THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

A Phase II Single-arm Study of the Efficacy and Safety of Oral Rigosertib in Patients with Myelofibrosis (MF) and Anemia
2014-0546

Core Protocol Information

Short Title	Phase II - Rigosertib in MF
Study Chair:	Jorge Cortes
Additional Contact:	Maria Rhona B. Pinsoy Rachel R. Abramowicz Leukemia Protocol Review Group
Additional Memo Recipients:	**Recipients List** **OPR Recipients** (for OPR use only) None **Study Staff Recipients** None
Department:	Leukemia
Phone:	713-794-5783
Unit:	428
Full Title:	A Phase II Single-arm Study of the Efficacy and Safety of Oral Rigosertib in Patients with Myelofibrosis (MF) and Anemia
Protocol Type:	Standard Protocol
Protocol Phase:	Phase II
Version Status:	Activated 08/25/2017
Version:	08
Document Status:	Saved as "Final"
Submitted by:	Rachel R. Abramowicz--8/7/2017 2:47:00 PM
OPR Action:	Accepted by: Elizabeth Orozco -- 8/15/2017 3:09:53 PM

Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

Development Phase: II

Product: rigosertib sodium (ON 01910.Na), oral capsules

Principal Investigator: Jorge Cortes, MD
Professor of Medicine, Department of Leukemia
UT MD Anderson Cancer Center
1515 Holcombe Blvd, Unit 428
Houston, TX 77030
Email: jcortes@mdanderson.org

2014-0546 Protocol Body - CLEAN VERSION (08-07-17).docx

CLINICAL STUDY PROTOCOL

A Phase II Single-arm Study of the Efficacy and Safety of Oral Rigosertib in Patients with Myelofibrosis (MF) and Anemia

Development Phase:	II
Product:	rigosertib sodium (ON 01910.Na), oral capsules
Principal Investigator:	Jorge Cortes, MD Professor of Medicine, Department of Leukemia UT MD Anderson Cancer Center 1515 Holcombe Blvd, Unit 428 Houston, TX 77030 Email: jcortes@mdanderson.org
Supporter:	Onconova Therapeutics Inc. 73 Route 31 North Pennington, New Jersey 08534 (USA)

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AKT	Serine-threonine kinase
ALT	Alanine transaminase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ASH	American Society of Hematology
AST	Aspartate transaminase
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from 0 to infinity
AZA	Azacitidine
BID	Twice daily
BM	Bone marrow
BMBL	Bone marrow blast
BMCR	Bone marrow complete response
BUN	Blood urea nitrogen
C1D1, C2D1	Cycle 1 Day 1, Cycle 2 Day 1
C_{max}	Maximum plasma concentration
CBC	Complete blood count
CDC25	Cell division cycle 25
CDK	Cyclin-dependent kinase
CFR	Code of Federal Regulations
CI	Clinical improvement
CIV	Continuous intravenous
CRO	Contract research organization
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation	Definition
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMH	Extramedullar hematopoiesis
EOS	End of study
EPO	Erythropoietin
ER	Erythroid response
ERES	Electronic Records/Electronic Signatures
ERK	Extracellular signal-regulated kinase
ESA	Erythropoiesis-stimulating agent
ET	Essential thrombocythemia
FAS	Full analysis set
FDA	Food & Drug Administration
FISH	Fluorescent in-situ hybridization
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factor
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
hr	Hour
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
Int-1	Intermediate-1
IPSS	International Prognostic Scoring System

Abbreviation	Definition
IRAE	Immediately Reportable Adverse Event
IRB	Institutional Review Board
IV	Intravenous
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK2	Janus kinase 2
LCM	Left coastal margin
LDH	Lactate dehydrogenase
MAPK	Mitogen-activated protein kinase
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MFSAF	Myelofibrosis self assessment form
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHLBI	National Heart Lung and Blood Institute
ON 01910.Na	rigosertib sodium (rigosertib); sodium salt of (E)-2,4,6-trimethoxystyryl-3-carboxymethylamino-4-methoxybenzyl sulfone
OS	Overall survival
PB	Peripheral blood
PD	Progressive disease
P-gp	P-glycoprotein
PI3K	Phosphatidylinositol-3 kinase
PK	Pharmacokinetic
PLK	Polo-like kinase
PLT	Platelet
PMF	Primary myelofibrosis

Abbreviation	Definition
PP	Per protocol
PRBC	Packed red blood cells
PT	Preferred Term (MedDRA)
PV	Polycythemia vera
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QC	Quality control
QOL	Quality of life
QW	Every week
RAEB, -1, -2	Refractory anemia with excess blasts, -type 1, -type 2
RBC	Red blood cell
RBD	Ras binding domain
RPTD	Recommended Phase II dose
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SC	Subcutaneous(ly)
SOC	System Organ Class (MedDRA)
SUSAR	Suspected unexpected serious adverse reaction
T_{max}	Time to maximum plasma concentration
TEAE	Treatment-emergent adverse event
TI	Transfusion independence
ULN	Upper limit of normal
US	United States
UTI	Urinary tract infection
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Description of the Investigational Product

Rigosertib sodium (ON 01910.Na; rigosertib hereafter) is a first-in-class dual phosphatidylinositol 3-kinase (PI3K)/polo-like kinase (PLK) pathway inhibitor that targets critical signals involved in the growth and survival of cancer cells. At the molecular level, rigosertib acts by selectively targeting 2 of the PI3K subunits (α and β), while also inhibiting downstream signals in the pathway such as the phosphorylation of serine-threonine kinase (AKT) and translation of cyclin D1 (Prasad 2009, Olnes 2012). Rigosertib also acts by inhibiting the PLK pathway, leading to a reduction in the activity of pro-mitotic proteins such as cell division cycle 25 (CDC25) and cyclin-dependent kinase (CDK)/cyclin B (Jimeno 2010). The dual molecular mechanism of action of rigosertib results in induction of multiple centrosomes during cell division, leading to multi-polar spindle formation (Reddy 2008), total disorganization of the mitotic apparatus causing chromosomal catastrophe (Reddy 2008), and modulation of the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) (growth) and AKT (survival) pathways, promoting cell death (apoptosis) in cancer cells (Chapman 2012). Recent data suggest that rigosertib binds to the Ras binding domain (RBD) of Ras effector proteins (ie, PI3K and Raf), thereby leading to their inactivation (data on file). This novel mechanism may help explain the multi-faceted effects of rigosertib, such as inhibition of the PI3K and PLK pathways.

Rigosertib was granted orphan drug status for the treatment of MDS by the Office of Orphan Products Development (HF-35) at the Food & Drug Administration (FDA) on September 3, 2009 (designation request #09-2894).

1.2. Summary of Clinical Findings Relevant to the Trial

Two formulations of rigosertib are currently being studied: intravenous (IV) and oral. At the time of the latest compilation of information (Investigator's Brochure [IB] edition 21; Rigosertib IB), 1176 patients with either MDS or other hematologic malignancies (N = 661) or advanced cancer and solid tumors (N = 515) were enrolled in 26 Phase I-III clinical studies of IV (N = 839) and oral (N = 337) rigosertib conducted by Onconova. Six other Phase I studies of rigosertib in a total of 51 patients with MDS and other hematologic malignancies were completed or are being conducted by other Sponsors (NHLBI and SymBio Pharmaceuticals) under different INDs..

In Phase I/II studies of IV rigosertib in adult patients with MDS and acute myeloid leukemia (AML), rigosertib was administered as 2- to 6-day continuous intravenous (CIV) infusions. Overall, rigosertib was reasonably well tolerated (see Rigosertib IB). Significant activity in reducing bone marrow blasts (BMBL) was found to be correlated to overall survival (OS).

A Phase I dose escalation study of oral rigosertib in MDS patients was completed at Moffitt Cancer Center and Columbia University Medical Center (#09-01). The study was divided into 3 parts: Part I evaluated the bioavailability and tolerability of single oral doses (70 mg, 140 mg, 280 mg, 560 mg, and 700 mg) administered weekly for 5 weeks. Part II (maximum tolerated dose [MTD] evaluation) assessed the tolerability of the same oral escalating doses (ie, 70 mg, 140 mg, 280 mg, 560 mg, and 700 mg), administered twice daily (BID) for 14 days of a 21-day cycle. Part III was a confirmation of the recommended Phase II dose (RPTD) with absolute bioavailability and food effect studies. Eligibility criteria included any International Prognostic Scoring System (IPSS) MDS risk group with at least 1 cytopenia; failure to respond to at least 1 prior standard treatment; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; and adequate kidney and liver functions. Key exclusion criteria included hypoplastic MDS (< 10% cellularity), ascites, history of seizures, uncontrolled hypertension, and history of human immunodeficiency virus (HIV) infection. Dose-limiting toxicity (DLT) was defined as ≥ Grade 3 non-hematologic drug-related toxicity (based on National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]) or delay in recovery of blood counts to Baseline levels for more than 30 days in the absence of response. A total of 37 MDS patients were enrolled. Pharmacokinetic (PK) dose proportionality was established in the 70 mg to 700 mg single-dose range in the first 3 patients enrolled, and pharmacodynamically active concentrations were reached. During the subsequent escalation phase, the RPTD was identified as 560 mg BID.

Overall rigosertib capsules were reasonably well tolerated, with dysuria as the most frequent treatment-emergent adverse event (TEAE). One patient on 700 mg experienced 2 DLTs (dysuria and shortness of breath) during the first 3-week cycle. Another patient on 700 mg experienced Grade 3 dysuria during Cycle 2.

