, Osaki et al 2004}. The activity of PI3K is opposed by lipid phosphatases that include phosphatase and tensin homolog (PTEN), a known tumor suppressor that is expressed in all cells and inositol polyphosphate 5-phosphatase (SHIP1 and SHIP2), enzymes that are expressed in hematopoietic cells.

PI3Kδ shows an expression pattern that is largely restricted to cells of hematopoietic origin {Vanhaesebroeck et al 2005}. Mice deficient in PI3Kδ have no gross abnormalities, reproduce, and live a normal life span without an increased susceptibility to infections {Okkenhaug et al 2002, Okkenhaug et al 2003a, Okkenhaug et al 2003b}. However, effects on intracellular signaling, proliferation, migration, and differentiation have been observed in cells of myeloid and lymphoid lineages {Sujobert et al 2005}.

The importance of the PI3K/AKT signaling pathway has been shown in a number of hematopoietic malignancies including non-Hodgkin lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia, and Hodgkin disease (HD). PI3Kδ is critical for multiple signaling pathways that are hyperactive in B-cell malignancies and confer survival, proliferation and homing to malignant B cells. A survey of multiple lymphoma cell lines showed uniform expression of PI3Kδ and in many cases constitutive activation of the PI3K pathway as indicated by expression of phosphorylated AKT (pAkt) {Lannutti et al 2011}. Inhibition of PI3Kδ by idelalisib reduced the viability of cell lines-derived from NHL. In Hodgkin's disease, the importance of the PI3K/Akt/mTOR pathway has been demonstrated {Castellares et al 2008, Georgakis et al 2005, Meadows et al 2010}. In an evaluation of RS cells in primary lymph node sections from patients with Hodgkin Lymphoma (HL), 27 of 42 (64.3%) demonstrated pAkt, indicating that constitutive PI3K activity is a feature of these cells. Further studies in HL-derived cells lines confirmed overexpression of pAkt, showing that pAkt expression can be induced through PI3K by external stimuli such as coculture with stromal cells and that this effect was blocked by idelalisib. Idelalisib showed dose- and time-dependent antiproliferative effects and enhanced apoptosis in cell lines derived from patients with HD {Meadows et al 2010, Meadows et al 2012}.

1.2.1.2. Drug Substance and Formulation

Idelalisib is an orally bioavailable, novel chemical entity with a molecular weight of ~415 daltons. For toxicological and clinical testing, idelalisib has been manufactured and formulated according to current Good Manufacturing Practices.

For further information refer to idelalisib Investigator's Brochure (IB).

1.2.2. Preclinical Pharmacology and Toxicology

1.2.2.1. Nonclinical Pharmacology

Idelalisib exhibits high selectivity and potency. The concentration of idelalisib inducing 50% inhibition (IC_{50}) of PI3Kδ is 19 nM, whereas the IC_{50} values for PI3Kα, PI3Kβ, and PI3Kγ were 8600, 4000, and 2100 nM, respectively. In addition, idelalisib at 10 μM did not significantly interact with any of 402 kinases tested other than the PI3K isoforms. Radioligand displacement assays that measure functional binding interactions demonstrated that idelalisib (10 μM) did not significantly inhibit binding of any of the 68 radio-ligands tested.

The effects of idelalisib on signaling and apoptosis in malignant B cells were assessed through a series of in vitro experiments in cell lines and samples from adult subjects with follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and CLL. These studies demonstrated that idelalisib causes a dose-dependent reduction of Akt phosphorylation at clinically achievable exposure. In samples derived from FL patient fine needle biopsies, treatment with 0.1 μM idelalisib led to 50% to 90% inhibition of Akt phosphorylation. Concentrations inducing a 50% reduction of Akt phosphorylation and growth inhibition (EC_{50}) were in the range of 0.1 to 0.5 μM in 2 indolent non-Hodgkin lymphoma (iNHL) cell lines (WSU-NHL nodular histiocytic lymphoma and WSU-FSCCL, low-grade follicular small cleaved cell lymphoma). In these 2 cell lines, idelalisib at 0.5 μM resulted in a 3- to 5-fold increase in the population of apoptotic (Annexin V-positive) cells as assessed by flow cytometry. This and other testing in nonclinical models of lymphoid neoplasia confirm the importance of the PI3Kδ pathway in iNHL and document idelalisib activity in suppressing the growth and survival of these malignant cell types.

In vitro and in vivo safety pharmacology studies with idelalisib have demonstrated a favorable non-clinical safety profile (Gilead data on file). These studies indicate that the drug may minimally slow bone marrow progenitor proliferation and differentiation and that it has expected inhibitory effects on B-cell response to antigen challenge. However, the data indicate that idelalisib is unlikely to cause serious off-target effects or adverse effects on critical organ systems. Idelalisib has no meaningful effect on the human ether-à-go-go-related gene (hERG) channel, indicating that idelalisib would not be expected to induce clinical QT prolongation.

Idelalisib has also proved to be well tolerated in standard in vivo Good Laboratory Practice (GLP) studies of pharmacological safety. A functional observation battery in rats revealed no adverse effects on behavior or on autonomic, neuromuscular, or sensorimotor function. In a cardiopulmonary function study in awake, telemeterized male beagle dogs, single doses of idelalisib induced no meaningful abnormalities in pulmonary, cardiovascular, arterial blood gas, or ECG (including QT interval) parameters. In an assessment of bacterial challenge in rats, idelalisib enhanced, rather than impaired, the phagocytic host clearance of staphylococcal bacteria.

1.2.2.2. Nonclinical Metabolism and Pharmacokinetics

Consistent with the moderate to high bioavailability seen in nonclinical species, idelalisib shows high permeability across human Caco-2 cell monolayers. At lower concentrations, the reverse permeability at low concentration exceeds forward permeability, indicating efflux driven by transporters [eg, human P-glycoprotein (MDR1) and breast cancer resistance protein (BCRP)]; idelalisib is a substrate for the efflux transporters MDR1 and BCRP; however, the permeability increases in a concentration-dependent manner, resulting in a lower efflux ratio at higher, clinically relevant concentrations of idelalisib.

Further details can be found in the idelalisib IB.

1.2.2.3. Toxicology

The toxicological profile of idelalisib was well characterized through the conduct of single dose, repeat dose, developmental and reproductive, genetic toxicology and local tolerance studies. The primary target organ toxicities following repeated dosing include the lymphoid, hepatic, male reproductive systems in rats and dogs, and gastrointestinal system in dogs. Adverse effects in the lymphoid system were primarily the result of on target pharmacology resulting in decreased lymphocytes in multiple lymphoid organs, primarily involving typical B-cell regions.
Liver effects were transient and reversible with continued dosing and did not result in chronic liver injury. Reduction in sperm numbers in males were reversible and did not impact fertility or reproductive performance. Gastrointestinal effects in dogs were minor, superficial, and considered secondary to effects on lymphocytes in Peyer's Patches. Idelalisib was shown to be teratogenic and associated with embryo-fetal lethality. Effects on the reproductive system have been reported for inhibitors which target other isoforms of PI3K. The dose-dependence and potential of idelalisib to selectively inhibit additional PI3K isoforms may be responsible for this off-target toxicity. Additionally, the drug may have the potential to produce phototoxic reactions in humans. These findings represent toxicities that can be monitored, are considered clinically manageable, or are considered acceptable risks in the intended patient population.

Further details can be found in the idelalisib IB.

1.2.3. Clinical Trials of Idelalisib

1.2.3.1. Clinical Experience with Idelalisib

For additional or updated information, please refer to the current version of the idelalisib IB.

1.2.3.2. Phase 1 Studies in Healthy Subjects and in Patients with Allergic Rhinitis (Studies 101-01, 101-04, and 101-05)

Three studies in healthy subjects (Studies 101-01, 101-04, and 101-05) have provided information regarding drug safety, pharmacokinetics, food effects, and the potential for drug interactions with CYP3A4 inhibitors{Webb et al 2010}. One of these trials also included a preliminary evaluation of absorption, metabolism and excretion in healthy volunteers; in this trial, unlabeled idelalisib was co-administered with a trace amount of [^{14}C] idelalisibgiven either orally or intravenously and biological samples were assessed by accelerator mass spectrometry.

Safety results from these studies indicated that idelalisib was well tolerated when administered to healthy subjects at single doses through 400 mg (the highest dose level tested) and was also generally well tolerated when administered to healthy subjects over 7 days at dose levels through 200 mg/dose twice daily (the highest dose level tested). Dosing with 200 mg/dose twice daily for 7 days resulted in a skin rash in 3 out of 6 subjects; histological findings were consistent with a delayed-type hypersensitivity maculopapular exanthema. Rashes have sometimes occurred in patients with hematological malignancies receiving idelalisib, but have not typically proved dose- or treatment-limiting. In placebo controlled single-dose and multiple-dose trials, repeated electrocardiogram (ECG) evaluations performed in tandem with pharmacokinetic monitoring showed no evidence of drug-, dose-, or exposure-dependent effects on cardiac rhythm or cardiac intervals (eg, QT interval).

Pharmacokinetic results indicated that idelalisib appeared rapidly in plasma with a median T_{max} of 1 to 1.5 hours. C_{max} and AUC increased in a less-than-dose-proportional manner and mean $t_{1/2}$ values across the dose range were 6.5 to 9.8 hours.

Idelalisib dosing after a high-fat, high-calorie meal delayed median time of maximum concentration (T_{max}) from 0.75 to 3 hours; mean C_{max} was unaffected and mean AUC was ~40% higher. These changes in idelalisib exposures are considered modest/clinically non-relevant; thus, idelalisib may be given with or without food.

Idelalisib is metabolized in humans primarily by aldehyde oxidase, with some involvement of CYP3A4 and UGT1A4. Accordingly, when idelalisib was administered following 4 days of daily dosing with ketoconazole (a potent inhibitor of CYP3A4), modest/moderate increases in mean idelalisib Cmax and AUC values of ~30% and ~80% higher, respectively, which is not considered to be clinically relevant and suggesting that idelalisib is a weak CYP3A substrate. GS-563117 is formed from idelalisib primarily via aldehyde oxidase.

The ^{14}C-labeled idelalisib human mass balance results showed that the drug has moderate to high oral bioavailability. Idelalisib is eliminated mainly via hepatic metabolism and biliary excretion in the feces (~78% of dose); recovery in urine was < 15%. GS-563117 was the only circulating metabolite observed in human plasma, and was also observed in urine and feces.

Results from the Study GS-US-313-0130 indicate that idelalisib does not affect the pharmacokinetics of substrates of Pgp, BCRP, OATP1B1, or OATP1B3 transporters. idelalisib is not expected to affect the exposures of coadministered agents via transporter mediated interactions. As such, coadministration of potent inducers of CYP3A such as rifampin, carbamazepine, phenytoin, and St. John's Wort with idelalisib should be avoided.

The exposures (AUC) of probe CYP3A substrate, midazolam, were ~5-fold upon coadministration with idelalisib versus midazolam alone, driven by competitive and time-dependent CYP3A inhibition by GS-563117, the only circulating metabolite of idelalisib. Coadministration of the highly potent CYP3A inducer rifampin resulted in a ~75% reduction in idelalisib systemic exposures, likely driven by a higher relative contribution to CYP3A to overall idelalisib clearance under the induced state.

Pharmacodynamic results showed that an idelalisib dose of 200 mg inhibited ex vivo basophil activation via the PI3Kδ-specific, high-affinity IgE receptor (anti FCεR1) in basophils collected from healthy volunteers. The findings were confirmed when the drug was assessed over 7 days in a Phase 1b study in subjects with allergic rhinitis. In this study, idelalisib at a dose level of 100 mg/dose twice daily showed clinical and pharmacodynamic activity (attenuating adverse responses to allergenic challenge and decreasing markers of inflammation) and was well tolerated.

1.2.3.2.1. Clinical Studies in Patients with Hematologic Malignancies

Idelalisib as monotherapy or in combination with other agents (such as bendamustine, chlorambucil) and immunotherapy (rituximab, ofatumumab) has been shown to be tolerable and demonstrated clinical efficacy in clinical trials in patients with iNHL, CLL and other hematological malignancies.

1.3. Information about Companion Drug

1.3.1. Ruxolitinib

Ruxolitinib phosphate is a kinase inhibitor marketed for the treatment of intermediate or high-risk myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis. The approval of ruxolitinib is based on the results of the COMFORT-1 study which demonstrated that ruxolitinib, as compared with placebo, provided significant clinical benefits in patients with myelofibrosis by reducing spleen size, ameliorating debilitating myelofibrosis-related symptoms, and improving overall survival. These benefits came at the cost of more frequent anemia and thrombocytopenia in the early part of the treatment period {Verstovsek et al 2012}. In this study 41.9% of patients on ruxolitinib achieved a spleen response defined as at least 35% reduction in spleen volume from baseline to Week 24, versus 0.7% of patients on placebo ($p < 0.001$). In addition, 45.9% of patients on ruxolitinib achieved improvement in myelofibrosis related symptoms compared to 5.3% of patients in the placebo arm ($p < 0.001$) {Verstovsek et al 2012}. In the COMFORT-2 study where patients with intermediate-2 or high risk myelofibrosis received either ruxolitinib or best available therapy (BAT), 28% of patients in the ruxolitinib arm achieved a spleen response defined as at least a 35% reduction in spleen volume from baseline at Week 48, versus 0% of patients on best available therapy ($p < 0.001$) {Harrison et al 2012}. The benefits of ruxolitinib are not limited to only those with mutated *JAK2*V617F {Cervantes et al 2013}.

Dosing of ruxolitinib at initiation of treatment is predicated upon a patient's platelet count, with dose reduction indicated for various degrees of thrombocytopenia. For patients with platelet count above 200 x 10^9/L prior to starting treatment, the recommended starting dose of ruxolitinib is 20 mg orally twice daily, while for those with platelet count between 100 x 10^9/L and 200 x 10^9/L, recommended starting dose is 15 mg orally twice daily. For those with platelet count between 50 x 10^9/L and less than 100 x 10^9/L, the recommended starting dose goes down to 5 mg orally twice daily (ruxolitinib package insert). Anemia and thrombocytopenia were the most common hematologic adverse events (AE) for subjects on the ruxolitinib arm in the COMFORT-1 study, with approximately half of all Grade 3 or 4 anemia events occurring

during the first 8 weeks of treatment, followed by attainment of a new steady state of hemoglobin level that was approximately 1.0 g/dL below baseline by Week 24. For those subjects on the ruxolitinib arm who developed Grade 3 or 4 thrombocytopenia, approximately half of the thrombocytopenia events also occurred during the first 8 weeks of treatment and resulted in ruxolitinib dose adjustments or dose interruptions on study {Verstovsek et al 2012}. In the COMFORT-2 study, thrombocytopenia and anemia were also the most common hematologic AE, consistent with the mechanism of ruxolitinib. Thrombocytopenia was the most common reason for dose adjustment of ruxolitinib in the COMFORT-2 study (41%), compared to the BAT arm (1%). There were also more patients who required at least one transfusion of packed red blood cells on the ruxolitinib arm (51%), compared to those on the BAT arm (38%) {Verstovsek et al 2012}.

Ruxolitinib is predominantly metabolized by CYP3A4. The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively, following coadministration with strong CYP3A4 inhibitor ketoconazole 200 mg twice daily for 4 days, compared to ruxolitinib dosed alone. There was an 8% and 27% increase in the C_{max} and AUC of ruxolitinib, respectively, following coadministration with erythromycin, a moderate CYP3A4 inhibitor, at 500 mg twice daily for 4 days, compared to ruxolitinib dosed alone.

For current information about ruxolitinib, refer to the package insert.

1.4. Rationale for this Study

Gilead is conducting this Phase 1b study to evaluate the safety, tolerability and PK of idelalisib in subjects receiving ruxolitinib as therapy for PMF, post-PV MF, or post-ET MF who are maintained on a stable dose of ruxolitinib for at least 4 weeks prior to initiating therapy with idelalisib. Though ruxolitinib has demonstrated efficacy in patients with MF, the responses primarily relate to mitigation of splenomegaly and constitutional symptoms. In most patients, reversion of marrow fibrosis and reduction of *JAK2*V617F allele burden are not observed. Two to three year improvement in survival has been observed in ruxolitinib-treated patients vs those initially randomized to placebo (COMFORT-I) or best available therapy (COMFORT-II), which may be related to improvement of the metabolic profile of patients. Suboptimal responses may in part relate to re-activation of JAK activity through its heterodimerization with JAK family members, and persistent activity/upregulaton of signaling pathways, such as PI3K/AKT.

Preclinical data indicate that PI3K and/or mTOR inhibitors are active against MPN cells and their combination with JAK1/2 inhibitors produced synergism. Thus, concurrent targeting of PI3K and JAK/STAT pathways may represent a new therapeutic strategy to optimize efficacy and reduce toxicity in patients with MPN.

Idelalisib at 50 mg once daily, 50 mg twice daily, 150 mg once daily, and 150 mg twice daily will be tested in this study. Given the EC_{90} for PI3K of approximately 301 nM (~125 mg/mL), the median trough concentration following 150 mg twice daily was above the EC_{90} and the median trough concentration following 150 mg once daily was below the EC_{90}. Together with 50 mg once daily, the proposed dose regimens will facilitate the evaluation of the exposure-response relationship in the study population over a wide range of idelalisib exposures.

The doses of idelalisib selected for this study are informed by the metabolism of idelalisiband ruxolitinib and the potential for drug-drug interaction. There are currently no clinical data on monotherapy for idelalisib in MF or the combination of idelalisib and ruxolitinib. Therefore, to minimize the exposure of subjects to toxicities cohort expansion will occur sequentially.

1.5. Compliance

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

2. OBJECTIVES

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of idelalisib through 28 days in subjects receiving ruxolitinib as therapy for intermediate to high risk PMF, post-PV MF, or post-ET MF with progressive or relapsed disease
- To determine the PK of idelalisib and ruxolitinib, in subjects receiving ruxolitinib with PMF, post-PV MF, or post-ET MF with progressive or relapsed disease

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of continuous daily administration of idelalisib beyond 28 days in subjects receiving ruxolitinib with PMF, post-PV MF, or post-ET MF
- To evaluate the efficacy of idelalisib in subjects receiving ruxolitinib with PMF, post-PV MF, or post-ET MF by 2013 Revised IWG-MRT and ELN response criteria

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[redacted]

3. STUDY DESIGN

3.1. Endpoints

The endpoints for this study are described in Section 8.

3.2. Study Design

This is a Phase 1b, open-label, dose escalation study. The planned number of subjects in each cohort is 6. There will be 4 cohorts (A, B, C and D), which will be enrolled sequentially. Cohort A will be enrolled first.

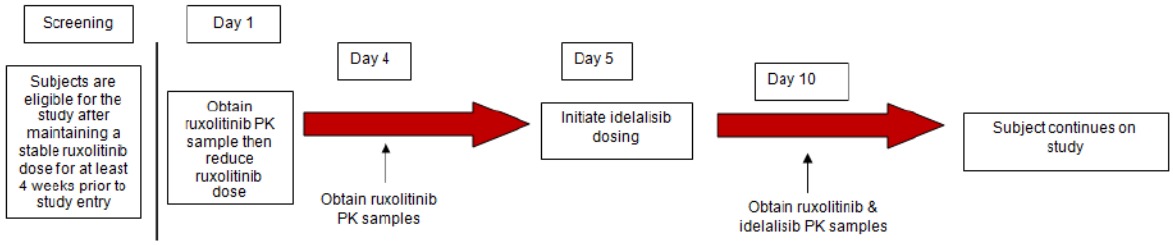
Idelalisib will be administered in subjects receiving ruxolitinib as therapy for PMF, post-PV MF, or post-ET MF and who have been maintained on a stable dose of ruxolitinib for at least 4 weeks prior to study entry. On Day 1 subjects will have a PK sample drawn and then reduce the ruxolitinib dose as follows:

- Subjects on a stable ruxolitinib dose of greater than or equal to 10 mg twice daily, will have their ruxolitinib dose reduced by 50% (rounded up to the closest available tablet strength).
- Subjects on a stable ruxolitinib dose of 5 mg twice daily, will have their ruxolitinib dose reduced to 5 mg once daily.

Idelalisib will be administered starting on Day 5.

PK samples will be obtained on Days 1, 4 and 10 as shown in the schema below:

Schema



The starting doses of Iidelalisib in Cohorts A, B, C, and D are 50 mg once daily, 50 mg twice daily, 150 mg once daily, and 150 mg twice daily, respectively. Enrollment into the study will be on hold while the safety review team (SRT) evaluates the data prior to cohort expansion and dose escalation.

The first 3 subjects will be enrolled in Cohort A at 50 mg once daily idelalisib. After the third subject has completed Day 28 (4 weeks), the SRT will review the safety data. Enrollment will be on hold until the SRT determines the cohort can be expanded to enroll an additional

3 subjects. After the sixth subject in Cohort A completes Day 56 (8 weeks), the SRT will review the cumulative safety and PK data from all subjects in Cohort A. Enrollment will be on hold until the SRT determines Cohort B can be open to enrollment. If the SRT deems the combination of idelalisib with ruxolitinib safe and tolerable at the 50 mg once daily dose, Cohort B will be open to enrollment.

Enrollment and safety assessment by the SRT in Cohort B at 50 mg twice daily idelalisib will proceed as follows: The first 3 subjects will be enrolled. After the third subject has completed Day 28 (4 weeks), the SRT will review the cumulative safety data for Cohorts A and B. Enrollment will be on hold until the SRT determines Cohort B can be expanded to enroll an additional 3 subjects. After the sixth subject in Cohort B completes Day 28 (4 weeks), the SRT will review the cumulative safety data from all subjects in Cohorts A and B, and the cumulative PK data for Cohort B. Enrollment will be on hold until the SRT determines Cohort C can be open to enrollment. If the SRT deems the combination of idelalisib with ruxolitinib safe and tolerable at the 50 mg twice daily dose, Cohort C will be open to enrollment.

Enrollment and safety assessment by the SRT in Cohort C at 150 mg once daily idelalisib will proceed as follows: The first 3 subjects will be enrolled. After the third subject has completed Day 28 (4 weeks), the SRT will review the cumulative safety data for Cohorts A, B and C. Enrollment will be on hold until the SRT determines Cohort C can be expanded to enroll an additional 3 subjects. After the sixth subject in Cohort B completes Day 28 (4 weeks), the SRT will review the cumulative safety data from all subjects in Cohorts A, B and C, and the cumulative PK data for Cohort C. Enrollment will be on hold until the SRT determines Cohort D can be open to enrollment. If the SRT deems the combination of idelalisib with ruxolitinib safe and tolerable at the 150 mg once daily dose, Cohort C will be open to enrollment.

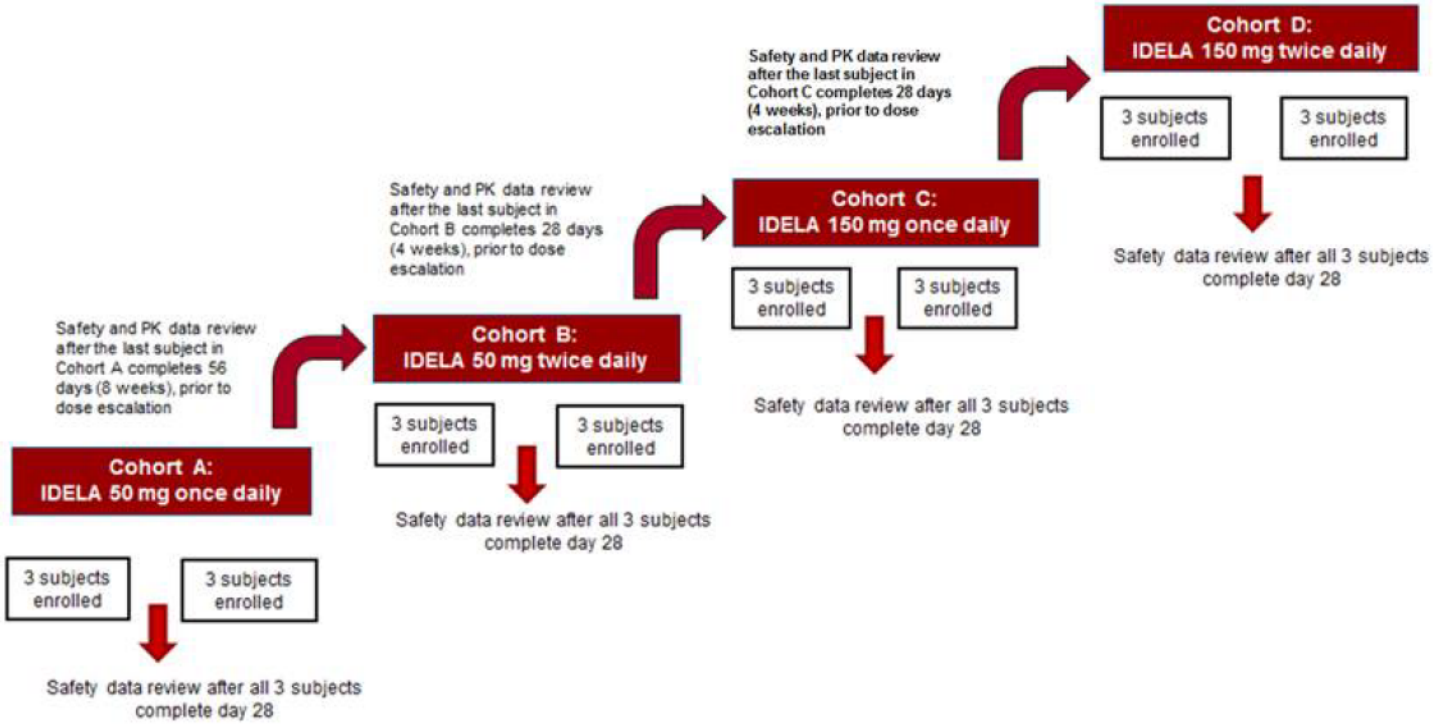
Enrollment and safety assessment by the SRT in Cohort D at 150 mg twice daily idelalisib will proceed as follows: The first 3 subjects will be enrolled. After the third subject has completed Day 28 (4 weeks), the SRT will review the cumulative safety data for Cohorts A, B, C and D. Enrollment will be on hold until the SRT determines Cohort D can be expanded to enroll an additional 3 subjects. After the sixth subject in Cohort C completes Day 28 (4 weeks), the SRT will review the cumulative safety data from all subjects in Cohorts A, B, C, and D, and the cumulative PK data for Cohort D.

Additional cohorts are not planned after enrollment in Cohort D is complete. Subjects who do not receive ≥ 1 dose of idelalisib will be deemed unevaluable and replaced.

In subjects without demonstrable clinical benefit, dose escalation (to a higher dose cohort) may be permitted by the SRT after Cohort C (idelalisib 150mg once daily) has been fully enrolled and the last subject has been on study drug for at least 28 days. The SRT will consider the following − the subject's compliance with therapy, tolerability of the combination of idelalisiband ruxolitinib, overall incidence and severity of AEs (related to idelalisib or ruxolitinib), dose reduction for severe toxicity and dose modifications. Additionally, subjects must show a lack of response by volumetric imaging (three dimensional [3D] magnetic resonance imaging [MRI] or computed tomography [CT], if MRI is not feasible), or by palpation of the liver and/or spleen after at least 12 weeks on study.

The SRT will consist of at least one investigator and the following Gilead study team members: the medical monitor, representatives from Drug Safety and Public Health (DSPH), Clinical Operations, and Biostatistics. Others may be invited to participate as members of the SRT if additional expertise is desired. The medical monitor serves as the chair of the SRT.

Figure 3-1. Study Schema



3.3. Study Treatments

The dose of idelalisib will be 50 mg once daily (Cohort A), 50 mg twice daily (Cohort B), 150 mg once daily (Cohort C), and 150 mg twice daily (Cohort D) administered orally continuously. The treatment period for individual subjects is expected to be 24 weeks in duration. Subjects will receive the first dose of idelalisib on Day 5.

The study drug, idelalisib, will be supplied by Gilead. The formulation, packaging, and dosing regimen are described in Section 5.