Twelve patients in the confirming cohort underwent full PK evaluation (absolute bioavailability vs. the IV formulation, and food effect). Following a single fasting dose, oral rigosertib was rapidly absorbed (time to maximum plasma concentration [T_{max}] ~ 1 hr). Systemic exposure, as determined by maximum plasma concentration (C_{max}) and the area under the plasma concentration-time from 0 to infinity ($AUC_{0-\infty}$), increased in a linear and dose-proportional manner over the dose range of 70 mg to 700 mg. The plasma concentration-time profile exhibited a rapid distribution phase followed by a slower elimination phase. The elimination half-life from plasma after oral rigosertib dosing was comparable to estimates obtained after IV dosing. The absolute bioavailability of rigosertib (560 mg dose) was 35%. Food significantly reduced the rate and extent of rigosertib absorption. Oral administration of rigosertib after a meal decreased C_{max} and $AUC_{0-\infty}$ by 77% and 61%, respectively, compared to fasting conditions, with an estimated bioavailability of 14%.

Encouraging signs of activity were observed. Two bone marrow complete responses (BMCR) were observed in refractory anemia with excess blasts type 1 (RAEB-1) patients previously treated with azacitidine (AZA) at the 140 mg and 560 mg dose levels. In addition, transitions to transfusion

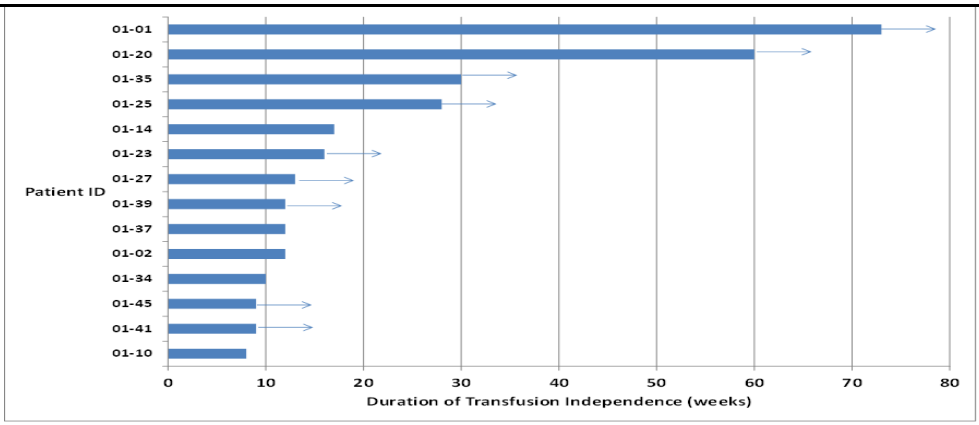
independence (TI) and erythroid response (ER) were observed in a subgroup of 16 patients with Low/intermediate-1 (Int-1) transfusion-dependent MDS patients in the 560 mg and 700 mg cohorts. Of the 12 evaluable patients treated for at least 8 weeks (of which 10 were in the 560 mg group), TI (defined as no red blood cell [RBC] transfusions needed over a period of 8 consecutive weeks) occurred in 4 patients, all in the 560 mg cohort. Erythropoiesis-stimulating agents (ESA) were administered before or after the onset of TI, suggesting a possible synergy between rigosertib and ESA for patients receiving ESA before the onset of TI. Duration of TI varied from 8 weeks to more than 47 weeks, with an onset of TI between Week 3 and Week 10. One additional patient in the 560 mg cohort had an ER, defined as reduction of at least 4 units of transfused RBC over 8 weeks.

The Phase II trial (09-05) is designed to evaluate oral rigosertib as a single agent in transfusion-dependent, lower-risk MDS patients. This trial is a randomized, 2-arm study of oral rigosertib, which was administered initially as 560 mg BID continuously. The 560 mg BID continuous regimen was changed to an intermittent 2-weeks on/1-week off regimen after 9 patients were enrolled, due to an excess of urinary side effects. The 560 mg BID intermittent regimen was further reduced to 560 mg in the morning and 280 mg in the afternoon to try and further minimize adverse urinary effects. This intermittent reduced regimen resulted in a much improved urinary tolerability, particularly the absence of Grade 3 urinary toxicity. The study was then amended to a 560 mg/280 mg continuous regimen. In the study, transfusion-dependent patients must have received at least 4 units of RBC transfusions over 8 weeks before randomization and can receive transfusions and ESA while on study.

Enrollment of 57 patients from 5 clinical sites in Study 09-05 was completed on November 5, 2013. Interim results are available and were reported during the annual meeting of the American Society of Hematology (ASH) in New Orleans in December 2013 (Raza 2013).

Of the 36 evaluable patients on intermittent dosing (of which 35 were receiving the original 560 mg BID regimen and 1 the reduced 560/280 mg regimen) treated for at least 8 consecutive weeks, 14 (39%) achieved TI (no RBC transfusion for at least 8 consecutive weeks) lasting from 8 weeks to 73 weeks (median not reached) (see Figure 1). Of the 9 patients who received continuous dosing, of which 8 were treated for at least 8 weeks, 2 achieved TI, the first for 10 weeks and the second for more than 18 weeks. In addition, 4 patients with ≥ Grade 3 neutropenia at Baseline (absolute neutrophil count [ANC] values < 1.0 K/μL) had neutrophil improvement for at least 8 weeks. One patient achieved a minor ER (transfusion decrease of 4 units RBC over 8 weeks).

Figure 1
Transfusion Independence in 14 of 36 Evaluable Patients (39%) Treated for at Least 8 Weeks with Intermittent Rigosertib Regimen (Original or Reduced)



Overall oral rigosertib was reasonably well tolerated with the exception of urinary side effects. The most frequent adverse events (AEs) in the 560 mg BID continuous dosing arm (≥ 20% of patients) were nausea, dysuria, pollakiuria, and urinary tract infection (UTI) (33% each), and cystitis, hematuria, micturition urgency, diarrhea, oedema peripheral, and pyrexia (22% each). The most frequent AEs in the 560 mg BID intermittent dosing arm (≥ 20% of patients) were pollakiuria (51%), fatigue (40%), micturition urgency and urinary tract pain (34% each), hematuria and dysuria (31% each), constipation (26%), nausea and UTI (23% each), and diarrhea (20%). There was a clinically significant reduction of urinary events in patients receiving the 560/280 mg intermittent regimen: the most frequent AE to date in this arm (≥ 20% of patients) is fatigue (31%). The following urinary events were observed in 1 patient each: nocturia, pollakiuria and UTI.

In the group receiving the continuous regimen, 2 patients (22%) developed Grade 3 cystitis, 1 patient each (11%) developed Grade 3 hematuria and Grade 3 UTI. The incidence of Grade 3 urinary events seemed to be reduced when patients were administered the original intermittent regimen (6% of patients each with Grade 3 cystitis, Grade 3 UTI and Grade 3 urinary tract pain, and 11% of patients with hematuria). No patients receiving the reduced intermittent regimen developed Grade 3 urinary events to date. The only Grade 3 AE in that group was progression to AML in 1 patient.

The causality of urinary side effects is being investigated. Since no nephrotoxicity was evident and significant urinary excretion of unmetabolized drug was noted, it was hypothesized that the residence time of rigosertib in the urinary bladder was a mitigating factor in causing irritation or inflammation of the bladder epithelia. Limited cystoscopy and other observations supported this hypothesis and lead to an improvement program based on hydration, bicarbonate tablets as needed, and judicious dose reduction. In general, symptoms can be relieved or reduced by these approaches.

Final study results are pending.

1.3. Summary of Potential Risks

The Reference Safety Information for this study is in the latest Rigosertib's IB A summary of expected drug-related treatment-emergent adverse events (AEs) in studies of oral rigosertib is presented below (Table 1).

Table 1
Reference Safety Information (RSI)
Summary of Expected Drug-related Treatment-emergent Adverse Events by Preferred Term, Sorted by Frequency, in Studies of Oral Rigosertib
Safety-Evaluable (N=337)
Rigosertib Integrated Analysis

MedDRA Preferred Term [1][2]	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Dysuria	103 (30.6%)	35 (10.4%)	61 (18.1%)	7 (2.1%)	0	0
Pollakiuria	67 (19.9%)	25 (7.4%)	42 (12.5%)	0	0	0
Haematuria	62 (18.4%)	27 (8.0%)	25 (7.4%)	10 (3.0%)	0	0
Micturition urgency	43 (12.8%)	20 (5.9%)	22 (6.5%)	1 (0.3%)	0	0
Fatigue	40 (11.9%)	18 (5.3%)	19 (5.6%)	3 (0.9%)	0	0
Nausea	39 (11.6%)	27 (8.0%)	9 (2.7%)	3 (0.9%)	0	0
Urinary tract pain	31 (9.2%)	11 (3.3%)	18 (5.3%)	2 (0.6%)	0	0
Diarrhoea	28 (8.3%)	19 (5.6%)	8 (2.4%)	1 (0.3%)	0	0
Urinary tract infection	27 (8.0%)	3 (0.9%)	21 (6.2%)	3 (0.9%)	0	0
Decreased appetite	18 (5.3%)	15 (4.5%)	2 (0.6%)	1 (0.3%)	0	0
Cystitis	17 (5.0%)	2 (0.6%)	8 (2.4%)	7 (2.1%)	0	0
Constipation	13 (3.9%)	11 (3.3%)	2 (0.6%)	0	0	0
Neutropenia	10 (3.0%)	0	1 (0.3%)	1 (0.3%)	8 (2.4%)	0
Vomiting	10 (3.0%)	8 (2.4%)	1 (0.3%)	1 (0.3%)	0	0
Nocturia	9 (2.7%)	3 (0.9%)	6 (1.8%)	0	0	0
Abdominal pain	8 (2.4%)	7 (2.1%)	1 (0.3%)	0	0	0
Hyponatraemia	8 (2.4%)	4 (1.2%)	0	4 (1.2%)	0	0
Proteinuria	8 (2.4%)	2 (0.6%)	4 (1.2%)	2 (0.6%)	0	0
Thrombocytopenia	8 (2.4%)	1 (0.3%)	0	2 (0.6%)	5 (1.5%)	0
Dyspepsia	7 (2.1%)	6 (1.8%)	1 (0.3%)	0	0	0
Headache	7 (2.1%)	5 (1.5%)	2 (0.6%)	0	0	0
Urinary incontinence	7 (2.1%)	0	7 (2.1%)	0	0	0
Neutrophil count decreased	6 (1.8%)	0	0	0	6 (1.8%)	0