The companion drug, ruxolitinib, will be acquired by the investigators through commercially available means. Ruxolitinib will be administered per standard of care during screening. On Day 1, the ruxolitinib dose will be reduced by 50% as described in Study Design (Section 3.2). Subjects will continue ruxolitinib dosing during screening and throughout the study treatment period.

3.4. Duration of Treatment

The duration of treatment for individual subjects is expected to be 24 weeks.

The screening period is 28 days, treatment period is 24 weeks, and the safety follow-up period is 30 days after the end of study (EOS) visit. Subjects who are on idelalisib beyond week 24, and in the opinion of the investigator are deriving clinical benefit, can remain on the study and receive both ruxolitinib and idelalisib treatment for the extension period until disease progression.

3.5. Discontinuation Criteria for Cohorts

The 4 cohorts (A, B, C, and D) planned for this study will be enrolled sequentially. Cohort A will be the first cohort open to enrollment. The SRT will not open Cohorts B, C, or D to enrollment if the cumulative data reveals unexpected treatment-related AE to idelalisib in the preceding cohorts.

3.6. Source Data

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

CCI [redacted]

CCI [redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 24 subjects who meet the eligibility criteria will be enrolled.

4.2. Inclusion Criteria

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

1) Age ≥ 18 years of age

2) Subjects must have been on a stable dose of ruxolitinib for at least 4 weeks prior to study entry

3) Subjects with PMF, post-PV MF, or post-ET MF classified as high risk or intermediate risk as defined by the Dynamic International Prognostic Scoring System (DIPSS) for PMF(Appendix 4) or DIPSS Plus, if cytogenetics are available (Appendix 5)

4) Subjects with PMF, post-PV MF, or post-ET MF who are receiving ruxolitinib and meet 2013 Revised IWG-MRT and ELN response criteria with progressive and relapsed disease, with modifications for progressive disease

   a) Progressive disease:

   - Appearance of a new splenomegaly that is palpable at least 5 cm below the left costal margin (LCM), or
   - A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm, or
   - A 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm, or
   - An increase in palpable splenomegaly from best ruxolitinib response of > 25% but < 50% in a subject who does not meet criteria for complete remission (CR), partial remission (PR), or clinical improvement (CI)

   b) Relapsed disease:

   - No longer meeting criteria for at least CI after achieving CR, PR, or CI, or
   - Loss of anemia response persisting for at least 1 month, or
   - Loss of spleen response persisting for at least 1 month

5) Life expectancy > 24 weeks in the opinion of the investigator

6) European Cooperative Oncology Group (ECOG) performance status of ≤ 2

7) Required screening laboratory values as shown in the table below:

Organ System	Parameter	Required Value
Hepatic	Serum total bilirubin	≤ 1.5 × ULN (unless elevated due to Gilbert's syndrome or hemolysis)
	Serum ALT Serum AST	≤ 2.5 × ULN
Hematopoietic	ANC	≥ 1.0 × 10^9/L
	Peripheral blood blast or bone marrow blood blast count	< 20%
	Platelets	≥ 50 × 10^9/L
Renal	$_eC_{Cr}$[a]	≥ 30 mL/min
Pregnancy	β-hCG[b]	Negative
Infection	HIV	Negative HIV antibody
	HBV	Negative HBsAg and negative HBc antibody, or positive HBc antibody and negative HBV DNA by quantitative PCR
	HCV	Negative viral RNA (if HCV antibody is positive)
	CMV	Negative CMV PCR or pp65 antigen

a As calculated by the Cockcroft-Gault formula or measured
b For women of childbearing potential only
Abbreviations: HBc antibody=anti-hepatitis B core antibody

8) Female subjects of childbearing potential, willing to use a protocol-recommended method of contraception during heterosexual intercourse from signing of informed consent throughout the study treatment period and to 30 days from the last dose of idelalisib (see Appendix 10 for more information)

9) Male subjects having intercourse with females of childbearing potential, willing to use a protocol recommended method of contraception from Day 1 throughout the study treatment period and for 90 days following the last dose of idelalisib and to refrain from sperm donation from Day 1 throughout the study treatment period and for 90 days following the last dose of idelalisib (see Appendix 10 for more information)

10) In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current myelofibrosis disease status, medical condition, the potential benefits and risks of alternative treatments for myelofibrosis

11) Willing and able to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions, including mandatory prophylaxis for PJP

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

4.3. Exclusion Criteria

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

1) Subjects on a stable ruxolitinib dose of 5 mg once daily

2) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation

3) Ongoing drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver

4) Ongoing drug-induced pneumonitis

5) Ongoing inflammatory bowel disease

6) Ongoing alcohol or drug addiction

7) CMV: Ongoing infection, treatment, or prophylaxis within the past 28 days

8) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled bacterial, fungal, or viral infection, or active or chronic bleeding event within 4 weeks prior to first dose of investigational medicinal product (IMP) that would limit compliance with study requirements as judged by the treating physician

9) History of a concurrent or second malignancy except for adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥ 1 year, adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥ 5 years

10) Participation in an ongoing investigational drug or device trial or use within 6 weeks of chemotherapy (with exception made for hydroxyurea, see Section 5.4.6), investigational agent, immunomodulating therapy, biologic therapy or radiation therapy. Erythropoietin stimulating agents (ESA) are allowed as long as a subject has been on a stable dose for a minimum of 12 weeks for the treatment of anemia.

11) Symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or unstable cardiac arrhythmia requiring medication

12) Known hypersensitivity to the study IMP, the metabolites, or formulation excipients

13) Unwilling or unable to take oral medication

14) Unresolved non-hematologic toxicities from prior therapies that are
> Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 (with the exception of alopecia [Grade 1 or 2 permitted])

15) Pregnant or lactating females

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Description and Handling of Idelalisib and Ruxolitinib

5.1.1. Formulation

Idelalisib will be provided in tablet form intended for oral administration. Each tablet contains 50 mg, 100 mg, or 150 mg of active idelalisib. The 50 mg and 150 mg tablets will be used for initial therapy; the 100 mg tablets are provided for use by those subjects who require a dose reduction (see Table 5-1).

The 50 mg and 150 mg tablets are pink; the 100 mg tablets are orange. Both tablets are film-coated, and include the following inactive excipients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, red iron oxide (50 mg and 150 mg tablets only), FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake (100 mg tablets only), polyethylene glycol, talc, polyvinyl alcohol (PVA), and titanium dioxide.

Refer to the ruxolitinib package insert for the ruxolitinib formulation.

5.1.2. Packaging and Labeling

Idelalisib tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 60 tablets of one of the relevant dose strengths (50 mg, 100 mg, or 150 mg) and polyester packing material. Each bottle is enclosed with a white, continuous-thread, child-resistant, polypropylene screw cap with an induction-sealed and aluminum faced liner.

Study drug (idelalisib) to be distributed to centers in the US will be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA) and/or other local regulations.

Refer to the ruxolitinib package insert for ruxolitinib packaging and labeling.

5.1.3. Storage and Handling

Idelalisib 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). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Refer to the ruxolitinib package insert for ruxolitinib storage and handling.

5.2. Dosage and Administration of Idelalisib

The clinic pharmacist or an alternative qualified person will be responsible for dispensing idelalisib. Tablets should be kept in the original bottles provided.

5.2.1. Dosing Instructions

The prescribed dose of idelalisib will be taken orally. At each dose administration, idelalisib is to be swallowed whole with 120 to 240 mL (approximately 4 to 8 ounces) of water. In case of breakage of the tablets in the oral cavity, additional water should be taken as a rinse.

Idelalisib may be taken with or without food. There are no known dietary restrictions related to study drug use. When idelalisib is dosed once daily, it will be taken in the morning. When idelalisib is dosed twice daily it should be taken at approximately the same times each day. Ideally, doses should be taken at approximately 12 hour intervals (eg, at 7 AM and at 7 PM).

At specified clinic visits, idelalisib and/or ruxolitinib will be administered in the clinic at the same time with dosing appropriately timed relative to blood sampling for pharmacokinetics. Clinic staff will record idelalisib and ruxolitinib administration information, including the exact clock time of each dose, for doses administered in the clinic or hospital. Prior to these visits, subjects will be reminded not to take their morning dose of idelalisib and/or ruxolitinib before coming into the clinic. Subjects will also be reminded to bring idelalisib and ruxolitinib with them to clinic for dosing. Thereafter, subjects will be given an adequate supply of tablets to take at home.

Subjects who have a delay in administration of idelalisib of < 6 hours should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay in administration of idelalisib of ≥ 6 hours, the dose should not be taken. Idelalisib administration may continue but the missed dose should not be made up and the planned timing of subsequent study drug dosing should not be altered. Vomited doses may be retaken, but only if the tablet is visible in the vomitus.

Subjects will continue on the same schedule of administration of ruxolitinib prior to initiation of idelalisib. Refer to the ruxolitinib package insert for additional information on ruxolitinib dosage and administration.

5.2.2. Dose Levels

Idelalisib dose levels and tablet numbers for all the cohorts are provided in Table 5-1. The lower dose level (Dose Level −1) is provided in case a subject requires idelalisib dose modification. Dose modifications may be made in response to toxicity as described below (Table 5-1 and Table 5-2).

Table 5-1. Idelalisib Dose Reduction Algorithm

Cohort A

Dose Level	Dosing Regimen	Tablet Strength	Tablet Number Per Dose
Starting dose	50 mg/dose once daily	50 mg	1
−1	No dose reduction permitted	Not applicable	Not applicable

Cohort B

Dose Level	Dosing Regimen	Tablet Strength	Tablet Number Per Dose
Starting dose	50 mg/dose BID	50 mg	1
−1	50 mg/dose once daily	50 mg	1

Cohort C

Dose Level	Dosing Regimen	Tablet Strength	Tablet Number Per Dose
Starting dose	150 mg/dose once daily	150 mg	1
−1	100 mg/dose once daily	100 mg	1

Cohort D

Dose Level	Dosing Regimen	Tablet Strength	Tablet Number Per Dose
Starting dose	150 mg/dose BID	150 mg	1
−1	100 mg/dose BID	100 mg	1

If a subject experiences an AE that is suspected to be related to idelalisib during the course of study, then idelalisib administration will be managed as in Table 5-2.

After an idelalisib dose reduction, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates the lower dose level of idelalisib for ≥ 4 weeks, then the dose may be increased to the starting dose, at the discretion of the investigator. Such a re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not related to idelalisib.

5.3. Dose Adjustments

The dose adjustment recommendations in Table 5-2 are based on the CTCAE v 4.03 (Appendix 11). However, exceptions are expected for subjects who initiate study treatment with low blood counts. Clinical judgment should apply, and in cases of uncertainty, the study medical monitor should be contacted.

The dose modification instructions focus on the types of events most commonly attributed to idelalisib. The management for idelalisib attributed adverse events is provided in Table 5-2 and comprises required and recommended actions. Variations may be warranted based on an investigator's individual judgment in considering potential risks, benefits, and therapeutic alternatives available to each subject; variation from the guidelines outlined in Table 5-2 requires written approval from the Gilead medical monitor.

If idelalisib or ruxolitinib is withheld for more than 4 consecutive weeks due to treatment-related toxicity, it will be permanently discontinued.

If idelalisib or ruxolitinib is withheld for reasons other than treatment-related toxicity for more than 4 consecutive weeks either drug may be restarted with approval from the Gilead medical monitor.

Table 5-2. Idelalisib Dose Adjustment Guidelines

NCI CTCAE v 4.03 Grade	Required Action	Recommended Action
HEMATOLOGICAL ADVERSE EVENTS:		
Neutropenia [a]		
Grade ≤ 2 neutropenia	Maintain current dose level and schedule.	
Grade 3 neutropenia	Maintain current dose level and schedule. Monitor CBC at least weekly until neutropenia has recovered to Grade 2.	
Grade 4 neutropenia (or occurrence of neutropenic fever or infection)	Interrupt idelalisib dosing. Monitor CBC weekly until neutropenia has improved to ≤ Grade 2.	Idelalisib dosing may be resumed at a lower dose level when ANC grade is ≤ Grade 3.
Thrombocytopenia [a]		
Grade ≤ 3	Maintain current dose level and schedule.	
Grade 4	Withhold for bruising or bleeding related to idelalisib along with adequate recovery of thrombocytopenia (Grade ≤3).	May resume idelalisib at initial or lower dose level at investigator discretion.
NON-HEMATOLOGICAL ADVERSE EVENTS:		
Dermatological		
Rash		
Grade ≤ 2	Maintain current dose level and schedule.	
Grade ≥ 3	Withhold idelalisib and monitor at least once weekly until rash Grade ≤ 1	May resume at lower dose level (Cohorts B, C, and D) or discontinue idelalisib at investigator discretion.

NCI CTCAE v 4.03 Grade	Required Action	Recommended Action
Stevens-Johnson Syndrome (SJS) /Toxic Epidermal Necrolysis (TEN)		
Any Grade	1. Discontinue idelalisib. 2. Interrupt coadministered medications potentially associated with SJS or TEN. 3. Institute treatment per institutional standards	
Diarrhea or colitis		
Any Grade	1. Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents. 2. Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (e.g., evaluate for sepsis, bowel obstruction, dehydration).	1. Provide anti-diarrheal and maintain current idelalisib dose level and schedule. 2. Differentiate between small-bowel and large-bowel diarrhea on a clinical basis. If unclear, consider upper and lower tract endoscopy with biopsy. -Small bowel diarrhea is characterized by large volume diarrhea (more than one per day), possible associated dehydration, weight loss and paraumbilical pain. Consider an endoscopic small-bowel biopsy and evaluate other etiologies such as celiac disease. -Large-bowel diarrhea may present with lower pelvic pain, tenesmus, and generally smaller stool volumes with gross blood frequently found in the stool. Consider a colonoscopic evaluation and biopsy. 3. Ensure good hydration status
Grade $\geq$ 2 diarrhea or colitis (unless clinical diagnosis is established from medical history and physical examination)	1. Stool culture for routine pathogens (Salmonella, Shigella, Campylobacter species), testing for Clostridium difficile toxin, Rotavirus, Cytomegalovirus (CMV), and Adenovirus 2. Stool for Ova and Parasites (Cryptosporidium parvum, Isospora belli, Enterocytozoon bieneusi, Septata intestinalis, Strongyloides, Microsporidia, Entamoeba histolytica, Cyclospora), Giardia antigen	

NCI CTCAE v 4.03 Grade	Required Action	Recommended Action
Grade ≥ 3 diarrhea or colitis or persistent Grade 2 diarrhea or colitis without clear etiology	1. Withhold idelalisib. 2. Consider anti-diarrheal (eg, loperamide) and/or addition of anti-inflammatory agent (eg, sulfasalazine, budesonide).	1. Endoscopy with biopsy is strongly recommended to asses by immunohistochemistry (IHC) and PCR for CMV, Adenovirus. [redacted] 3. At Grade ≤1, may resume idelalisib at lower dose or discontinue at investigator discretion.
Bowel Perforation		
	Discontinue idelalisib.	
HEPATIC ADVERSE EVENTS (ELEVATIONS IN ALT, AST, OR BILIRUBIN):		
Grade ≤ 2 (ALT/AST >3-5×ULN) (Bilirubin >1.5-≤ 3×ULN)		Monitor ALT, AST, ALP, and bilirubin at least weekly until all abnormalities are Grade ≤1. Thereafter, maintain current dose level.
Grade 3 (ALT/AST > 5-20×ULN) (Bilirubin >3-10×ULN)		1. Withhold idelalisib. 2. Monitor ALT, AST, ALP, and bilirubin at least weekly until all abnormalities are Grade ≤1. 3. If bilirubin abnormality was Grade < 3, resume idelalisib at same dose level. If bilirubin abnormality was Grade ≥3, resume idelalisib at lower dose level (Cohorts B, C, and D) or re-challenge at same dose level (Cohort A).
Grade 4 (ALT/AST > 20×ULN) (Bilirubin > 10×ULN)	1. Withhold idelalisib. 2. Monitor ALT, AST, ALP, and bilirubin at least weekly until all abnormalities are Grade ≤ 1. 3. If bilirubin abnormality was Grade 4, discontinue idelalisib	If bilirubin abnormality was Grade <4, resume idelalisib at lower dose level (Cohorts B, C, and D), re-challenge at same dose level (Cohort A).
Pneumonitis (with new onset or worsening of baseline dyspnea, cough, or hypoxia without obvious infectious cause)		
Grade 1(asymptomatic)	Withhold idelalisib until resolution to baseline. May resume at lower dose level or discontinue at investigator discretion.	
Grade ≥2	Discontinue idelalisib permanently in subjects with any severity of symptomatic pneumonitis and institute therapy as clinically appropriate.	

NCI CTCAE v 4.03 Grade	Required Action	Recommended Action
Pneumocystis pneumonia		
Any Grade	Discontinue idelalisib	
CMV infection[b]/Reactivation		
Any Grade	1. Interrupt idelalisib upon unequivocal clinical or laboratory evidence of CMV infection. 2. Treat according to established clinical guidelines. 3. If the benefits of resuming idelalisib are judged to outweigh the risks, consideration should be given to administering pre-emptive CMV therapy	
OTHER NON-HEMATOLOGICAL ADVERSE EVENTS:		
Grade ≤ 2	Maintain current dose level and schedule and monitor at least weekly until resolved.	
Grade ≥ 3	If felt to be related to idelalisib, withhold idelalisib until Grade ≤ 1. May resume idelalisib at same or lower dose level or discontinue idelalisib at investigator discretion.	

a Refer to Appendix 11 for CTCAE 4.03 grading
b CMV should be diagnosed using clinical or laboratory criteria per established institutional standard.

There will be no dose reductions for subjects in Cohort A at 50 mg once daily idelalisib. Modifications to ruxolitinib dosing will be based on its package insert.

5.4. Prior and Concomitant Medications

To the extent possible, administration of any prescription or over-the-counter drug products other than study medication should be minimized during the study period. Subjects should be discouraged from use of street drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol at any time during the clinical study of idelalisib.

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The decision to authorize the use of any drug other than idelalisib or ruxolitinib should take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study.

Subjects should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the course of the study. Any concomitant drugs taken by a subject during the course of the study and the reason for use will be recorded on the electronic case report forms (eCRFs).

Information regarding use or restrictions on specific concomitant medications, dietary measures, or other interventions is provided below.

5.4.1. Anticancer or Experimental Therapies Other than Idelalisib

No other anticancer therapies (including chemotherapy, radiation, antibody therapy, immunotherapy, or other experimental therapies) of any kind are permitted while the subject is on study except as indicated in Section 5.4.6. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

5.4.2. Antiemetics

Nausea and/or vomiting have not been commonly observed with idelalisib in prior studies. However, subjects who experience nausea or vomiting while on study will be managed based on the judgment of the treating physician and local institutional practices.

5.4.3. Granulocyte Colony-Stimulating Factors and Erythropoietin

Granulocyte-macrophage colony-stimulating factors (GM-CSF) should not be administered given the potential for GM-CSF-related inflammatory symptoms. The use of Granulocyte colony-stimulating factor (G-CSF) is permitted in compliance with regional prescribing information. The indication, use, dose and duration of G-CSF will be documented in the eCRF. The use of erythropoietic stimulating agents while on study is not permitted if the subject has not been on ESAs for at least 12 weeks prior to study entry.

5.4.4. Drugs that Undergo CYP3A-Dependent Metabolism

The major metabolite of idelalisib, GS-563117, is a reversible and time dependent inhibitor of CYP3A; accordingly coadministration of idelalisib with midazolam, a probe CYP3A substrate, resulted in an approximately 5-fold increase in midazolam systemic exposure (AUC), indicating that idelalisib is a strong inhibitor of CYP3A . Coadministration of CYP3A substrates with idelalisib may result in an increase in their systemic exposures (eg, certain antiarrhythmics, calcium channel blockers, benzodiazepines, HMG-CoA reductase inhibitors, phosphodiesterase-5 [PDE5] inhibitors, warfarin). Avoid coadministration of narrow therapeutic index CYP3A substrates (eg, alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine, astemizole, terfenadine) with idelalisib.

5.4.5. Drugs that Inhibit/Induce CYP3A-Dependent Metabolism

Ruxolitinib is primarily metabolized by CYP3A4. The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively, following coadministration with strong CYP3A4 inhibitor ketoconazole 200 mg twice daily for 4 days, compared to ruxolitinib dosed alone. When administering ruxolitinib with strong CYP3A4 inhibitors a dose reduction is recommended.

Idelalisib is metabolized primarily via aldehyde oxidase and in part by CYP3A. A clinical drug-drug interaction study (study 101-05) indicated that administration of a potent CYP3A inhibitor together with idelalisib resulted in an approximately 80% increase in idelalisib plasma exposures (AUC), which is not considered to be clinically relevant and suggesting that idelalisib

is a weak CYP3A substrate. Results from a clinical drug-drug interaction study (GS-US-313-0130) indicate that when co-administered with rifampin, a highly potent inducer of CYP3A, idelalisib exposures are approximately 75% lower. Coadministration of potent inducers of CYP3A with idelalisib should be avoided; a list of potent inducers is provided in Table 5-3 below:

Table 5-3. Known Potent Inducers of CYP3A

Effect on CYP3A	Drug Class	Medications
Potent CYP3A Inducers	Antimycobacterials	Rifampin
	Anticonvulsants	carbamazepine, phenytoin
	Foods/herbs	St. John's wort

Abbreviation: CYP=cytochrome P450 enzyme

5.4.6. Immunization

Because of its actions to inhibit PI3Kδ-dependent B-cell function, high doses of idelalisib can impair primary or secondary responses to immunization in animals. Subjects who are at substantial risk of an infection (eg, influenza) that might be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of idelalisib. Of note, the safety of immunization with live viral vaccines following idelalisib therapy has not been studied and vaccination with live virus vaccines during study is not recommended.

5.4.7. Hydroxyurea

The use of hydroxyurea is permissible to control blood counts when deemed required in the medical judgment of the investigator. The dose, duration, and indication for hydroxyurea will be documented and captured in the eCRF.

5.4.8. Surgery

There are no known effects of idelalisib on coagulation or wound healing. The ruxolitinib product insert should be consulted for information on coagulation, wound healing, or surgery.

5.4.9. Diet

There are no specific dietary restrictions in the study. Idelalisib may be taken with or without food. Ruxolitinib can be taken with or without food.

5.5. Accountability for Idelalisib

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

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

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

5.5.1. Investigational Medicinal Product Return or Disposal

Idelalisib should be retrieved from each subject at the end of each dispensing interval. The quantity of study drug and the date returned by the subject will be recorded in the study drug accountability records. All study drug returned by the subject will be retained for review by the study site monitor prior to return to Gilead or destruction on-site.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows. The investigator must document any deviation from protocol procedures and notify the sponsor.

6.1. Subject Enrollment and Treatment Assignment

All subjects or legally acceptable representatives must personally sign, date and receive a copy of the informed consent form (ICF) before any study specific screening procedures are performed. Subjects will be assigned a unique screening number at the time of consent.

It is the responsibility of the investigator to ensure that subjects are eligible for the study prior to enrollment. Once eligibility is confirmed a subject will be assigned another unique subject number. This number will be used to identify the subject throughout the study and must remain the same. This is an open label study.

6.2. Study Procedure Descriptions

6.2.1. Informed Consent

All subjects must sign and date the IRB approved informed consent form before any study procedures are performed. CCI [redacted]

6.2.2. Medical and Medication History

A complete medical, surgical and concomitant medication history will be obtained during screening and recorded on the eCRF. This includes the *JAK2*V617F mutation status if known. A history of medications taken within 3 months prior to screening, and during the screening period (eg, ruxolitinib dose) will be obtained and recorded in the eCRF.

The transfusion history within 3 months of screening and transfusion events throughout the study including screening will be recorded and reported in the eCRF.

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

The DIPSS will be completed for all subjects at screening. If cytogenetics is available for the subject, the DIPSS Plus should be completed instead of the DIPSS.

6.2.4. Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, and oral temperature, will be measured by the investigator or qualified designee at every visit as listed in the study procedures (Appendix 2).

6.2.5. Physical Examination

The physical examination (PE), including palpation of the liver and spleen, may be performed by a physician, physician's assistant or nurse practitioner qualified to perform the assessment at the time points listed in the study procedures (Appendix 2).

At Screening, a complete PE will be performed including height, body weight, and clinical signs, and symptoms. Height will be measured at screening only. Body weight assessments will be performed throughout the study per institutional practice. Breast, genital, and rectal examinations are not required at any study visit unless warranted in the opinion of the investigator. Physical examination findings during the screening period will either be reported as medical history or adverse events based on the requirements in Section 7.1.1.

At subsequent study visits, the PE will be an interim examination to monitor any changes and will include an assessment of disease-related clinical signs and symptoms. Physical exams will be scheduled every 4 weeks during the extension period until a subject has been on study for 1 year, when it will be scheduled every 12 weeks.

More frequent examinations may be performed at the investigator's discretion, if clinically indicated.

6.2.6. ECOG Performance Status

Performance status will be assessed at Screening and at every visit a physical exam is scheduled as outlined in the study procedures (Appendix 2).

6.2.7. Patient-reported Outcomes (PRO) Assessments

PRO assessments performed at study visits should be completed prior to any other visit assessments.

6.2.7.1. Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)

The full MPN-SAF (Appendix 8) is a 27-item questionnaire that consists of the 9-question Brief Fatigue Inventory and expands on the assessment collected using the modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPNSAF TSS, Appendix 9). This will be completed weekly for the first 24 weeks, then monthly for the subjects on study beyond Week 24, and at EOS. Whenever study visits are scheduled the questionnaire should be completed in the clinic. Subjects will receive a copy of the questionnaire to complete at home between clinic visits beginning Week 4.

The MPN-SAF is self-administered. In the event a translated version of the questionnaire is not available in the primary language in which the subject reads or converses, PRO data will not be collected.

6.2.8. Electrocardiogram

A standard 12-lead ECG reporting will be performed at the Screening visit per institutional practice and whenever clinically indicated at the discretion of the investigator. The investigator or qualified designee will review all ECGs. The original ECG tracings will be maintained in the source documentation of each subject and the appropriate data reported on the eCRF.

6.2.9. Laboratory Assessments

Blood samples for local laboratory testing will be collected according to the study procedures in Appendix 2. Additional safety laboratory assessments may be performed if clinically indicated.

Table 6-1. Analytes

Chemistry	Hematology	Urinalysis[c]	Other
Albumin	ANC	Specific gravity	Serum β-hCG or urine pregnancy test[d]
Alkaline phosphatase	RBC	pH	HIV antibody
ALT/SGPT	Hemoglobin	Occult blood	Hepatitis B surface antigen
AST/SGOT	Hematocrit	Protein	Hepatitis B core antibody[e]
Bicarbonate	Platelets	Glucose	Hepatitis C antibody
BUN	Reticulocytes (%)		Hepatitis C viral RNA[f]
Calcium	WBC	Microscopic[c]	ESR
Chloride		RBC casts	
Creatinine[a]	Differential	WBC casts	CMV (quantitative PCR or pp65 antigen)
GGT	Neutrophils		
Glucose	Bands		
Iron[b]	Eosinophils		
LDH	Basophils		
Magnesium	Lymphocytes		Immune monitoring:
Phosphorus	Monocytes		• Lymphocyte subset panel using flow cytometry (immunophenotyping)
Potassium			• Quantitative immunoglobulins: IgG, IgM, IgA
Sodium	Blasts		• Serum CH50 level
Total bilirubin	Promyelocytes		
Direct bilirubin	Myelocytes		
Total protein	Metamyelocytes		
Uric acid	Nucleated Red Blood Cells		
	Coagulation	**Bone Marrow**	
	PT/INR aPTT/PTT	Blast (%)	

Abbreviations: ESR=erythrocyte sedimentation rate; GGT=gamma-glutamyltransferase;
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 Cockroft-Gault formula
b This includes serum iron, transferrin, transferrin saturation and ferritin.
c Dipstick will be used for urinalysis; microscopic will be performed only if dipstick results are abnormal.
d Females of childbearing potential
e Only if hepatitis B surface antigen is positive
f Only if hepatitis C antibody is positive

6.2.10. Immune Monitoring

Laboratory samples for immune monitoring will be collected at Screening, Week 4, 12, 24 and every 12 weeks thereafter and EOS visit:

- Lymphocyte subset panel using flow cytometry (immunophenotyping)
- Quantitative immunoglobulins: IgG, IgM, IgA
- Serum CH50 level

6.2.11. Pregnancy Test

Females of childbearing potential will have a pregnancy test during Screening (serum) and monthly throughout the study (urine) as outlined in the study procedures in Appendix 2.