Table 1
Reference Safety Information (RSI)
Summary of Expected Drug-related Treatment-emergent Adverse Events by Preferred Term, Sorted by Frequency, in Studies of Oral Rigosertib
Safety-Evaluable (N=337)
Rigosertib Integrated Analysis

MedDRA Preferred Term [1][2]	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Abdominal discomfort	5 (1.5%)	3 (0.9%)	2 (0.6%)	0	0	0
Anaemia	5 (1.5%)	3 (0.9%)	0	2 (0.6%)	0	0
Cystitis noninfective	5 (1.5%)	3 (0.9%)	2 (0.6%)	0	0	0
Dysgeusia	5 (1.5%)	5 (1.5%)	0	0	0	0
Aspartate aminotransferase increased	4 (1.2%)	4 (1.2%)	0	0	0	0
Chromaturia	4 (1.2%)	4 (1.2%)	0	0	0	0
Flatulence	4 (1.2%)	4 (1.2%)	0	0	0	0
Abdominal distension	3 (0.9%)	2 (0.6%)	1 (0.3%)	0	0	0
Abdominal pain upper	3 (0.9%)	1 (0.3%)	2 (0.6%)	0	0	0
Alanine aminotransferase increased	3 (0.9%)	1 (0.3%)	2 (0.6%)	0	0	0
Blood bilirubin increased	3 (0.9%)	3 (0.9%)	0	0	0	0
Platelet count decreased	3 (0.9%)	0	0	1 (0.3%)	2 (0.6%)	0
Urinary hesitation	3 (0.9%)	0	3 (0.9%)	0	0	0
Urinary retention	3 (0.9%)	3 (0.9%)	0	0	0	0
Bladder irritation	2 (0.6%)	1 (0.3%)	1 (0.3%)	0	0	0
Bladder spasm	2 (0.6%)	2 (0.6%)	0	0	0	0
Blood urine present	2 (0.6%)	1 (0.3%)	1 (0.3%)	0	0	0
Confusional state	2 (0.6%)	1 (0.3%)	1 (0.3%)	0	0	0
Frequent bowel movements	2 (0.6%)	2 (0.6%)	0	0	0	0
Leukopenia	2 (0.6%)	0	0	1 (0.3%)	1 (0.3%)	0
Lymphocyte count decreased	2 (0.6%)	2 (0.6%)	0	0	0	0
Malaise	2 (0.6%)	1 (0.3%)	1 (0.3%)	0	0	0
White blood cell count decreased	2 (0.6%)	1 (0.3%)	0	1 (0.3%)	0	0
Bladder pain	1 (0.3%)	0	1 (0.3%)	0	0	0

Table 1
Reference Safety Information (RSI)
Summary of Expected Drug-related Treatment-emergent Adverse Events by Preferred Term, Sorted by Frequency, in Studies of Oral Rigosertib
Safety-Evaluable (N=337)
Rigosertib Integrated Analysis

MedDRA Preferred Term [1][2]	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Bowel movement irregularity	1 (0.3%)	1 (0.3%)	0	0	0	0
Leukocyturia	1 (0.3%)	1 (0.3%)	0	0	0	0
Liver function test abnormal	1 (0.3%)	0	0	1 (0.3%)	0	0
Lymphopenia	1 (0.3%)	0	0	1 (0.3%)	0	0
Mental status changes	1 (0.3%)	1 (0.3%)	0	0	0	0
Neutropenic sepsis	1 (0.3%)	0	0	1 (0.3%)	0	0
Polyuria	1 (0.3%)	1 (0.3%)	0	0	0	0
Red blood cells urine	1 (0.3%)	0	1 (0.3%)	0	0	0
Red blood cells urine positive	1 (0.3%)	0	1 (0.3%)	0	0	0
Urethral pain	1 (0.3%)	1 (0.3%)	0	0	0	0
Urge incontinence	1 (0.3%)	0	1 (0.3%)	0	0	0
Urine analysis abnormal	1 (0.3%)	1 (0.3%)	0	0	0	0
Urine flow decreased	1 (0.3%)	1 (0.3%)	0	0	0	0
Urine output decreased	1 (0.3%)	1 (0.3%)	0	0	0	0
White blood cells urine positive	1 (0.3%)	1 (0.3%)	0	0	0	0

[1] Number of Patients used as denominator to calculate percentages.

[2] Patients with multiple TEAEs were only counted once within a summary category: preferred term, maximum grade, or relationship to treatment. Treatment-Emergent Adverse Events (TEAEs) were defined as all AEs that occurred after the first dose of study medication or within 30 day post-treatment period. MedDRA version 17.0.

Studies include 09-01, 09-02, 09-03, 09-04, 09-05, 09-07, 09-08, 09-09 and 09-12.

Based on nonclinical studies, the following effects could potentially be observed:

- Decrease in spleen or thymus weight;
- In men, reduction in sperm cell count and/or decrease of testicles' weight that could lead to infertility, and/or a decrease in the size of the prostate gland; these effects were partially or completely reversible in animals.
- Fetotoxicity (lower fetal weight) and teratogenicity (increased incidence of primarily craniofacial malformations); no maternal toxicity was observed in animals;
- Rigosertib was found to be an inhibitor or a substrate of the following transporters, which has the potential to lead to drug-drug interactions. Caution should be exercised and dose adjustments of the concomitant substrate or inhibitor drugs should be considered when dosing concurrently with rigosertib (see list of drugs that are substrates or inhibitors of these transporters at: FDA Guidance DDI).
    - Inhibition of CYP isoform 2C9 in vitro at clinically relevant concentrations. Additional in vitro studies to determine the effect of plasma protein binding showed that, when rigosertib was incubated with cryopreserved human hepatocytes in 100% human plasma to determine its potential for inhibition of CYP2C9, the potency of rigosertib decreased by 2.74-fold (12.5 μM) relative to that measured in the absence of protein. Based on these data, rigosertib has the potential for drug-drug interaction (DDI) with CYP2C9;
    - Time-dependent inhibition of CYP isoform 2C8. However, additional in vitro studies to determine the effect of plasma protein binding showed that, in the presence of plasma, the potency of rigosertib to inhibit CYP2C8 was very low (IC50 > 300 μM). Based on these data, rigosertib does not have the potential for DDI with CYP2C8;
    - Inhibition of OAT3, OATP1B1, and OATP1B3 at clinically relevant concentrations. Rigosertib could impair the excretion of co-medications that are known substrates of these transporters;
    - Rigosertib was found to be a substrate (but not an inhibitor) of P-gp and BCRP. Co-medications that are known inhibitors of these transporters should be taken with caution, as they could impair the hepatic excretion of rigosertib
    - Rigosertib is 98% protein bound and should be administered with caution to patients who are taking concomitant medications that are also highly protein bound (eg, warfarin).
- There was no evidence of ocular or cutaneous phototoxicity in female pigmented rats after 3 consecutive daily IV administrations of rigosertib with single solar-simulated ultraviolet radiation exposure simultaneously during the final administration.

Based on all clinical and nonclinical data available to date, and evaluating the frequency of reported events, the following are considered potential risks: Urinary disorders; Hyponatremia; pulmonary alveolar haemorrhage/respiratory distress; Hepatic effects; Central nervous system

(CNS) effects; Effects on spermatogenesis; Thymus involution; Teratogenicity/fetotoxicity; Potential carcinogenicity; and Retroperitoneal fibrosis have been identified as potentially important risks. The risk of phototoxicity was ruled out based on lack of evidence in animal studies but ongoing monitoring via routine proactive pharmacovigilance continues. Informed consents are being revised as needed to incorporate all the new potentially important risks. After evaluating the evidence in animal studies and the frequency of reporting in the clinical studies, the following AEs were deleted from this list: gallbladder hyperplasia, diabeltes insipidus, and phototoxicity. These events occurred in less than 0.1% of exposed patients and are unlikely to be risks associated with Rigosertib.

1.4. Study Rationale

Strong erythroid activity of oral rigosertib has been observed in lower-risk transfusion-dependent MDS patients (Section 1.2) treated with oral rigosertib. As 45% of patients receiving ruxolitinib experience Grade 3 or 4 anemia, it is hypothetized that oral rigosertib may improve anemia post-ruxolitinib.

In addition, Janus kinase 2 (JAK2) allelic reduction has been described in 1 patient in Study 04-05 conducted at Mount Sinai School of Medicine. This patient had MDS with evidence of myelofibrosis (MF) treated initially with AZA for 4 years. Splenomegaly, which was present at the outset of treatment, resolved completely. The patient was positive for presence of the JAK2 V617F mutation prior to the start of IV rigosertib. The JAK 2-positive allele burden was reduced by 41% between Cycle 2 and Cycle 4, suggesting that rigosertib could have activity in MF.

2. STUDY OBJECTIVES

The primary objective of this study is to assess, in patients with myelofibrosis and anemia, the efficacy of oral rigosertib in improving anemia and symptoms, and in decreasing the spleen size of those patients with splenomegaly.

This study will also assess the safety and tolerability of oral rigosertib in this patient population.