6.2.12. Pharmacokinetics (PK)

Blood samples for PK analysis will be collected throughout the study as outlined in the study procedures Appendix 2. Samples for ruxolitinib PK will be collected relative to ruxolitinib dosing on Day 1 predose and Day 4 at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post dose. Samples for idelalisib and ruxolitinib PK will be collected beginning Day 10 relative to idelalisib and ruxolitinib dosing at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post dose. For the 12 hour post dose PK time point on Day 4 and Day 10, the blood sample for PK will be collected prior to ruxolitinib and/or idelalisib dosing.

On Days 15, 36, 78, and 162 blood samples will be collected predose and 1.5 hours post dose. If the EOS visit coincides with Week 24 (Day 162), every effort should be made to collect the predose blood sample for idelalisib and ruxolitinib PK. A ± 5 minute window will be allowed for all PK sample collection time points.

6.2.13. Pneumocystis Jiroveci Pneumonia (PJP) Prophylaxis

Subjects must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment.

Prophylaxis will continue for a period of 2 to 6 months after idelalisib discontinuation. The duration of prophylaxis should be based on clinical judgment and may take into account risk factors such as concomitant corticosteroid treatment and prolonged neutropenia after idelalisib treatment ends.

CCI [redacted]

[redacted]

6.2.15. Bone Marrow Biopsy and Aspirate

Bone marrow biopsy and aspirate with cytogenetics, core biopsy, trichrome stain for reticulin, and iron stain will be performed as outlined in the study procedures (Appendix 2). It will be obtained at screening if one has not been done in the past 3 months or if the results are not available, Days 78, 162, and every 24 weeks during the extension period. At the EOS, a bone marrow biopsy and aspirate will be obtained if one has not been done in the past 24 weeks.

6.2.16. Magnetic Resonance Imaging (MRI)

A 3D MRI (or CT, if MRI not feasible) for the liver and spleen size by volumetric imaging will be performed at Screening, Weeks 12, 24, every 12 weeks during the extension period, and at the EOS visit if one has not been done within the past 12 weeks (see Appendix 2).

Volumetric imaging of the liver by 3D MRI (or CT, if MRI not feasible) performed as standard of care prior to signing the ICF, and within 8 weeks of enrollment, may be used to fulfill the screening requirement.

6.2.17. Adverse Events and Concomitant Medications

Subjects will be assessed for adverse events and concomitant medications during each visit. Any AE or concomitant medication use reported throughout the study will be recorded in the eCRF with appropriate source documentation

6.2.18. Assessment of Diarrhea/Colitis

- Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents

- Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration)

6.2.19. Evaluation for Gastrointestinal Events/Colitis

For Grade 2 colitis and diarrhea (unless clinical diagnosis is established from medical history and physical examination), the following testing is required:

- Stool culture for routine pathogens (Salmonella, Shigella, Campylobacter species, Clostridium difficile toxin, Rotavirus, Cytomegalovirus, Adenovirus)

- Stool for Ova and Parasites (Cryptosporidium parvum, Isospora belli, Enterocytozoon bieneusi, Septata intestinalis, Strongyloides, Microsporidia, Entamoeba histolytica, Cyclospora), Giardia antigen

For grade ≥ 3 or persistent grade 2 colitis or diarrhea without clear etiology (eg, clostridium difficile enterocolitis), endoscopy with biopsy is required. All biopsy samples should include immunohistochemistry (IHC) and PCR for CMV, Adenovirus.

CCI [redacted]

6.2.20. Differentiation Between Small-Bowel and Large-Bowel Diarrhea

Differentiation between small-bowel and large-bowel diarrhea: maybe possible on a clinical basis. If unclear, consider upper and lower tract endoscopy with biopsy.

- Small bowel diarrhea is characterized by large volume diarrhea (more than one per day), possible associated dehydration weight loss and paraumbilical pain. Consider an endoscopic small-bowel biopsy and evaluate other etiologies such as celiac disease.

- Large-bowel diarrhea may present with lower pelvic pain, tenesmus, generally smaller stool volume with gross blood frequently found in the stool; Consider a colonoscopic evaluation and biopsy.

6.3. Pretreatment Assessments

6.3.1. Screening Visit

The screening date is defined as the date the subject signs the informed consent form. The screening period begins once a subject has provided written informed consent to participate in the study and ends on the first day of the treatment period. Subjects will be screened within 28 days to determine eligibility for participation in the study. Assessments for this visit are outlined in study procedures Appendix 2. MRI (or CT, if MRI is not feasible) should be the last screening assessment scheduled after all other eligibility requirements have been met. With the exception of imaging and palpation of the liver and/or spleen, standard of care procedures conducted prior to a subject's participation in the study but are within the 28 day screening window may be used to determine eligibility, at the discretion of the investigator.

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

6.3.2. Baseline Assessments

The baseline assessments (see Appendix 2) will be conducted on Day 1 after subject eligibility has been established within the 28 day screening period. The study procedures in the clinic are scheduled relative to the morning dose of ruxolitinib. Prior to the scheduled visit, subjects should be reminded not to take their morning dose before coming to the clinic.

6.4. Treatment Period

The treatment period is Weeks 1 to 24, which includes the baseline assessments (Section 6.3.2) and the visit schedule is outlined in Appendix 2. The study procedures in the clinic are scheduled relative to the morning dose of ruxolitinib and/or idelalisib. Prior to the scheduled visits, subjects should be instructed to hold their morning dose before coming to the clinic on days where PK lab draws will be taken (Day 1 and 4 for ruxolitinib, and Day 10, 15, 36, 78, 162 for both idelalisib and ruxolitinib PK).

6.5. Extension Period

The extension period begins after Week 24 and the visit schedule is outlined in Appendix 2. Physical exams will be scheduled every 4 weeks until a subject has been on study for 1 year, when it will be scheduled every 12 weeks. Assessments scheduled every 12 and 24 weeks will overlap assessments scheduled every 4 weeks. The study procedures in the clinic are scheduled relative to the morning dose of ruxolitinib and/or idelalisib. Prior to the scheduled visits, subjects should be reminded not to take their morning dose before coming to the clinic.

6.6. Post-treatment Assessments

The EOS and Safety Follow-up visits may be performed on the same day, if the subject will be discontinuing study treatment and discontinuing the study at the same time (eg, withdrawal of consent). After discontinuing treatment, subjects will complete the following visit and discontinue study participation.

6.6.1. End of Study

End of Study assessments (see Appendix 2) will be completed once it has been determined that the subject will discontinue all study assessments. As stated in Section 6.8, even if a subject permanently discontinues idelalisib dosing, every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures.

If a bone marrow biopsy and aspirate has not been done within the past 24 weeks it will be scheduled at the EOS visit. A 3D MRI (or CT, if MRI not feasible) for the liver and spleen size by volumetric imaging will also be scheduled if one has not been done within the past 12 weeks.

If the EOS visit coincides with Week 24 (Day 162), every effort should be made to collect the predose blood sample for idelalisib and ruxolitinib PK.

6.6.2. Safety Follow-up Visit

The safety follow-up visit will be scheduled 30 days after the subject's EOS visit, within a window of ± 7 days as outlined in study procedures (Appendix 2).

6.6.3. Long-term Follow Up

No long-term follow up is planned for this study.

6.7. Unscheduled Visits

Unscheduled visits may occur at any time while the subject is enrolled on study. Vital signs, laboratory assessments, ECG, and physical examination may be conducted at these visits. Data generated during an unscheduled visit will be collected on the eCRF.

6.8. 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 until disease progression (see Section 6.6.1 and 6.6.2). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.9. Criteria for Discontinuation of Study Treatment

All study participants will be encouraged to receive idelalisib for 24 weeks and will receive ruxolitinib for the same period of time (excluding the preceding 4 week period prior to initiating idelalisib). Subjects who are on idelalisib beyond Week 24, and in the opinion of the investigator are deriving clinical benefit, can remain on the study for the extension period until disease progression. Subjects will be encouraged to complete idelalisib and/or ruxolitinib even if one of the individual agents must be discontinued due to agent-specific toxicity.

Study drug (idelalisib) may be discontinued in the following instances, in consultation with the Gilead Medical Monitor:

- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest
- Objective evidence of definitive disease progression (based on 2013 Revised IWG-MRT and ELN response criteria, Appendix 6)
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy or breastfeeding during the study

If permanent discontinuation of idelalisib occurs prior to definitive progression subjects shall remain on study until definitive progression or criteria for study discontinuation are met.

6.10. Criteria for Discontinuation from Study

Subject study participation may be ended due to any of the following reasons:

- Initiation of new or investigational therapy in the absence of progression
- Disease progression (based on 2013 Revised IWG-MRT and ELN criteria, Appendix 6)

- Withdrawal of consent
- Significant subject noncompliance with study drug administration, study procedures, or study requirements
- Investigator's decision to remove the subject from the study, in consultation with the Gilead medical monitor
- Pregnancy or breastfeeding
- Death
- Discontinuation of study by the sponsor, a regulatory agency, or an IRB

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. AE 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 AE.

An AE does not include the following:

- Laboratory abnormalities not requiring clinical intervention or further investigation. Such abnormalities will be captured as part of overall laboratory monitoring.
- 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 screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and will be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

An 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 SAE. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.2.1. Protocol-Specific Serious Adverse Event Instructions

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

- Progression of myelofibrosis
- Death related to progression of myelofibrosis

However, events of progression of myelofibrosis and death related to progression of myelofibrosis that are assessed by the investigator as related to IMP will be considered SAEs and will be reported to regulatory agencies in an expedited fashion by Gilead.

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

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

- **No:** Evidence exists that the AE has an etiology other than the IMP. For an SAE, 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 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 an AE will be graded using the CTCAE, Version 4.03 (Appendix 11). 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 above.

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 eCRF database and Gilead DSPH as instructed. This also includes any SAE resulting from protocol-associated procedures performed from screening onwards.

All AEs, regardless of cause or relationship, that occur from initiation of study medication until 4 weeks after last administration of study IMP must be reported to the eCRF database as instructed.

All special situations including pregnancy, regardless of cause or relationship, until 30 days for females or 90 days for males after last administration of study drug(s) must be reported to the eCRF database as instructed.

Any SAE and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IMP, 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 determine that the subject's condition is stable. However, Gilead may request that certain AEs be followed until resolution.

Investigators are not obligated to actively seek SAE after the 30 day period. However, if the investigator learns of any SAE that occurs after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead DSPH.

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

At the time of study start, SAEs will be reported using a paper serious AE reporting form.

Electronic Serious Adverse Event (eSAE) Reporting Process

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

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious AE 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 eCRF database within the timelines outlined in the eCRF completion guideline.

- 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.

- 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 eCRF and the event description section of the SAE form.

Serious Adverse Event Paper Reporting Process

- All SAEs will be recorded on the SAE report form and submitted by faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead DSPH.
- 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.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the European Union (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, SADRs, or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

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

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

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

Laboratory abnormalities without clinical significance are not recorded as AE or SAE. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal

assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Section 7.1.1 and Section 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

7.6. Recommendations for Evaluation, Intervention, and Drug Discontinuation for Specific Adverse Events or Conditions

7.6.1. Dermatological Events

Subjects receiving idelalisib with ≥ Grade 3 rash have generally presented with a maculopapular rash on the trunk and extremities that is occasionally associated with fever and/or pruritus and responded to treatment with diphenhydramine and/or topical or oral corticosteroids.

For subjects who develop a severe rash for which an underlying etiology cannot be identified (e.g., infection, co-suspect drug), study drug should be interrupted. Resumption of study drug should be considered once rash resolves.

Severe cutaneous reactions, including fatal events of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in subjects receiving idelalisb. Assessment of potential causal association between idelalisib and the occurrence of SJS or TEN has been confounded by the coadministration of antineoplastic agents (e.g., bendamustine, rituximab) and/or other concomitant medications known to be associated with SJS or TEN (e.g., allopurinol). If SJS or TEN is suspected, idelalisib and all coadministered medications associated with SJS or TEN should be interrupted and the subject treated accordingly per institutional standards.

Subjects should be monitored for the development of SJS, TEN, or other severe cutaneous reactions and idelalisib treatment should be discontinued if such events occur.

7.6.2. Gastrointestinal Events

Isolated cases of gastrointestinal inflammation (eg, stomatitis, colitis, cecitis) have been noted in subjects receiving idelalisib. Rare cases of gastrointestinal perforation have occurred, generally in the setting of occult carcinoma, mesenteric embolus or diverticular disease. Study treatment (idelalisib) should be discontinued in subjects who experience bowel perforation.

Cholangitis manifest as hyperbilirubinemia out of proportion to serum transaminase elevations has been observed. While disease-related factors, neutropenia, toxicity from prior therapies, effects of ongoing supportive care, or pre-existing cholelithiasis may have initiated such events, it is possible that idelalisib played a contributory role. In such subjects, rechallenge with idelalisib has been possible and has not been associated with other severe adverse events. Subjects who have developed evidence of enteritis during idelalisib therapy have been successfully treated with antidiarrheals (eg, loperamide) and with enteric steroidal (eg, budesonide) or non-steroidal (eg sulfasalazine [Azulfidine®]) anti-inflammatory agents and have been able to continue or resume idelalisib.

For study subjects who develop severe abdominal pain the possibility of a bowel obstruction or perforation should be considered. Appropriate clinical and radiographic examination should be performed and supportive care or surgical intervention should be considered.

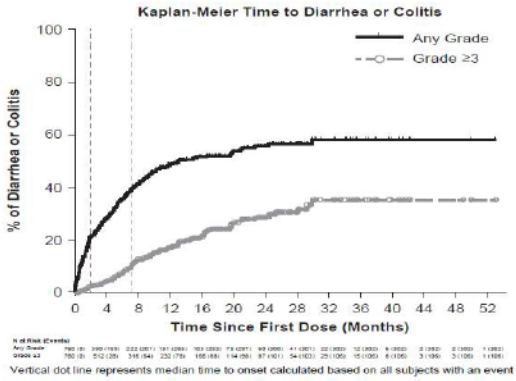
For subjects who develop persistent diarrhea, causes related to concomitant medications or gastrointestinal infections such as Clostridium difficile (particularly for patients recently treated with broad spectrum antibiotics), Shigella, Campylobacter, Yersinia and CMV should be considered and treated if appropriate. Depending upon the clinical circumstances, endoscopy and biopsy, with bacterial and viral IHC staining should be considered. In the event that an infectious cause is not identified, an antimotility agent (eg, loperamide) may lessen symptoms and intervention with enteric steroidal (eg, budesonide) or non-steroidal (eg, sulfasalazine) anti-inflammatory agents should be considered. In such subjects, rechallenge with idelalisib at a lower dose level has resulted in recurrence of symptoms in some but not all subjects and has not been associated with other severe adverse events. Withhold idelalisib for subjects with Grade 3 diarrhea and monitor at least weekly until resolved, then may resume idelalisib at same dose if in Cohort A, or at previous dose level if in Cohorts B through D. Discontinue idelalisib permanently for Grade 4 diarrhea.

7.6.2.1. Investigation for Idelalisib Late Onset or Severe Diarrhea/Colitis

See CTCAE Version 4.03 (Appendix 11) for definitions of colitis and diarrhea.

Among idelalisib-treated patients who reported diarrhea or colitis, the median time to onset of any grade diarrhea or colitis was 1.9 months (range, 0.0–29.8), of grade 1 or 2 was 1.5 months (range, 0.0–15.2) and of grade 3 or 4 was 7.1 months (range, 0.5–29.8). Kaplan–Meier curves of time to onset of diarrhea or colitis are shown for all idelalisib- treated patients in Figure 7-1 {Coutre et al 2015}.

Figure 7-1. Kaplan-Meier Time to Diarrhea or Colitis



Idelalisib-associated severe diarrhea responds poorly to antimotility agents however, median time to resolution ranged between 1 week and 1 month across trials following interruption of idelalisib treatment and, in some instances, initiation of corticosteroid treatment {Gilead Sciences Inc 2014}.

7.6.3. Hepatic Events

7.6.3.1. Transaminase Elevations

Consistent with observations in a dog toxicology study, reversible asymptomatic ALT/AST increases were also observed early in the idelalisib program in phase 1 studies (101-02 and 101-07) in subjects with hematologic malignancies. Transaminase elevations generally occurred within 4 to 12 weeks of drug initiation, and resolved spontaneously over a period of 2 to 4 weeks with drug being continued for Grade 1 and 2 elevations and drug withheld for Grade 3 or 4 elevations until resolution. These early observations have been consistent with the ongoing experience with idelalisib treatment and transaminase elevations are now well characterized as most frequently asymptomatic, transient and occurring within the first 3 months of treatment.

Grade 1 or 2 elevations commonly resolve despite continued idelalisib treatment and Grade 3 or 4 elevations can be managed by temporarily withholding idelalisib. Successful rechallenge after resolution at either the same or lower dose level of idelalisib has been achieved in the majority of subjects. There has been no evidence of impaired synthetic function. Close monitoring of hepatic laboratory tests during therapy is important to allow for appropriate idelalisib interruption and reinstitution so that subjects may continue with study drug treatment.

7.6.4. Hematological and Immunological Events

In the Phase 1 experience with idelalisib in patients with NHL and CLL, subjects with Grade ≥ 3 neutropenia, anemia, and/or thrombocytopenia were enrolled to clinical trials. Decreased levels of neutrophil counts, hemoglobin, or platelet counts during idelalisib administration were largely due to minor fluctuations in these parameters among subjects with pre-existing hematological abnormalities due to disease or prior therapy. Thus, idelalisib did not appear to induce overt myelosuppression. Obvious patterns of drug-mediated reductions in circulating CD4+ lymphocyte counts or suppression of serum IgG levels were also not observed.

Treatment-emergent Grade 3 or 4 neutropenia events, including febrile neutropenia, have occurred in subjects treated with idelalisib. All subjects are required to have their blood counts monitored at least every 2 weeks during the first 24 weeks of idelalisib dosing. For subjects who develop ANC 0.5 to $< 1.0 \times 10^9$/L (Grade 3), blood counts should be monitored at least weekly until ANC $\leq$ Grade 2. For subjects who develop ANC $< 0.5 \times 10^9$/L (Grade 4), idelalisib should be interrupted and blood counts monitored at least weekly until ANC is $\geq 1.0 \times 10^9$/L (Grade 2), at which point, idelalisib dosing may be resumed at same or lower dose level at investigator discretion. Neutropenia should be managed according to established clinical guidelines. No modification of any drug for changes in circulating CD4+ counts or Ig levels is planned.

7.6.5. Infectious Events

Patients with lymphoid cancers receiving idelalisib have developed serious and fatal infections during therapy. Opportunistic infections, most notably *Pneumocystis jiroveci* pneumonia (PJP) and CMV infection, have most frequently occurred within the first 6 months of treatment with idelalisib and are increased in the context of concurrent myelosuppressive therapy such as bendamustine.

Subjects must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment. Prophylaxis will continue for a period of 2 to 6 months after idelalisib discontinuation. The duration of prophylaxis should be based on clinical judgment and may take into account risk factors such as concomitant corticosteroid treatment and prolonged neutropenia after idelalisib treatment ends. Subjects must permanently discontinue idelalisib upon diagnosis of PJP.

CMV surveillance for active disease (quantitative PCR or pp65 antigen) must be conducted approximately every 4 weeks throughout the course of idelalisib treatment. CMV viral load testing should be performed from the same specimen type whenever possible and caution should be exercised when comparing CMV viral load results across different testing centers. If unequivocal clinical or laboratory evidence of CMV infection is present, the subject must permanently discontinue idelalisib treatment and undergo effective antiviral treatment according to established clinical guidelines.

In high-risk subjects (history of recurrent infection, allogeneic transplant, treatment with alemtuzumab, hypogammaglobulinemia) other infection prophylaxis should be considered per consensus guidelines. Administration of intravenous immunoglobulin is permitted per standard institutional practice {Raanani et al 2009}. For subjects who develop an infection, appropriate medical therapy should be instituted in a timely manner.

7.6.6. Pulmonary Events

Documented bacterial, fungal, viral, and pneumocystis pneumonias have been observed in patients receiving idelalisib, primarily in patients with CLL. Some study subjects receiving idelalisib alone or in combination have developed evidence of pneumonitis without documented pulmonary infection.

Given the potential for infectious or drug-related pulmonary adverse events, clinicians should be particularly observant for evidence of respiratory events in subjects participating in this trial. Subjects who describe pulmonary symptoms (eg, dyspnea on exertion, cough, shortness of breath); manifest a decline from baseline of $\geq$ 5% in oxygen saturation, or demonstrate evidence of pulmonary inflammation (eg, focal or diffuse interstitial pattern or ground-glass opacities on chest CT) should be evaluated. Potential bacterial, fungal, or viral etiologies should be assessed. Noninfectious etiologies such as pulmonary edema or thromboembolism should also be considered.

As appropriate for the clinical situation and culture results, subjects should be treated empirically or given specific antibiotics, antifungals, or antiviral agents for a cultured organism. Supportive care, including oxygen or mechanical ventilation, should be provided as necessary.

For subjects with suspected Grade 1 pneumonitis, withhold idelalisib until resolution to baseline. Upon resolution to baseline, idelalisib may be resumed at lower dose level or discontinued at investigator discretion. For subjects with suspected Grade $\geq$ 2 pneumonitis (eg, new onset or worsening of baseline cough, dyspnea, hypoxia and/or a diffuse interstitial pattern or ground-glass opacities on chest imaging without obvious infectious etiology), idelalisib must be discontinued permanently and therapy initiated as clinically appropriate.

7.6.7. Secondary Malignancies

Subjects receiving idelalisib for CLL or iNHL have developed pre-malignant and secondary malignant diseases, such as basal cell carcinoma, myelodysplastic syndrome, myeloproliferative disorders, and more aggressive lymphoid malignancies (eg, have had Richter transformation). Generally this has occurred in subjects who have received multiple previous lines of therapy and when idelalisib is combined with other therapies such as rituximab or bendamustine. The specific association of the therapeutic agents with these types of events has not been determined.

There are reports of pre-malignant and malignant diseases that have developed in subjects who have been treated with bendamustine, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, and bronchial carcinoma. The specific association of the therapeutic agents with these types of events has not been determined.

7.6.8. Tumor Lysis Syndrome

Tumor lysis syndrome has not been observed with neither idelalisib nor ruxolitinib monotherapy.

7.6.9. Pregnancy, Lactation, and Reproduction

Idelalisib has induced embryo lethality and teratogenicity when administered to pregnant female rats at maternally toxic doses. However, definitive reproductive toxicology studies in animals have not yet been performed and the specific effects of idelalisib on human embryogenesis or fetal development are unknown. Whether idelalisib is excreted in human breast milk is unknown. General toxicology studies of idelalisib in rats and dogs indicated dose-dependent reductions in testicular weights, with persistent minimal to mild degeneration of the seminiferous tubules and decreased spermatozoa in rats and hypospermatogenesis in dogs. The implications of these testicular changes for animal or human fertility are unknown.

Given the potential the risks to a fetus or infant as a result of exposure to idelalisib, women of reproductive potential entering this study must have a negative serum pregnancy test at baseline and must not be breastfeeding. Males and females of childbearing potential should abstain from sexual intercourse or use an effective form of contraception (see Appendix 10). If a female study participant becomes pregnant or decides to breastfeed during the course of the study, all study therapy (idelalisib/) must be discontinued.

7.6.9.1. PJP Prophylaxis

Trimethoprim sulfamethoxazole is rated a Pregnancy category C agent. In rats, oral doses of 533 mg/kg or 200 mg/kg produced teratologic effects manifested mainly as cleft palates. One survey found no congenital abnormalities in 35 children whose mothers had received oral sulfamethoxazole and trimethoprim at the time of conception or shortly thereafter. Because sulfamethoxazole and trimethoprim may interfere with folic acid metabolism it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Dapsone is rated a Pregnancy Category C agent. Extensive, but uncontrolled experience and two published surveys on the use of Dapsone in pregnant women have not shown that Dapsone increases the risk of fetal abnormalities if administered during all trimesters of pregnancy or can affect reproduction capacity. Because of the lack of animal studies or controlled human experience, Dapsone should be given to a pregnant woman only if clearly needed. Dapsone is excreted in breast milk in substantial amounts. Hemolytic reactions can occur in neonates. Because of the potential for tumorgenicity shown for Dapsone in animal studies a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of drug to the mother.

Atovaquone is rated a Pregnancy Category C agent. Atovaquone is teratogenic and did not cause reproductive toxicity in rats at plasma concentrations up to 2 to 3 times the estimated human exposure. Atovaquone can cause maternal toxicity in rabbits at plasma concentrations that were approximately one half the estimated human exposure. Mean fetal body lengths and weights were decreased and there were higher numbers of early resorption and post-implantation loss per dam. It is not clear whether these effects are caused by atovaquone directly or are secondary to maternal toxicity. Concentrations of atovaquone in rabbit fetuses averaged 30% of the concurrent maternal plasma concentrations. There are no adequate and well-controlled studies in pregnant women. Atovaquone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether atovaquone is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised when Atovaquone is administered to a nursing woman. In a rat study, atovaquone concentrations in the milk were 30% of the concurrent atovaquone concentrations in the maternal plasma.

Aerosolized Pentamidine (NebuPent) is a Pregnancy Category C agent. There are no adequate and well controlled studies of NebuPent in pregnant women. One literature report indicated that intravenously administered pentamidine in pregnant rats at 4 mg/kg/day was embryolethal; teratogenicity was not observed in this study. It is unknown whether pentamidine administered via the aerosolized route crosses the placenta at clinically significant concentrations. It is not known whether NebuPent can cause fetal harm when administered to a pregnant woman. NebuPent should be given to a pregnant woman only if clearly needed. It is not known whether NebuPent is excreted in human milk. NebuPent should not be given to a nursing mother unless the potential benefits are judged to outweigh the unknown risks.

7.6.10. Ultraviolet Exposure

In vitro studies indicate enhanced cytotoxicity when embryonic murine fibroblasts treated with GS-563117 (the major metabolite of idelalisib) are simultaneously exposed to ultraviolet light. While nonclinical findings suggest the hypothetical potential for phototoxicity in humans, available clinical data do not reveal a photosafety concern. Although specific clinical correlates for these nonclinical data are not available, investigators and study subjects should be observant for the possibility that study participants may have exaggerated sunburn reactions (eg, burning, erythema, exudation, vesicles, blistering, edema) involving areas of skin exposed to ultraviolet light.

7.6.11. Further Safety Information

Further safety information regarding the study drug may be found in the investigator brochure for idelalisib.

Further safety information regarding ruxolitinib is provided in the current product labeling.

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).

Lack of effect is defined as a situation where there is apparent failure of the medicinal product or medical technology to bring about the intended beneficial effect on the individual in a defined population with a given medical problem, under ideal conditions of use.

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 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. Gilead DSPH contact information is as follows:
Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH,
fax number PPD or email PPD

Refer to Appendix 10 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 Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP as well as any Gilead product taken as a concomitant medication, whether or not associated with an adverse event. This reporting requirement does not apply to non-Gilead concomitant medications. Except for situations that result in AE, special situations involving non-Gilead 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.