3. INVESTIGATIONAL PLAN

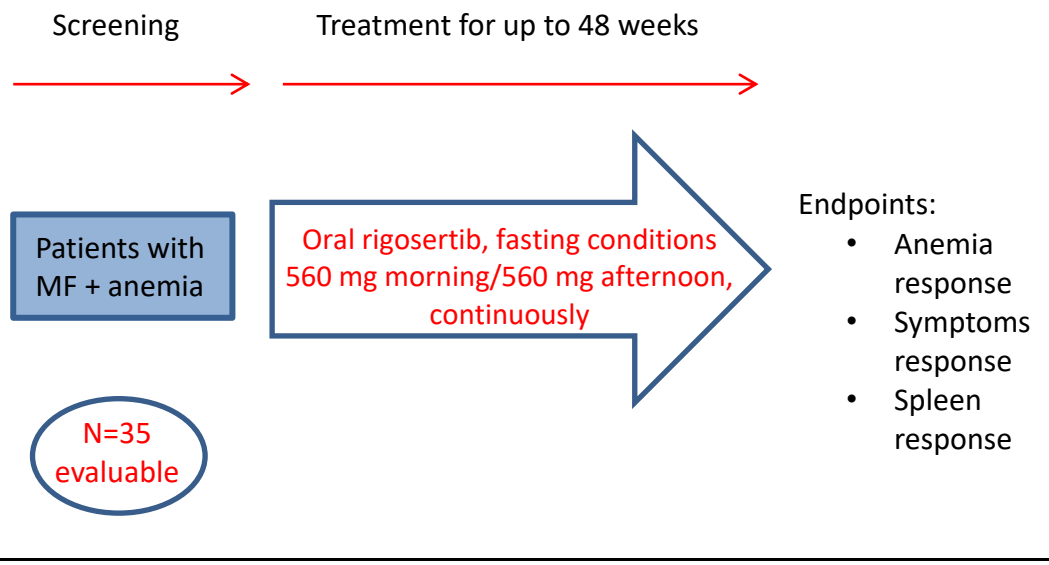
3.1. Study Design

This is planned as a Phase II, 2-stage, single-arm study. Up to 35 evaluable patients with MF and anemia will receive oral rigosertib BID daily, on a continuous basis (see Study Design in Figure 2). Patients will take 560 mg rigosertib (two 280 mg capsules) twice daily in fasting conditions (see fasting instructions in Section 3.5.2). To be evaluable, patients need to be treated for at least 24 weeks with oral rigosertib.

In the first stage, a total of 18 evaluable patients will be enrolled. If 2 or fewer responses are observed in the first 18 evaluable patients, the trial may terminate for futility. Otherwise, an additional 17 evaluable patients will be enrolled in the second stage. A summary of the composite response (as defined in Section 3.6.1) of the first 18 subjects should be submitted to the IND Medical Monitor before moving to the second phase of enrollment.

At least 7 responses in 35 evaluable patients treated for at least 24 weeks with oral rigosertib are required to confirm a 30% target response rate at a significance level of 0.05 (see Section 3.6.1, Sample Size Considerations).

Figure 2
2014-0546 Design



All study participants will be allowed, as medically justified, access to RBC and platelet (PLT) transfusions, and to filgrastim (granulocyte colony-stimulating factor, [G-CSF]). Rigosertib dosing adjustment policies are described in Section 3.5.4.

Patients will remain treated on study for 48 weeks or until progressive disease (PD) criteria according to 2013 revised International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) response criteria (Appendix 4) are met, unacceptable toxicity is observed, intercurrent illness or a change in the patient's condition prevents further administration of study drug treatment, or until death from any cause occurs, whichever comes first. Patients who have decreased splenomegaly and/or improvement of anemia and/or improvement in Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF

TSS) scoring of at least 50% (see Appendix 5) may continue to be treated in the study beyond 48 weeks until progression or until death from any cause, whichever comes first.

3.2. Selection of Study Population

The diagnosis of MF will be based on bone marrow (BM) aspirate and/or biopsy performed within 6 weeks prior to Screening. Measurement of JAK2 V617F allele burden in BM samples, if not done within 6 months prior to Screening, must be provided with the Screening BM biopsy/aspirate report.

3.2.1. Inclusion Criteria

Male and female patients who meet all of the following criteria are eligible for enrollment in the trial:

a. ≥18 years of age;

b. Diagnosis of primary myelofibrosis (PMF) or post-polycythemia vera (post-PV) MF or post-essential thrombocythemia (post-ET) MF based on the World Health Organization (WHO) criteria (Appendix 1) or the IWG-MRT criteria (Appendix 2), which must be confirmed by BM aspirate and/or biopsy within 6 weeks prior to Screening. Measurement of JAK2 V617F allele burden in BM samples, if not done within 6 months prior to Screening, must be provided with the Screening BM biopsy/aspirate report (patients are eligible regardless of JAK2 mutation status);

c. Anemia or RBC-transfusion dependence defined as follows:

    a. **Anemia:** defined for the purpose of this protocol as 1) a hemoglobin level <10 g/L on every determination over 84 days before study-entry, without RBC-transfusions, or 2) a hemoglobin level <10 g/L on a patient that is receiving RBC-transfusions periodically but not meeting criteria for transfusion-dependent patient as defined below. The baseline hemoglobin value for these subjects is the lowest hemoglobin level during the antecedent 84 days.

    b. **RBC**-transfusion-dependence: RBC-transfusion-frequency of >/=2 units PRBC/28 days averaged over 84 days immediately pre-study-entry. There must not be any consecutive 42 days without an RBC-transfusion during this interval.

d. ECOG performance status of 0, 1 or 2 (see Appendix 3);

e. Willing to adhere to the prohibitions and restrictions specified in this protocol (Notation: the subject's willingness to adhere to prohibitions and restrictions must be clearly communicated in the on-study note.);

f. The patient must signed an informed consent form (ICF) indicating that s/he understands the purpose of, and procedures required for, the study and is willing to participate.

3.2.2. Exclusion Criteria

Patients with any of the following will not be enrolled in the study:

a. Ongoing clinically significant anemia due to factors such as known iron, vitamin B12, or folate deficiencies, auto-immune or hereditary hemolysis, or gastrointestinal (GI) bleeding;
b. Serum ferritin < 50 ng/mL;
c. Any active malignancy within the past year, except basal cell or squamous cell skin cancer or carcinoma in situ of the cervix or breast; patients with history of prior malignancies should be free of disease for at least 3 years to be eligible for this study;
d. Uncontrolled intercurrent illness, including, but not limited to symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia;
e. Active infection not adequately responding to appropriate therapy;
f. Direct bilirubin ≥ 2.0 mg/dL not related to hemolysis or Gilbert's disease;
g. Alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 2.5 x the upper limit of normal (ULN);
h. Serum creatinine ≥ 2.5 mg/dL;
i. Ascites requiring active medical management including paracentesis;
j. Hyponatremia (defined as serum sodium level < 130 mEq/L);
k. Female patients who are pregnant or lactating;
l. Patients of childbearing potential (ie, women of childbearing potential and men with female partners of childbearing potential) who are unwilling to follow strict contraception requirements (including 2 reliable methods in combination: 1 non-hormonal, highly-reliable method [diaphragm, condoms with spermicidal foam or jelly, or sterilization] plus 1 additional reliable method [birth control pills, intrauterine device, contraceptive injections, or contraceptive patches]) before entry and throughout the study, up to and including the 30-day non-treatment follow-up period;
m. Female patients of childbearing potential who have a positive blood or urine pregnancy test at Screening;
n. Major surgery without full recovery or major surgery within 3 weeks of Screening;
o. Uncontrolled hypertension (defined as a sustained systolic pressure ≥ 160 mmHg and/or a diastolic pressure ≥ 110 mmHg);
p. New onset seizures (within 3 months prior to Screening) or poorly controlled seizures;
q. Any other concurrent investigational agent or chemotherapy, radiotherapy, or immunotherapy;
r. Chronic use (> 2 weeks) of corticosteroids (prednisone >/= 10 mg/24 hr equivalent) within 4 weeks of Screening;
s. Investigational therapy within 2 weeks of Screening;

t. Psychiatric illness or social situation that would limit the patient's ability to tolerate and/or comply with study requirements.

3.3. Removal of Patients from the Study

Patients will be discontinued in the following circumstances:

a. The patient dies;

b. There is evidence of clinically significant PD according to 2013 revised IWG-MRT criteria (Appendix 4);

c. There is no clinical improvement (CI) or anemia response per 2013 revised IWG-MRT criteria (Appendix 4) after 48 weeks of treatment;

d. The Investigator decides that the patient should be withdrawn from the study. If this decision is due to a serious adverse event (SAE) or a clinically significant abnormal laboratory value, the study drug must be discontinued and appropriate measures taken. The MD Anderson IND Office must be notified immediately;

e. The patient or attending physician requests that the patient be withdrawn from the study;

f. The MD Anderson IND Office, the supporter or a regulatory agency for any reason, terminates the study;

g. The patient develops unstable ascites requiring medical management including paracentesis;

h. The patient has bilateral Grade 4 edema (per CTCAE) with 10% increase in body weight;

i. The drug exhibits unacceptable toxicity;

j. The patient becomes pregnant or fails to use adequate birth control (for those patients of childbearing potential);

k. Non-compliance to condom use for male patients;

l. The patient exhibits a pattern of non-compliance with study procedures;

m. The patient is lost to follow-up. In such a case, every possible effort must be made by the study site personnel to contact the patient and determine the reason for discontinuation. The measures taken to contact the patient must be documented.

3.4. Study Procedures

The schedule of events and study procedures is detailed in tabular form in Appendix 6.

Each study procedure should be performed on the day dictated by the patient's dosing schedule. However, if a patient is unable to have a study procedure performed on the scheduled day, the procedure must be performed within the particular visit window; otherwise it will be considered a

missed procedure. Since significant failure to comply may result in the patient's being withdrawn from the study, repeated deviations from visit windows should be discussed with theMD Anderson IND Office.

3.4.2. Efficacy Assessments

3.4.2.1. Efficacy Outcomes

The following outcomes will be assessed:

- Symptoms response, as determined by change in QOL score before Week 48, using the MPN-SAF TSS (Appendix 5);
- Spleen response at Week 24 and Week 48 (defined as ≥ 35% spleen volume reduction from Baseline, which must be confirmed by MRI or CT measurement; see 2013 revised IWG-MRT response criteria for MF in Appendix 4);
- Duration of spleen response;
- Anemia response (see 2013 revised IWG-MRT response criteria for MF in Appendix 4) including change in Hgb and PRBC units transfusion requirements;
- Change in PLT count and PLT transfusion requirements;
- BM aspirate and/or biopsy at Week 24 and Week 48 to assess MF and measure JAK2 V617F allele burden;
- OS at Week 48.

3.4.2.2. Bone Marrow Examination and Cytogenetics

The percentage of BMBL will be quantified by morphology assessment of a specimen of BM aspirated smear (Wright-Giemsa stained) and/or biopsy (Hematoxylin-Eosin stained). If the proportion of BMBL is estimated as an interval (eg, 5% to 10% BMBL), then the interval mean value (ie, 7.5% in this example) will be used for BMBL evaluation. Automated quantification of CD34+ blasts by flow cytometry method will not routinely be used for quantification of BMBL. However, if the BM is too fibrotic to get a satisfactory BM aspirate, then quantification of BMBL using CD34 immunostaining on BM biopsy may be performed.

Cytogenetic analysis will be performed using the fluorescent in-situ hybridization (FISH) technique or the conventional G-banding technique (20-metaphases method).

Optional exploratory evaluations of genomics and proteomics exploring pathways potentially involved in the pathogenesis of MF and response to treatment will be carried out in BM samples collected before and during treatment.

Leftover blood and BM samples will be used for this testing. No additional samples will be collected.

3.4.2.3. Exploratory Genomics/Molecular Evaluation in Peripheral Blood Samples

Optional genomic and molecular evaluations exploring pathways potentially involved in the pathogenesis of MF and response to treatment may be carried out in aliquots of peripheral blood (PB) samples, which will be refrigerated and processed.

Leftover blood and BM samples will be used for this testing. No additional samples will be collected.

3.4.3. Safety Assessments

Specific safety parameters and procedures will include recording of medical history, medication history, and concomitant medications, physical examination, measurement of vital signs (blood pressure, temperature, respiration rate, and pulse), weight, standard 12-lead ECG at Screening, laboratory evaluations, and toxicity and AE assessments. Adverse events will be graded according to the NCI Common Terminology Criteria Version 4 (CTCAE v4). Adverse events will be recorded from the time of the first protocol-specific intervention up to 30 days after last dose of rigosertib.

Safety assessments will include the collection of AEs reported by the patient or observed by the Investigator or study site personnel. Questions should be of a general nature and should not suggest symptoms. Patients should be asked whether, since the time of the last observation or visit, any of the following occurred:

- They experienced any changes in well-being;
- They used any new medications;
- They changed medication regimens (both prescription and over-the-counter);
- They were hospitalized or had any accidents.

When an AE is suspected, all relevant evaluations will be carried out and appropriate treatment provided. Additional follow-up will be performed as necessary and recorded in the patient's source documents, with the results provided to theMD Anderson IND Office. Patients who experience any clinically significant AEs will remain under medical supervision until the Investigator or the MD Anderson IND Office deems the AE to be resolved, stabilized, or no longer serious enough to warrant follow-up. Laboratory values that are abnormal and not assessed as AEs may be followed at the discretion of the Investigator or the MD Anderson IND Office until resolved or stabilized.

For AE definitions and reporting requirements, refer to Section 4.1.

3.5. Treatments

3.5.1. Method of Assigning Patients to Treatment Groups

This is a Phase II, 2-stage, single-arm study. Up to 35 evaluable patients with MF and anemia will be enrolled. To be evaluable, patients need to be treated for at least 24 weeks with oral rigosertib.

Outside Physician Participation During Treatment

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record

2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix E)

3. Protocol required evaluations outside MDACC will be documented by fax. Faxed evaluations will be dated and signed by the MDACC physician/investigator indicating that they have reviewed it.

4. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.

5. Documentation to be provided by the local physician will include progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

6. The home physician will be requested to report to the MDACC physician/investigator all life threatening events within 24 hours of documented occurrence.

7. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

3.5.2. Treatments Administered

Rigosertib will be supplied as 280 mg and 70 mg capsules by Onconova. Study drug must be stored between 2°C and 8°C (ie, refrigerated), protected from light, whether at the patient's home or at the institution.

Rigosertib will be administered daily, continuously, on an outpatient basis. Patients will take 560 mg rigosertib in the morning (two 280 mg capsules) and 560 mg rigosertib in the afternoon.

See Section 3.5.4 for adjusted rigosertib dose regimens. Treatments should be started within 2 weeks of completion of screening and meeting eligibility criteria.

Patients should be instructed to take rigosertib in a fasting state BID as follows:

- The morning dose should be taken after an overnight fast, on an empty stomach, and patients should wait 1 hr after dosing to have breakfast.
- The afternoon dose should be taken at approximately 3 PM (±1 hr) at least 2 hr after lunch, on an empty stomach, and patients should wait 1 hr before the next meal.

Water is permitted during the fasting period. Any vomited dose will be reported as a missed dose. Good hydration (ie, at least 2 liters of water per day) is recommended for all patients.

3.5.3. Management of Clinical Supplies

The Investigator will have overall responsibility for the use of the study medication. Under no circumstances will the Investigator allow rigosertib to be used other than as directed by this protocol. The Investigator or designee will provide a signed acknowledgment for receipt of the study medications and a signed acknowledgment for return of study medication containers and unused study medication at the end of the study. An accurate record of the dispensing of all study medication must be maintained. Upon completion or termination of the study, remaining study drug will be returned to Onconova, unless otherwise instructed by the MD Anderson IND Office or Onconova.

Qualified study center personnel must receive study drug deliveries, record the receipt, and assure that the study drug is handled and stored safely and properly. The packing list must be reconciled against the bottles received. Any extra/damaged drug product containers will be destroyed at the site according to local procedures, or sent to Onconova for destruction, as instructed and documented by Onconova.

Study drug must be stored between 2°C and 8°C (ie, refrigerated), protected from light, whether at the patient's home or at the institution.

Copies of all dispensing records for the study drug must be kept at the study center as part of required study documentation. At the end of the study, the study center must be able to reconcile delivery records with records of study drug received, dispensed, and returned. The Investigator must account for any discrepancies.

Rigosertib may not be relabeled or reassigned for use. Rigosertib may not be used for any purposes other than what is outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

3.5.4. Rigosertib Dosing Adjustments

The number of capsules to be taken as a function of adjusted dose is presented in Table 2.

Table 2
Rigosertib Dosing Adjustments

	Original Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Morning dose	560 mg (Two 280 mg capsules)	560 mg (Two 280 mg capsules)	420 mg (One 280 mg + two 70 mg capsules)	280 mg (One 280 mg capsule)
Afternoon dose	560 mg (Two 280 mg capsules)	280 mg (One 280 mg capsule)	210 mg (Three 70 mg capsules)	140 mg (Two 70 mg capsules)

3.5.4.1. Hematologic Toxicity

If ANC and/or PLT nadir are decreased by ≥ 50% from Baseline count and to > Grade 3 levels unrelated to disease, comorbidities or concomitant medications, the next rigosertib dose may be delayed until the ANC has increased to $> 1 \times 10^9$/L and the PLT count has increased to $> 75 \times 10^9$/L. If the next dose has to be delayed by more than 14 days after the last dose, rigosertib will be restarted at the next lower dose level (see Table 2). If the delay is ≤ 14 days after the last dose, rigosertib may be restarted at 100% of scheduled dose. Patients who experience treatment-related neutropenia and/or thrombocytopenia of 6 weeks duration or more (consecutive) in more than two occasions may continue on study (after appropriate dose adjustments as per Table 2) only after discussion with the IND office to justify the appropriateness of continued therapy.

3.5.4.2. Non-hematologic Toxicity - Hyponatremia

If a patient develops ≥ Grade 3 hyponatremia, rigosertib will not be administered until resolution to Grade 2 and serum and urine osmolality, serum albumin, BUN, serum creatinine, and serum and urinary sodium will be measured to assist in the medical management of hyponatremia. Additional tests may be carried out as clinically warranted.

3.5.4.2.1. Treatment-related Urinary Symptoms

If any treatment-related urinary symptoms of Grade 2 or higher in severity that are at least 1 grade higher than Baseline, develop during the treatment period, treatment will be withheld until resolution to ≤ Grade 1 or Baseline status and resumed using the schedule displayed in Table 3.

Table 3 **Oral Rigosertib Step-by-step Dose Reductions for Urinary Toxicity**				
Episodes of Urinary Toxicity	**Starting Dose**		**Dose Adjustment**	
	Morning	**Afternoon**	**Morning**	**Afternoon**
1	560 mg	560 mg	560 mg	280 mg
2	560 mg	280 mg	420 mg	280 mg
3	420 mg	280 mg	420 mg	210 mg
4	420 mg	210 mg	280 mg	210 mg
5	280 mg	210 mg	280 mg	140 mg
6	280 mg	140 mg	140 mg	140 mg
7	140 mg	140 mg	140 mg	70 mg
8	140 mg	70 mg	70 mg	70 mg
9	70 mg	70 mg	140 mg every other day	0 mg

Should a further episode of urinary toxicity occur, the patient will be withdrawn from the trial and followed.

3.5.4.2.2. Treatment-related ≥Grade 3 Toxicity other than Urinary Symptoms

If any treatment-related non-hematologic toxicity of Grade 3 or higher is present on the day of administration of rigosertib:

1. Rigosertib treatment will be withheld until resolution to ≤ Grade 1 or Baseline toxicity grading, whichever is greater, then dosing will be resumed at *full dose*;
2. If the same treatment-related toxicity of Grade 2 or higher reoccurs, rigosertib dosing will be reduced (see Table 2) at the next administration;
3. If the same treatment-related non-hematologic toxicity of ≥ Grade 2 reoccurs, rigosertib dose will be reduced further (see Table 2) after resolution to ≤ Grade 1 or Baseline status;
4. If the same toxicity persists and is not tolerable, the patient will be withdrawn from the study.