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of idelalisib through 28 days in subjects receiving ruxolitinib as therapy for intermediate to high risk PMF, post-PV MF, or post-ET MF with progressive or relapsed disease
- To determine the PK of idelalisib and ruxolitinib, in subjects receiving ruxolitinib with PMF, post-PV MF, or post-ET MF with progressive or relapsed disease

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of continuous daily administration of idelalisib beyond 28 days in subjects receiving ruxolitinib with PMF, post-PV MF, or post-ET MF
- To evaluate the efficacy of idelalisib in subjects receiving ruxolitinib with PMF, post-PV MF, or post-ET MF by 2013 Revised IWG-MRT and ELN response criteria

CCI [redacted]

8.1.2. Primary Endpoint

The primary endpoints are:

- Overall safety profile of idelalisib and ruxolitinib after 28 days of exposure characterized by the type, frequency, severity, timing, and relationship to idelalisib of AE, abnormal laboratory tests, drug discontinuations due to AEs and SAEs. Toxicity will be assessed by grading of AEs according to the CTCAE V 4.03 (Appendix 11).
- Pharmacokinetic parameters of ruxolitinib (and metabolite[s], as applicable) and idelalisib and/or its primary metabolite, GS-563117 (C_{max}, T_{max}, AUC, and C_{trough})

8.1.3. Secondary Endpoint

The secondary endpoints are:

- Overall safety profile of idelalisib and ruxolitinib continuous daily administration beyond 28 days of exposure characterized by the type, frequency, severity, timing, and relationship to idelalisib of any AE, abnormal laboratory tests, drug discontinuations due to AEs and SAEs. Toxicity will be assessed by grading of AEs according to the CTCAE V4.03

- Rate of overall response as defined by 2013 Revised IWG-MRT and ELN response criteria (Appendix 6), ie, CR, PR, or CI (the achievement of anemia, spleen, or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia). Clinical improvement will be measured as any of the following:
  - Best spleen or liver response (for splenectomized subjects) rate by palpation
  - Best anemia response rate
  - Best symptoms response

CCI [redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Intent-to-Treat (ITT) Analysis Set

The ITT analysis set consists of all subjects who receive ≥ 1 dose ofidelalisib. This analysis set will be used in the analyses of subject characteristics, study drug treatment administration, safety and efficacy endpoints.

8.2.1.2. Pharmacokinetic Analysis Sets

The PK analysis sets consist of all subjects in the ITT set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.3. Data Handling Conventions

By-subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, median, standard deviation, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% confidence intervals (CIs) on the percentage, where appropriate. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution. Data will be described and summarized for all subjects and by analysis set and time point. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized. Graphical techniques (eg, waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative.

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

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

- Duration of response (DOR) and PFS: Data from surviving, non-progressing subjects will be censored at the last adequate response assessment date prior to the initiation of PV or ET treatment (whichever is applicable) other than the study treatment or the last time that lack of definitive progression was objectively documented.

8.4. Demographic Data and Baseline Characteristics

A listing of ITT analysis set subjects will be generated to describe site, subject number, first screening date, first treatment date, malignancy, stage, the longest duration of study drug (idelalisib) treatment, and the reason for discontinuing study treatment. Available information on subjects who were screened or registered but not treated may be listed separately. A table will be created summarizing these categories in terms of number and percent for the ITT analysis set.

Subject baseline characteristics will be listed and summarized for the ITT analysis set.

8.5. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed up to the date of last dose of study drug plus 30 days will be summarized. Data for the pretreatment will be included in data listings. Interim safety summaries for SRT will be shown by cohort and combining all cohorts.

8.5.1. Extent of Exposure

Descriptive information will be provided regarding the number of doses of study drug prescribed, the total number of doses taken, the percent of expected doses taken, the number of days of study drug, and the number and timing of prescribed dose modification and interruptions.

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

8.5.2. Adverse Events

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

AE 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 AE 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 IMP will be categorized as related or unrelated.

Treatment-emergent AE will be summarized. Summary tables will be presented to show the number of subjects reporting treatment-emergent AE by severity grade and corresponding percentages. A subject who reports multiple treatment-emergent AE 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 and PT. Separate listings and summaries will be prepared for the following types of treatment emergent AEs:

- Study-drug-related AE
- AE that are Grade ≥ 3 in severity
- AE leading to idelalisib or ruxolitinib interruption and/or dose modification
- AE leading to idelalisib or ruxolitinib discontinuation
- SAE

8.5.3. 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 study drug (idelalisib) to 30 days after the last dose of study drug. 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.

8.6. Pharmacokinetic Analysis

Plasma concentrations of idelalisib and metabolite (if appropriate) will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum). Plasma concentrations of idelalisib and metabolite (if appropriate) over time will be plotted in semi logarithmic and linear formats as mean ± standard deviation. Relevant PK parameters will be calculated and summarized.

8.7. Efficacy Analysis

The secondary endpoint is the rate of overall response as defined by 2013 Revised IWG-MRT and ELN response criteria (Appendix 6) ie, CR, PR, or CI (the achievement of anemia, spleen, or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia). Response rates will be presented with corresponding exact 95% CIs. Subjects who have missing baseline or on-study response assessment will be counted as non-responders.

PFS and DOR 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 95% CIs.

Categorical endpoints will be described. Subjects who do not have sufficient baseline or on study assessments to characterize response, will be counted as non-responders. Response rates will be presented with corresponding exact 95% CIs.

Percent change from baseline at Weeks 12 and 24 and best change from baseline for spleen, liver and TSS will be presented with corresponding median, standard deviation, minimum, and maximum.

8.8. Sample Size

As this is a Phase 1b study with a primary objective of assessing safety, the sample size is not based on formal power calculations. The sample size of approximately 6 subjects per dose cohort in Cohort A, B, C, and D is considered adequate for an initial assessment of safety and tolerability for subsequent evaluations.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

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

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

9.1.2. Institutional Review Board (IRB) Review and Approval

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

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

9.1.3. Informed Consent

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

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB, 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, eCRF, the IMP, 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, query forms, IRB and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

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

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

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

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. 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 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 IRB, or to regulatory authority inspectors.

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency. 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 eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (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) and IRBs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 1b Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Idelalisib in Subjects Receiving Ruxolitinib as Therapy for Primary, Post-Polycythemia Vera, or Post-Essential Thrombocythemia Myelofibrosis with Progressive or Relapsed Disease

GS-US-397-1245, Amendment 5, 26 October 2016

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

PPD

Signature

10/25/16

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

Weeks 1 to 4

Period	Screening	Treatment																								
Week		1												2											3	4
Study Day	-28 to -1	1	4											10											15	22
Hours relative to dosing			Pre dose	0	0.5	1	1.5	2	3	4	6	8	12	Pre dose	0	0.5	1	1.5	2	3	4	6	8	12		
Informed consent	X																									
MPN-SAF[a]		X												X											X	X
Medical & medication history[b]	X																									
Vital signs[c]	X	X	X											X											X	X
Physical exam[d]	X	X												X											X	X
ECOG	X	X												X											X	X
DIPSS[e]	X																									
12-lead ECG	X																									
Hematology[f]	X	X												X											X	X
Chemistry[g]	X	X												X											X	X
Urinalysis	X																									
ESR		X																								
Coagulation	X																									
Pregnancy test[h]	X	X																								
HIV screen	X																									
Pneumocystis jiroveci pneumonia (PJP) Prophylaxis [s]			X											X											X	X
CMV Testing[r]	X																									X

Period	Screening	Treatment																								
Week		1												2											3	4
Study Day	-28 to -1	1	4											10											15	22
Hours relative to dosing			Pre dose	0	0.5	1	1.5	2	3	4	6	8	12	Pre dose	0	0.5	1	1.5	2	3	4	6	8	12		
Immune Monitoring	X																									X
Hepatitis serology	X																									
Ruxolitinib PK[i]		X	X		X	X	X	X	X	X	X	X	X													
Idelalisib & Ruxolitinib PK[j]														X		X	X	X	X	X	X	X	X	X	X	
CCI																										
Bone marrow biopsy and aspirate[l]	X																									
Ruxolitinib dosing[m]		X		X									X		X								X	X	X	X
Idelalisib dosing[n]															X								X	X	X	X
Idelalisib dispensing, accountability[o]			X											X										X	X	X
AE, Conmeds[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MRI[q]	X																									

a The MPN-SAF will be completed weekly from Week 1 to 24 then monthly after Week 24 and at EOS. When visits are scheduled, it should be completed at the clinic. Subjects will receive a copy of the questionnaire to complete at home between clinic visits beginning Week 4.

b The medical and medication history will include the *JAK2*V617F mutation status if known, ruxolitinib dose and transfusion history within 3 months of screening.

c Vital signs include blood pressure, heart rate, respiratory rate, and oral temperature.

d Body weight, palpation of the spleen and liver will be performed at each PE. Height will be performed at screening only.

e DIPSS Plus should be completed for subjects who have cytogenetics information.

f Hematology: CBC with differential, reticulocyte count. ANC monitored at least every 2 weeks for the first 24 weeks of idelalisib treatment. For subjects who develop neutropenia of ANC 0.5 to < 1.0 x 10^9/L (Grade 3), ANC should be monitored at least weekly until ANC≤ Grade 2 . For subjects who develop ANC < 0.5 x 10^9/L (Grade 4), idelalisib should be interrupted and ANC should be monitored at least weekly until ANC is ≥ 1.0 x 10^9/L 0.5 x 10^9/L (Grade 2).

g Chemistry: Comprehensive metabolic panel with ALT, AST, GGT, iron, LDH, magnesium, phosphorus total bilirubin, direct bilirubin, uric acid.

h For females of childbearing potential only. Serum pregnancy test will be performed during screening only. A urine pregnancy test will be obtained throughout the rest of the study.
i The ruxolitinib Day 1 PK sample will be drawn predose. The 12 hour postdose PK time point on Day 4 will be performed prior to the second ruxolitinib dosing.
j Blood samples will be collected for ruxolitinib, idelalisib and/or metabolite PK beginning Day 10. The 12 hour post dose PK time point on Day 10 will be performed prior to idelalisib and ruxolitinib dosing. Beginning Day 15 PK samples will be collected predose and 1.5 hours postdose.
[redacted]
l Bone marrow biopsy and aspirate will be collected at Screening if one has not been done in the past 3 months or results are not available, Days 78, 162 and every 24 weeks during the extension period. It will also be collected at EOS, if one has not been done in the past 24 weeks. Bone marrow studies include cytogenetics, core biopsy, trichrome stain for reticulin, and iron stain.
m Ruxolitinib dosing will be in clinic when visits are scheduled. Prior to the scheduled visits, subjects should be instructed to hold their morning dose before coming to the clinic on days where PK lab draws will be taken (Day 1 and 4 for ruxolitinib, and Day 10, 15, 36, 78, 162 for both idelalisib and ruxolitinib PK).
n Idelalisib dosing will be in the clinic when visits are scheduled. Prior to the scheduled visits, subjects should be instructed to hold their morning dose before coming to the clinic on days where PK lab draws will be taken (Day 1 and 4 for ruxolitinib, and Day 10, 15, 36, 78, 162 for both idelalisib and ruxolitinib PK).
o Idelalisib will be dispensed in clinic on Day 4 for the subject to self-administer beginning Day 5. Idelalisib accountability should be done at every clinic visit.
p Adverse events and concomitant medications will be assessed and documented throughout the study. For assessment of Diarrhea/Colitis see Section 6.2.18.
q Three dimensional MRI (or CT, if MRI not feasible) for the liver and spleen size by volumetric imaging. An MRI should be done at the EOS visit only if it has not been done within 12 weeks of the visit.
r CMV testing will be performed every 4 weeks starting at Screening and continuing through EOS.
s Subjects must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment. Prophylaxis will continue for a period of 2 to 6 months after idelalisib discontinuation. The duration of prophylaxis should be based on clinical judgment and may take into account risk factors such as concomitant corticosteroid treatment and prolonged neutropenia after idelalisib treatment ends.

Weeks 6 to 24

Period	Treatment										Extension period[o]			EOS[q]	Follow Up[r]
Week	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**Q4W**	**Q12W[p]**	**Q24W[p]**		**30 ± 7 days after EOS**
Study Day	**36**	**50**	**64**	**78**	**92**	**106**	**120**	**134**	**148**	**162**					
Visit Window (Days)	**±3**	**±3**	**±3**	**±3**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
MPN-SAF[a]	X	X	X	X	X	X	X	X	X	X	X			X	
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X			X	X
Physical exam[c]	X	X	X	X		X		X		X	X			X	X
ECOG	X	X	X	X		X		X		X	X			X	X
Hematology[d]	X	X	X	X	X	X	X	X	X	X	X			X	X
Chemistry[e]	X	X	X	X	X	X	X	X	X	X	X			X	X
Pneumocystis jiroveci pneumonia (PJP) Prophylaxis[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CMV Testing[s]		X		X		X		X		X	X	X	X	X	
Immune Monitoring				X						X		X	X	X	
Pregnancy test[f]	X			X		X		X		X	X			X	X
Idelalisib & Ruxolitinib PK[g]	X			X						X					
CCI															
Bone marrow biopsy and aspirate[i]				X						X			X	X	
Ruxolitinib dosing[j]	X	X	X	X	X	X	X	X	X	X	X				
Idelalisib dosing[k]	X	X	X	X	X	X	X	X	X	X	X				
Idelalisib dispensing, accountability[l]	X	X	X	X	X	X	X	X	X	X	X			X	
AE, Conmeds[m]	X	X	X	X	X	X	X	X	X	X	X			X	X
MRI[n]				X						X		X		X	

a The MPN-SAF will be completed weekly from Week 1 to 24 then monthly after Week 24 and at EOS. When visits are scheduled, it should be completed at the clinic. Subjects will receive a copy of the questionnaire to complete at home between clinic visits beginning Week 4.

b Vital signs include blood pressure, heart rate, respiratory rate and oral temperature.

c Body weight, palpation of the spleen and liver will be performed at each PE. Height will be performed at screening only. Physical exams will be scheduled every 4 weeks during the extension period except after a subject has been on study for 1 year, when it will be scheduled every 12 weeks.

d Hematology: CBC with differential, reticulocyte count. ANC monitored at least every two weeks for the first 24 weeks of idelalisib treatment. For subjects who develop neutropenia of ANC 0.5 to < 1.0 x 10^9/L (Grade 3), monitor ANC at least weekly until ANC≤ Grade 2 . For subjects who develop ANC < 0.5 x 10^9/L (Grade 4), idelalisib should be interrupted and monitor ANSC at least weekly until ANC is ≥ 1.0 x 10^9/L 0.5 x 10^9/L(Grade 2)

e Chemistry: Comprehensive metabolic panel with ALT, AST, GGT, iron, LDH, magnesium, total bilirubin, phosphorus, uric acid.

f For females of childbearing potential only. Serum pregnancy test will be performed during screening only. A urine pregnancy test will be obtained throughout the rest of the study.

g Blood samples will be collected for ruxolitinib, idelalisib and/or metabolite PK beginning Day 10. Beginning Day 15 PK samples will be collected predose and 1.5 hours postdose.