3.5.5. Treatment Compliance

Each dose of rigosertib should be administered on the day dictated by the patient's dosing schedule. Patients should not take missed doses. Patients will be given a diary to document compliance with study drug.

3.5.6. Management of Urinary Symptoms

Good hydration (ie, at least 2 liters of water per day) is recommended for all patients. If dysuria develops, the following therapies may be prescribed:

- *Sodium bicarbonate tablets* if the patient is not on a sodium-restricted diet: 650 mg tablets given BID with two 8-ounce glasses of water 1 hr after rigosertib administration;
- *Pyridium* if the patient has a normal creatinine value and is not allergic to phenazopyridine: 100 mg 3 times daily orally, taken with a full glass of water and food; pyridium should not be taken for more than 2 days.

Please refer to Section 3.5.4.2.1 for dosing adjustments in case of ≥ Grade 2 urinary toxicity.

3.5.7. Concomitant Therapy

All concomitant medications (including non-prescription drugs and herbal therapies) received from 30 days prior to study entry until the end of study will be recorded in the patient's chart. The information should include the name of the drug, indication, daily dose with units, and the start and stop date(s) of administration.

All patients may be transfused when judged to be medically necessary by the Investigator. The date and type of transfusion, the Hgb and/or PLT values prior to transfusion (obtained at the time of type/cross match), and the number of units transfused must be recorded on the eCRF. The reason for transfusion should also be documented.

Recombinant G-CSF or granulocyte-monocyte colony stimulating factor (GM-CSF) can be used as clinically indicated (e.g., for Grade 3 or 4 neutropenia with recurrent or resistant bacterial infections). Recommended dosage for G-CSF is 5 µg/kg subcutaneous (SC) daily (NCCN 2011).

Based on findings from nonclinical studies, rigosertib inhibits CYP isoforms 2C9 and 2C8 in vitro at clinically relevant concentrations. Caution should be exercised and dose reduction of the concomitant substrate drugs should be considered when dosing rigosertib concurrently with medications with narrow therapeutic range that are substrates of CYP2C9 or CYP2C8 (see Appendix 8). In addition, rigosertib was found to be a P-gp substrate, but not a P-gp inhibitor (see list of potential P-gp inhibitors in Appendix 9).

3.6. Statistical Methods

This study is a Phase II, proof-of-concept, single-arm study of the efficacy and safety of oral rigosertib in patients with MF and anemia.

3.6.1. Sample Size Considerations

The primary endpoint will be the proportion of patients achieving spleen response by Week 24 or Week 48 (defined as ≥ 35% spleen volume reduction from Baseline, which requires confirmation

by MRI or CT; see 2013 revised IWG-MRT criteria in Appendix 4) and/or anemia response by Week 24 or Week 48 (defined as the proportion of transfusion-independent patients with Hgb increase of at least 2 g/dL from Baseline or the proportion of transfusion-dependent patients becoming transfusion independent for at least 12 weeks as defined in 2013 IWG-MRT criteria; Appendix 4) and/or symptoms response (defined as the proportion of patients achieving ≥ 50% reduction in the MPN-SAF TSS score; see Appendix 5) at any time before Week 48. These response criteria will be referred to as "composite response".

A response rate (composite response described above) of 30% or more is considered clinically meaningful, against a minimal or "uninteresting" response rate of 10% or less. A Simon 2-stage optimal design is used in order to minimize the expected sample size if the regimen has low activity. If there are 2 or fewer responses in the first 18 evaluable patients, the trial may terminate for futility. Otherwise, 17 more evaluable patients will be enrolled, for a total of 35 evaluable patients. At least 7 responses in 35 evaluable patients are required to confirm the 30% target response rate at a significance level of 0.05, assuming a power of 0.90. Probability of termination at Stage 1 is 73% and 6% for underlying responses rates of ≤ 10% and ≥ 30%, respectively.

Descriptive statistics (mean, standard deviation, and coefficient of variation, median, minimum and maximum) will be calculated for safety and efficacy parameters.

3.6.2. Analysis Populations

The analyses will be done on the 3 following populations:

- The *full analysis set (FAS)* population will include all patients enrolled and treated.
- The *per-protocol (PP)* population will include all patients who complete the study without major protocol violations and are treated for a minimum of 24 weeks.
- The *safety* population will include all patients who received at least 1 dose of rigosertib. It is identical to the FAS population.

3.6.3. Final Analyses

3.6.3.1. Efficacy Analyses

Analyses of the primary and secondary efficacy outcomes will be performed on the FAS and PP populations.

The primary endpoint will be the proportion of patients with splenomegaly at Baseline achieving spleen response at Week 24 or Week 48 (defined as ≥ 35% spleen volume reduction from Baseline, which requires confirmation by MRI or CT; see 2013 revised IWG-MRT criteria in Appendix 4) and/or anemia response at Week 24 or Week 48 (defined as the proportion of transfusion-independent patients with Hgb increase of at least 2 g/dL from Baseline or the proportion of

transfusion-dependent patients becoming transfusion independent for at least 12 weeks as defined in 2013 IWG-MRT criteria; Appendix 4) and/or symptoms response (defined as the proportion of patients achieving ≥ 50% reduction in the MPN-SAF TSS score; see Appendix 5) at any time before Week 48.

3.6.3.2. Safety Analyses

Safety analyses will be performed on the safety population. Safety definitions are found in Section 4.1.

Adverse Events:
Adverse events will be coded using the most recent version of the Common Terminology Criteria for Adverse Events v4 (CTCAE). Adverse events will be summarized by patient, not by event. Investigators will be asked to assess the relationship of AEs to study drug. The relationship of each AE to study drug will be categorized as not related, unlikely related, possibly related, probably related, or definitely related to study drug.

Disease progression will not be considered an AE.

~~A listing of all AEs will be provided using the most recent version of CTCAE and will include (but will not be limited to) onset and resolution dates, seriousness, severity, relationship, action taken with study drug, and outcome.~~ Adverse Events (AEs) will be evaluated according to current CTC version in each protocol. Only unexpected and related AEs will be recorded in the Case Report Form (CRF). Appendix D "Leukemia Specific AE Recording Guidelines" will be followed.

Deaths:
The number of patients who died will be summarized. A by-patient listing of deaths including death date, cause of death, number of days from first and last dose of rigosertib, and relationship to study drug will also be provided.

Laboratory Assessments:
Laboratory test data may be analyzed using summary statistics on changes from Baseline or distributions of worst on-study laboratory values based on CTCAE grade.

Vital Signs:
Vital signs may be analyzed using summary statistics on changes from Baseline or distribution of worst on-study values based on CTCAE grade.

3.6.3.3. Additional Analyses

ECOG Performance Status:

ECOG performance status has integer values from 0 (fully active) to 4 (completely disabled) (see Appendix 3). The number and percentage of patients with each result for the latest pre-enrollment examination will be summarized. For each patient, the best post-screening ECOG performance status (lowest score) will be summarized over the entire time on study. A shift table will be presented indicating the change from baseline ECOG status to maximum ECOG for the entire time on study. Graphical displays may be generated if appropriate.

Population Pharmacokinetics:
Blood samples for measurement of rigosertib will be taken in all patients 1 hr after rigosertib administration on Baseline/C1D1 visit (morning dose), and at predose and 1 hr after rigosertib administration on Day 28 (+/-5 days) (morning dose). Population PK analyses will consider relationships between mean blood levels of rigosertib and the efficacy outcomes.

4. INVESTIGATOR'S OBLIGATIONS

4.1. Reporting Adverse Events

4.1.1. Serious Adverse Event Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB for participants enrolled at MDACC.
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the Investigator at UT MD Anderson Cancer Center (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, UT MD Anderson Cancer Center, and Institutional Review Board policy.

4.1.2 Case Report Form

In this study all AEs will be reported electronically via the AE Recording Form (PDMS/CORe).

4.2 Investigator Communications with Onconova

Adverse Event Reporting to Supporting Company:

SAEs must be reported to Onconova within 24 hours of the study center's knowledge of the AE. SAEs are to be emailed to USDrugSafety@onconova.us.

.

4.3 Pregnancies

In pregnant rats, rigosertib was found to be fetotoxic (as evidenced by lower fetal weights) and teratogenic (increased incidence of primarily craniofacial malformations). No maternal toxicity was observed (see Rigosertib IB). Pregnancies occurring between the signing of the ICF up to

30 days after the last dose of study drug must be reported on the Pregnancy Notification Form by the investigational staff within 24 hr of their knowledge of the event. Any patient who becomes pregnant during participation in this study must be promptly withdrawn from the study. These patients will be asked to consent to allow their treating physician to provide Onconova with follow-up information on the pregnancy itself and its outcome. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

5. REFERENCE LIST

Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-thrombocythemia myelofibrosis: a consensus statement from the international working group for myelofibrosis research and treatment. Leukemia. 2008; 22:437-8

Chapman CM, Sun X, Roschewski M, et al. ON 01910.Na is selectively cytotoxic for chronic lymphocytic leukemia cells through a dual mechanism of action involving PI3K/AKT inhibition and induction of oxydative stress. Clin Cancer Res. 2012; 18:1979-91.

Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol. 2012; 30:4098-4103

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.aspx. Accessed 2013/02/04.

Food & Drug Administration. Drug development and drug interactions: table of substrates, inhibitors and inducers. http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#PgpTransport

Jimeno A, Rubio-Viqueira B, Rajeshkumar NV, Chan A, Solomon A, Hidalgo M. A fine-needle aspirate-based vulnerability assay identifies polo-like kinase 1 as a mediator of gemcitabine resistance in pancreatic cancer. Mol Cancer Ther. 2010; 9:311-8.

Manoharan A, Horsley R, Pitney WR. The reticulin content of bone marrow in acute leukemia in adults. Br J Haematol. 1979; 43:185-90.

Mesa RA, Gotlib JR, Gupta V et al. Results using the modified myelofibrosis Symptom Assessment Form (MFSAF v2.0) in Comfort I: a randomized, double-blind, phase III trial of Jak ½ inhibitor ruxolitinib vs. Placebo in myelofibrosis. Poster 912; 16th Congress EHA; June 2011

NCCN clinical practice guidelines in oncology (NCCN Guidelines™). Myelodysplastic syndromes. Version 2.2011.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-55.

Olnes MJ, Shenoy A, Weinstein B et al. Directed therapy for patients with myelodysplastic syndromes (MDS) by suppression of cyclin D1 with ON 01910.Na. Leukemia Res. 2012; 36:982-9.

Prasad A, Park IW, Allen H, et al. Styryl sulfonyl compounds inhibit translation of cyclin D1 in mantle cell lymphoma cells. Oncogene. 2009; 28:1518–28.

Raza A, Tycko B, Sangmin L, et al. Oral rigosertib (ON 01910.Na) treatment produces an encouraging rate of transfusion independence in lower risk myelodysplastic syndrome (MDS) patients; a genomic methylation profile is associated with responses. ASH 2013, New Orleans, LA. Abstract #2745.

Reddy MV, Mallireddigari MR, Cosenza SC, et al. Design, synthesis, and biological evaluation of (E)-styrylbenzylsulfones as novel anticancer agents. J Med Chem. 2008; 51: 86-100.

Rigosertib (ON 01910.Na) Investigator's Brochure. Edition 19, November 20, 2013.

Tefferi A, Thiele J, Orazi A, et al. Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an *ad hoc* international expert panel. Blood 2007; 110:1092-7.

Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. Blood. 2013;122:1395-8.

Thiele J, Kvasnicka HM, Facchetti F, Franco V, Ven der Walt J, Orazi A. et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica. 2005; 90:1128.

Vardiman JW, Thiele J, Arber DA, et al. The 2008 revisions of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114:937-51.

6. APPENDICES

Appendix 1: WHO Criteria for Diagnosis of Primary Myelofibrosis, Essential Thrombocythemia, and Polycythemia Vera

Reference: Vardiman 2009

Criteria for Primary Myelofibrosis(PMF)
Diagnosis requires meeting all 3 major criteria and 2 minor criteria.
Major Criteria
1. Presence of megakaryocyte proliferation and atypia,(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 polycythemia vera,(b) *BCR-ABL1*–positive chronic myelogenous leukemia,(c) myelodysplastic syndrome,(d) or other myeloid disorders 3. Demonstration of *JAK2* V617F or other clonal marker (eg, *MPL*W515K/L), or, in the absence of the above clonal markers, no evidence that bone marrow fibrosis is secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies(e)
Minor criteria
1. Leukoerythroblastosis(f) 2. Increase in serum lactate dehydrogenase level(f) 3. Anemia(f) 4. Palpable splenomegaly(f)
(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 level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels. Red cell mass measurement is not required. (c) Requires the absence of *BCR-ABL1*. (d) Requires the absence of dyserythropoiesis and dysgranulopoiesis. (e) It should be noted that patients with conditions associated with reactive myelofibrosis are not immune to primary myelofibrosis, and the diagnosis should be considered in such cases if other criteria are met. (f) Degree of abnormality could be borderline or marked.

Criteria for Essential Thrombocythemia (ET)
Diagnosis requires meeting all 4 criteria
1. Sustained platelet count $\geq 450 \times 10^9$/L[(a)] 2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes. No significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis. 3. Not meeting WHO criteria for polycythemia vera,[(b)] primary myelofibrosis,[(c)] *BCR-ABL1*–positive CML,[(d)] or myelodysplastic syndrome,[(e)] or other myeloid neoplasm. 4. Demonstration of *JAK2* V617F or other clonal marker, or in the absence of *JAK2* V617F, no evidence of reactive thrombocytosis[(f)]
ET = essential thrombocythemia; BM = bone marrow; WHO = World Health Organization; CML = chronic myelogenous leukemia. (a) Sustained during the work-up process. (b) Requires the failure of iron replacement therapy to increase hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels, and red cell mass measurement is not required. (c) Requires the absence of relevant reticulin fibrosis, collagen fibrosis, peripheral blood leukoerythroblastosis, or markedly hypercellular marrow accompanied by megakaryocyte morphology that is typical for primary myelofibrosis—small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering. (d) Requires the absence of *BCR-ABL1*. (e) Requires the absence of dyserythropoiesis and dysgranulopoiesis. (f) Causes of reactive thrombocytosis include iron deficiency, splenectomy, surgery, infection, inflammation, connective tissue disease, metastatic cancer, and lymphoproliferative disorders. However, the presence of a condition associated with reactive thrombocytosis does not exclude the possibility of ET if other criteria are met.

Criteria for Polycythemia Vera (PV)
Diagnosis requires the presence of both major criteria and 1 minor criterion or the presence of the first major criterion together with 2 minor criteria
Major Criteria
1. Hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume* 2. Presence of *JAK2* V617F or other functionally similar mutation such as *JAK2* exon 12 mutation
Minor criteria
1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation 2. Serum erythropoietin level below the reference range for normal 3. Endogenous erythroid colony formation in vitro
*Hemoglobin or hematocrit > 99th percentile of method-specific reference range for age, sex, altitude of residence *or* hemoglobin > 17 g/dL in men, 15 g/dL in women if associated with a documented and sustained increase of at least 2 g/dL from a person's baseline value that cannot be attributed to correction of iron deficiency *or* elevated red cell mass > 25% above mean normal predicted value.

Appendix 2: 2008 IWG-MRT Diagnosis Criteria for Post-Polycythemia Vera and Post-Essential Thrombocythemia Myelofibrosis

Reference: Barosi 2008

IWG-MRT Recommended Criteria for Post-Polycythemia Vera (PV) Myelofibrosis (MF) and Post-Essential Thrombocythemia (ET) MF
Criteria for Post-PV MF
Required Criteria:
1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria (Tefferi 2007 and **Error! Reference source not found.**)
2. Bone marrow fibrosis grade 2-3 (on a 0-3 scale) (Thiele 2005)[a] or grade 3-4 (on a 0-4 scale) (Manoharan 1979)[a]
Additional Criteria (two are required):
1. Anemia[b] or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 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 ≥ 1 of 3 constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5^{0}C)
Criteria for Post-ET MF
Required Criteria:
1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria (Tefferi 2007)
2. Bone marrow fibrosis grade 2–3 (on 0–3 scale) (Thiele 2005)[a] or grade 3–4 (on 0–4 scale) (Manoharan 1979[a]
Additional Criteria (2 are required):
1. Anemia[b] and a ≥ 2 mg/mL (Tefferi 2007) decrease from baseline hemoglobin level
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable 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 (LDH) (above reference level)

IWG-MRT Recommended Criteria for Post-Polycythemia Vera (PV) Myelofibrosis (MF) and Post-Essential Thrombocythemia (ET) MF
5. Development of ≥ 1 of 3 constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5^0C)
IWG-MRT = International Working Group for Myelofibrosis Research and Treatment; LDH = lactate dehydrogenase; (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 collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis (b) Below the reference range for appropriate age, sex, gender and altitude considerations

Appendix 3: Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG toxicity and response criteria are summarized below (Oken 1982).

ECOG Score	Description
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 housework, 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.

Appendix 4: 2013 IWG-MRT Revised Response Criteria for Myelofibrosis

Reference: Tefferi 2013

Revised IWG-MRT and ELN Response Criteria for Myelofibrosis	
Response Categories	**Required Criteria (For all response categories, benefit must last for ≥ 12 weeks to qualify as a response)**
Complete response (CR)	*Bone marrow*(1): Age-adjusted normocellularity; < 5% blasts; ≤ Grade 1 MF(2) and *Peripheral blood*: Hemoglobin ≥ 100 g/L and < ULN; neutrophil count ≥ 1 x 10^9/L and < ULN; platelet count ≥ 100 x 10^9/L and < ULN; < 2% immature myeloid cells(3) and *Clinical*: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Partial response (PR)	*Peripheral blood*: Hemoglobin ≥ 100 g/L and < ULN; neutrophil count ≥ 1 x 10^9/L and < UNL; platelet count ≥ 100 x 10^9/L and < ULN; < 2% immature myeloid cells(3) and *Clinical*: resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or *Bone marrow*(1): Age-adjusted normocellularity; < 5% blasts; ≤ Grade 1 MF(2) and peripheral blood: Hemoglobin ≥ 85 but < 100 g/L and < ULN; neutrophil count ≥ 1 x 10^9/L and < ULN; platelet count ≥ 50, but < 100 x 10^9/L and < ULN; < 2% immature myeloid cells(3) and *Clinical*: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Clinical improvement (CI)	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia(4)
Anemia response	Anemia response is a composite endpoint defined as an increase in hemoglobin (hemoglobin response; defined below) in a subject with anemia (5) OR becoming RBC-transfusion-independent in a subject who is RBC-transfusion-dependent (6) defined as follows: o Hemoglobin-response is defined as an increase in hemoglobin level of ≥1.5 g/L (compared to baseline) on every determination consecutively for a ≥84 d interval, without RBC-transfusions. o RBC-transfusion-independence is defined as no RBC-transfusion in any "rolling" 84 day interval during the treatment period, in patients who were RBC-transfusion dependent at enrollment.
Spleen response(7)	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable(8) A baseline splenomegaly that is palpable at > 10 cm, below the LCM, decreases by ≥ 50%(8) A baseline splenomegaly that is palpable at < 5 cm, below the LCM, is not

Revised IWG-MRT and ELN Response Criteria for Myelofibrosis	
	eligible for spleen response A spleen response requires confirmation by MRI or computed tomography showing ≥ 35% spleen volume reduction
Symptoms response	A ≥ 50% reduction in the MPN-SAF TSS(9)
Progressive disease (PD)(10)	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or A 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm or Leukemic transformation confirmed by a bone marrow blast count of ≥ 20% or A peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1 x 10^9/L that lasts for at least 2 weeks
Stable disease (SD)	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or Loss of anemia response persisting for at least 1 month or Loss of spleen response persisting for at least 1 month
Recommendations for assessing treatment-induced cytogenetic and molecular changes	
Cytogenetic remission	At least 10 metaphases must be analyzed for cytogenetic response evaluation and requires confirmation by repeat testing within a 6-months window CR: eradication of a preexisting abnormality PR: ≥ 50% reduction in abnormal metaphases (PR applies only to patients with at least 10 abnormal metaphases at baseline)
Molecular remission	Molecular response evaluation must be analyzed in peripheral blood granulocytes and requires confirmation by repeat testing within 6 months window CR: Eradication of a pre-existing abnormality PR: ≥ 50% decrease in allele burden (PR applies only to patients with at least 20% mutant allele burden at baseline)
Cytogenetic/molecular relapse	Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing

EMH = extramedullar hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven nonhepatosplenic EMH); LCM = left costal margin; ULN = upper limit of normal; MPN-SAF TSS = myeloproliferative neoplasm symptom assessment form total symptom score;.

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

(2) Grading of MF is according to the European classification (Thiele 2005). It is underscored that the consensus definition of a CR bone marrow is to be used in only those patients in whom all other criteria are met, including resolution of leukoerythroblastosis. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.

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

Revised IWG-MRT and ELN Response Criteria for Myelofibrosis

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

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

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

(7) In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy.

(8) 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.

(9) Symptoms are evaluated by the MPN-SAF TSS (Emanuel 2012). The MPN-SAF TSS is assessed by the patients themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). Symptoms response requires ≥ 50% reduction in the MPN-SAF TSS.

(10) 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 pretreatment baseline and not to post-treatment measurements.

Appendix 5: Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

MRN _____ Name _____

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 <u>WORST</u> level of fatigue during the <u>past 24 hours</u>	(No fatigue) **0 1 2 3 4 5 6 7 8 9 10** (Worst Imaginable)

Circle the one number that describes how, <u>during the past week,</u> much difficulty you have had with each of the following symptoms	
Numbess/Tingling in hands and feet	(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 (Worst Imaginable)**
Unintentional weight loss last 6 months	(Absent) **0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)**
Filling up quickly when you eat (Early satiety)	(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 concentration – compared to prior to my MPD	(Absent) **0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)**

Appendix 6: Schedule of Events and Procedures

Schedule of Events and Procedures						
Tests/Evaluations	**Screening[a]**	**Baseline/ C1D1[b]**	**QW[b]**	**Q4W for 12 Wk then Q8W[b]**	**Week 24 and Week 48[b]**	**End-of-study/ Early Withdrawal[c]**
Informed consent	X					
Demographics	X					
Inclusion/exclusion criteria	X					
Medical history[d]	X	X				
Prior & current therapy[d]	X	X				
Concomitant medications		X		X		X
Transfusion history[e]	X	X		X		X
Physical examination	X	X[f]		X		X
ECOG performance status	X	X[f]		X		X
Vital signs	X	X		X		X
Height and weight[g]	X	X		X		X
12-lead ECG	X					
CBC with differential[h]	X	X[f]	X			X
Serum chemistry panel[i]	X	X[f]	X			X
Serum erythropoietin	X					
Serum ferritin	X					
Blood/urine pregnancy test[j]	X				X	X
Urinalysis[k]	X	X[f]		X		X
BM aspirate and/or biopsy and cytogenetics[l]	X				X	
QOL questionnaire (MPN-SAF-TSS)		X		X		
Spleen volume (MRI or CT) in patients with palpable splenomegaly at baseline		X			X	
Blood PK samples[m]		X		X[m]		
Study drug dispensing		X		X		
Assessment of compliance				X		

Schedule of Events and Procedures						
Tests/Evaluations	**Screening[a]**	**Baseline/ C1D1[b]**	**QW[b]**	**Q4W for 12 Wk then Q8W[b]**	**Week 24 and Week 48[b]**	**End-of-study/ Early Withdrawal[c]**
Adverse events[n]	X	X	X	⇨	⇨	⇨

[a] Screening procedures will occur up to 14 days before Baseline/C1D1 visit, except for urine pregnancy test (to be done within 7 days prior to Baseline/C1D1 visit). Bone marrow aspirates and biopsies performed up to 6 weeks before Baseline/C1D1 visit do not need to be repeated. JAK2V617F allele burden measurement in BM samples, if not done within 6 months prior to Screening, must be provided with the Screening BM biopsy/aspirate report.

[b] A 2-day window is allowed for Baseline/C1D1 and QW; a 5-day window for Q4W and Q8W visits. A 1-week window is allowed for Weeks 24 and 48 visits.

[c] The end-of-study/early withdrawal procedures should be performed 30 days after study completion. If a study procedure cannot be performed on the scheduled day, the procedure must be performed within 1 week.

[d] Includes date and diagnosis of MF and JAK2V617F status. The last available karyotype report prior to Screening should be collected. Prior treatment with ruxolitinib if applicable needs to be documented. Medical and medication history should be updated at Baseline/C1D1 visit.

[e] This includes number and dates of PRBC and PLT units administered within the past 12 weeks prior to enrollment, and Hgb and PLT values prior to transfusion.

[f] Does not need to be repeated at Baseline/C1D1 visit if Screening took place within 72 hours.

[g] Height measured at Screening only.

[h] Automated and/or manual differential per institution's standard; the method should be consistent throughout the study.

[i] Includes serum albumin, total protein, total bilirubin, direct bilirubin (if total bilirubin > ULN), ALT, AST, LDH, alkaline phosphatase, bicarbonate, sodium, potassium, chloride, serum creatinine, BUN, calcium, phosphorus, uric acid, and glucose. Note: If a patient develops ≥Grade 3 hyponatremia, rigosertib will not be administered and serum and urine osmolality, serum albumin, BUN, creatinine, and serum and urinary sodium will be measured to assist in the medical management of hyponatremia. Additional tests may be carried out as clinically warranted.

[j] Blood or urine pregnancy test in female patients of childbearing potential only; must be completed within 7 days prior to Baseline/C1D1 visit. Pregnancy tests must have sufficient sensitivity (ie, at least 25 mIU/mL) to guarantee positive identification of pregnancy.

[k] Includes glucose, protein, white blood cells (WBC), blood/occult blood, ketone, pH and specific gravity, and crystals.

[l] Bone marrow aspirate and/or biopsy and cytogenetics must be performed within 6 weeks prior to Screening visit; JAK2 V617F allele burden measurement in BM samples, if not done within 6 months prior to Screening, must be provided with the Screening BM biopsy/aspirate report. BM aspirate and/or biopsy will be performed every 12 weeks only in patients with more than 5% pre-treatment BMBL.

[m] Blood samples for Population PK analysis will be obtained in all patients at Baseline/C1D1 visit 1 hr after rigosertib administration (morning dose), and on Day 28 (+/- 5 days) from start of therapy at predose and 1 hr after administration of rigosertib (morning dose).

[n] AEs will be monitored from the time of the first protocol-specific intervention up to 30 days after the last dose of rigosertib.

Appendix 7: List of Clinical Laboratory Tests

Serum Chemistry Panel :	**Complete Blood Count with Differential:**
Serum albumin Total protein Total bilirubin Direct bilirubin (if total bilirubin > ULN only) Aspartate transaminase (AST) Alanine transaminase (ALT) Lactate dehydrogenase (LDH) Alkaline phosphatase Bicarbonate Sodium Potassium Chloride Serum creatinine BUN Glucose Calcium Phosphorus Uric acid	White blood cells (WBC) Neutrophils (absolute count) Lymphocytes (absolute count) Monocytes (absolute count) Basophils (absolute count) Eosinophils (absolute count) Red blood cells (RBC) Hematocrit Hemoglobin (Hgb) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Platelets (PLT) Mean platelet volume
Hyponatremia Panel (if ≥ Grade 3 Hyponatremia):	**Urinalysis:**
Serum osmolality Urine osmolality Serum albumin BUN Serum creatinine Serum sodium Urinary sodium	pH Specific gravity Protein Glucose WBC Blood/occult blood Ketone Crystals (microscopic analysis)
Other Serum Laboratory Tests:	**Pregnancy test (if childbearing potential):**
Serum endogenous erythropoietin Serum ferritin	Blood or urine pregnancy tests

Appendix 8: List of Potential Substrates of CYP 2C8 and 2C9

Reference: Flockhart 2007

Substrates of CYP 2C8 and 2C9 include, but are not limited to, drugs below:

2C8 Substrates	2C9 Substrates
amodiaquine	**NSAIDs:**
cerivastatin	diclofenac
paclitaxel	ibuprofen
repaglinide	lornoxicam
sorafenib	meloxicam
torsemide	S-naproxen→Nor
	piroxicam
	suprofen
	Oral Hypoglycemic Agents:
	tolbutamide
	glipizide
	Angiotensin II Blockers:
	losartan
	irbesartan
	Sulfonylureas:
	glyburide
	glibenclamide
	glipizide
	glimepiride
	tolbutamide
	Others:
	amitriptyline
	celecoxib
	fluoxetine
	fluvastatin
	glyburide
	nateglinide
	phenytoin-4-OH2
	rosiglitazone
	tamoxifen
	torsemide
	S-warfarin
	Sulfamethoxazole

Appendix 9: List of Potential Inhibitors of P-gp

Reference: FDA Guidance

Examples of In Vivo Inhibitors of Human Transporter P-gP (MDR1)
Amiodarone
Azithromycin
Captopril
Carvedilol
Clarithromycin
Conivaptan
Cyclosporine
Diltiazem
Dronedarone