[redacted]

i Bone marrow biopsy and aspirate will be obtained at screening if one has not been done in the past 3 months or results are not available, Days 78, 162 and every 24 weeks during the extension period. It will also be obtained at EOS if one has not been done in the past 24 weeks. Bone marrow studies include cytogenetics, core biopsy, trichrome stain for reticulin, and iron stain.

j Ruxolitinib dosing will be in clinic when visits are scheduled.

k Idelalisib dosing will be in the clinic when visits are scheduled.

l Idelalisib will be dispensed in clinic on Day 4 for the subject to self-administer beginning Day 5. Idelalisib accountability should be done at every clinic visit.

m Adverse events and concomitant medications will be assessed and documented throughout the study. For assessment of Diarrhea/Colitis please see Section 6.2.18.

n Three dimensional MRI (or CT, if MRI not feasible) for the liver and spleen size by volumetric imaging. An MRI should be done at the EOS visit only if it has not been done within 12 weeks of the visit.

o If subjects are deriving clinical benefit (as determined by the investigator) and complete Week 24, subjects can enter extension period until they demonstrate progressive disease and/or have unacceptable toxicity, as defined by the protocol. Physical exams will be scheduled every 4 weeks during the extension period except after a subject has been on study for 1 year, when it will be scheduled every 12 weeks.

p Q12W and Q24W assessments will overlap with Q4W assessments and will be scheduled at the same visit.

q If the EOS visit coincides with Week 24 (Day 162), the predose blood sample for PK must be collected.

r The safety follow up visit is within 30 days of EOS.

s CMV testing will be performed every 4 weeks starting at Screening and continuing through EOS.

t Subjects must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment. Prophylaxis will continue for a period of 2 to 6 months after idelalisib discontinuation. The duration of prophylaxis should be based on clinical judgment and may take into account risk factors such as concomitant corticosteroid treatment and prolonged neutropenia after idelalisib treatment ends.

Appendix 3. Diagnostic Criteria and Prognostic Scoring System for Myelofibrosis

2008 WHO Diagnostic Criteria for PMF[5]
(Diagnosis requires meeting all 3 major criteria and 2 minor criteria.)

Major Criteria

1. Presence of megakaryocyte proliferation and atypia[a], usually accompanied by either reticulin or collagen fibrosis; **or** in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease)
2. Not meeting WHO criteria for PV[b], *BCR-ABL*1+ CML[c], MDS[d] or other myeloid neoplasms
3. Demonstration of *JAK2*V617F or other clonal marker (eg, *MPL*W515L/K); or in the absence of a clonal marker, no evidence that the bone marrow fibrosis is secondary to infection, autoimmune disorder or other chronic inflammatory condition; hairy cell leukemia or other lymphoid neoplasm; metastatic malignancy; or toxic (chronic) myelopathies[e]

Minor Criteria[f]

1. Leukoerythroblastosis
2. Increase in serum lactate dehydrogenase level
3. Anemia
4. Palpable splenomegaly

WHO=World Health Organization; PMF=primary myelofibrosis; PV=polycythemia vera; BCR-ABL=breakpoint cluster region-abelson leukemia virus protein; CML=chronic myelogenous leukemia; MDS=myelodysplastic syndrome; JAK=Janus kinase; MPL=thrombopoietin receptor.

a Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous or irregularly folded nuclei and dense clustering.
b Requires the failure of iron replacement therapy to increase hemoglobin (Hb) level to the PV range in the presence of decreased serum ferritin. Exclusion of PV is based on Hb and hematocrit levels; red cell mass measurement is not required.
c Requires the absence of *BCR-ABL*1.
d Requires the absence of dyserythropoiesis and dysgranulopoiesis.
e Patients with conditions associated with reactive myelofibrosis are not immune to PMF, and the diagnosis should be considered in such cases if other criteria are met.
f Degree of abnormality could be borderline or marked.

{Tefferi et al 2007}

2008 IWG-MRT Diagnosis Criteria for Post PV- MF and Post-ET MF	
Diagnostic Criteria for Post-PV MF	**Diagnostic Criteria for Post-ET MF**
Required Criteria[6]	
1. Documentation of a previous diagnosis of ET or PV as defined by the WHO criteria 2. Bone marrow fibrosis Grade 2-3 (on a 0-3 scale) or Grade 3-4 (on a 0-4 scale)[a]	
Additional criteria (2 are required)	**Additional criteria (2 are required)**
1. Anemia[b] or sustained loss of requirement for either phlebotomy (in the absence of cytoreductive therapy) or for cytoreductive treatment for erythrocytosis 2. A leukoerythroblastic peripheral blood picture[a] 3. Increasing splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly 4. Development of ≥ of 3 constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)	1. Anemia[b] and a ≥2 ml/mL^{-1} decrease from baseline hemoglobin level 2. A leukoerythroblastic peripheral blood picture 3. Increasing splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly 4. Increased lactate dehydrogenase (above reference level) 5. Development of ≥1 of 3 constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

IWG-MRT=International Working Group for Myelofibrosis Research and Treatment; PV=polycythemia vera; MF=myelofibrosis; ET=essential thrombocythemia; WHO=World Health Organization

a Grade 2-3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3-4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collaged and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteoporisis.

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

{Barosi et al 2008}

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

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

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

Risk Level	DIPSS Score
Low	0
Intermediate-1	1 or 2
Intermediate-2	3 or 4
High	> 4

{Passamonti et al 2010}

Appendix 5. Dynamic International Prognostic Scoring System Plus (DIPSS Plus)

Prognostic variable	Value		
	0	1	2
Age	≤ 65	> 65	
WBC	≤ 25	> 25	
Hgb	≥ 10		< 10
Peripheral Blast	< 1	≥ 1	
Constitutional symptoms	No	Yes	
Platelet count	$>100 \times 10^9$/l	$<100 \times 10^9$/l	
RBC transfusion (ongoing need)	No	Yes	
Poor risk BM cytogenetics (+8,-7/7q-, i(17q), inv(3), -5/5q, 12p-, or 11q23 rearrangements).	None	≥1	

The risk category is obtained by adding up the values of each prognostic variable.
Risk categories are defined as:

- **Low**: 0 adverse points
- **Intermediate-1**: 1 adverse point
- **Intermediate-2**: 2-3 adverse points
- **High**: ≥ 4 adverse points

{Gangat et al 2011}

Appendix 6. Revised International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) Response Criteria for Myelofibrosis

Complete remission (CR)	Bone marrow: age-adjusted normocellularity; < 5% blasts; ≤ Grade 1 myelofibrosis, AND Peripheral blood: hemoglobin ≥ 10 g/dL and < ULN; neutrophil count ≥ 1 × 10^9/L and < ULN; platelet count ≥ 100 × 10^9/L and < ULN, < 2% immature myeloid cells, AND Clinical: resolution of disease symptoms; spleen and liver not palpable; no evidence of extramedullary hematopoiesis
Partial remission (PR)	Peripheral blood: hemoglobin ≥ 10 g/dL and < ULN; neutrophil count ≥ 1 × 10^9/L and < ULN; platelet count ≥ 100 × 10^9/L and < ULN, < 2% immature myeloid cells, AND Clinical: resolution of disease symptoms; spleen and liver not palpable; no evidence of extramedullary hematopoiesis **OR** Bone marrow: age-adjusted normocellularity; < 5% blasts; ≤ Grade 1 myelofibrosis, AND Peripheral blood: hemoglobin ≥ 8.5 but < 10 g/dL and < ULN; neutrophil count ≥ 1 × 10^9/L and < ULN; platelet count ≥ 50 but < 100 x 10^9/L and < ULN; < 2% immature myeloid cells, AND Clinical: resolution of disease symptoms; spleen and liver not palpable, no evidence of extramedullary hematopoiesis
Clinical improvement	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia or neutropenia
Anemia response	Transfusion-independent patients: a ≥ 2 g/dL increase in hemoglobin level (applicable only to patients with baseline hemoglobin < 10 g/dL) Transfusion-dependent patients: becoming transfusion-independent
Spleen response	A baseline splenomegaly that is palpable at 5-10 cm, below the left costal margin, becomes not palpable, **OR** A baseline splenomegaly that is palpable at > 10 cm, below the left costal margin, decreases by ≥ 50% A baseline splenomegaly that is palpable at < 5 cm, below the left costal margin, is not eligible for spleen response
Symptoms response	A ≥ 50% reduction in the Myeloproliferative Neoplasm Symptom Assessment Form total symptom score (MPNSAF TSS)

Progressive disease	Appearance of a new splenomegaly that is palpable at least 5 cm below the left costal margin, **OR** A ≥100% increase in palpable distance, below left costal margin, for baseline splenomegaly of 5-10 cm, **OR** A 50% increase in palpable distance, below left costal margin, for baseline splenomegaly of > 10 cm, **OR** Leukemic transformation confirmed by a bone marrow blast count of ≥ 20%, **OR** A peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1×10^9/L that lasts for at least 2 weeks
Stable disease (SD)	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least clinical improvement after achieving CR, PR, or clinical improvement, **OR** Loss of anemia response persistent for at least 1 month, **OR** Loss of spleen response persisting for at least 1 month

a Baseline and post-treatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.

b Grading of myelofibrosis is according to the European classification {Thiele et al 2005}. It is underscored that the consensus definition of "a complete remission bone marrow" is to be used only in those patients where all other criteria, including resolution of leukoerythroblastosis, are met.

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

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

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

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

g Progressive disease assignment for splenomegaly requires confirmation by MRI or CT showing a ≥ 25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pre-treatment baseline and not to post-treatment measurements.

{Tefferi et al 2013}

Appendix 7. ECOG Performance Status Scoring System

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, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 8. MPN Symptom Assessment Form (MPN-SAF)

Instructions: Please fill out all questions, as best able, reflecting how these symptoms affected you over the **LAST WEEK** unless directed otherwise. Complete forms until the STOP instruction toward the end of the packet.

Symptom	**1 to 10 (0 if absent) ranking*** 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right **NOW**	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your **USUAL** Level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your **WORST** level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your	
• General Activity	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Mood	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Walking ability	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Normal Work (includes work both outside the home and daily chores)	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Relations with other people	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Enjoyment of life	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
Circle the one number that describes how, during the past Week how much difficulty you have had with each of the following symptoms	
• Filling up quickly when you eat (Early Satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Abdominal pain	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Problems with Headaches	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Problems with Concentration – Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Circle the one number that describes how, during the past Week how much difficulty you have had with each of the following symptoms (continued)	
• Dizziness/Vertigo /Lightheadedness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Numbness/Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Difficulty sleeping	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Depression or sad mood	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Problems with Sexual Desire or Function	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Cough	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Night Sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Bone Pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
• Fever (>100°F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
• Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
What is your Overall Quality of Life?	(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As Bad as it can be)

Appendix 9. Modified Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score

1) Rate your worst incidence of tiredness in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst Imaginable

2) Rate your worst incidence of filling up quickly when you eat (early satiety) in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst Imaginable

3) Rate your worst incidence of abdominal discomfort in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst Imaginable

4) Rate your worst incidence of night sweats in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst Imaginable

5) Rate your worst incidence of itching (pruritus) in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst Imaginable

6) Rate your worst incidence of bone pain (diffuse not joint pain or arthritis) in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst Imaginable

7) Rate your worst incidence of pain under ribs on the left side in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst Imaginable

8) Rate your worst incidence of inactivity in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
Absent Worst Imaginable

Appendix 10. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations

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

Idelalisib is contraindicated in pregnancy as animal studies in rats and rabbits have shown that study drug is teratogenic. Pregnancy must be excluded before the start of treatment with study drug and prevented thereafter by reliable contraceptive methods. Pregnancy tests will be performed regularly (refer to Appendix 2) throughout this study. 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 (StD 1.73) years

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

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

3) Contraceptive Requirements

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

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

Protocol specified contraceptive methods are as follows: (1) a combination of one hormonal method and one barrier method; (2) two barrier methods where one method is the male condom; or (3) use of an intrauterine device (IUD) or tubal sterilization; see Appendix Table 1 below. Acceptable hormonal methods include injectable progesterone, progesterone implants, combination oral contraceptives, transdermal contraceptive patch, and vaginal ring. Acceptable barrier methods include diaphragm with spermicide, cervical cap with spermicide, and the male condom. Female subjects must use either a hormonal method or a barrier method if the partner has a vasectomy. If a subject has undergone tubal sterilization or has had a Copper T 380A IUD or LNg 20 IUD inserted, no other contraception is needed.

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 (idelalisib). Lactating females must discontinue nursing before IMP administration.

Appendix Table 1. Protocol Specified Contraceptive Methods

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

Tubal Sterilization</td><td>Estrogen and Progesterone
• Oral contraceptives
• Transdermal patch
• Vaginal ring

Progesterone
• Injection
• Implant</td><td>• Diaphragm with spermicide
OR
• Cervical cap with spermicide
• Male condom (with or without spermicide)</td></tr>
<tr><td colspan="2">Partner’s vasectomy must be used with a hormone or barrier method.</td></tr>
</table>

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

4) Contraceptive 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 study medication.

Use of condoms, with or without spermicide, has been proven to decrease the risk of transmission of HIV and other sexually transmitted diseases. The use of spermicide is not recommended if the subject or subject's partner is infected with HIV.

5) Contraceptive Requirements for Female Subjects

It is recommended that females of childbearing potential do not become pregnant during this study. Women who are able to become pregnant and women who have not had surgery to become sterile (either a hysterectomy, vasectomy, or a bilateral tubal ligation), must use medically effective and reliable means to avoid pregnancy from the screening/enrollment visit throughout this study period and for 30 days following the last dose of study drug.

The investigator or the subject's health care provider must recommend effective means of contraception and discuss the risks and benefits of medically effective methods with the subject.

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.

6) Procedures to be Followed in the Event of Pregnancy

Subjects will 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 (idelalisib) dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug (idelalisib) immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

Appendix 11. CTCAE version 4.03

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf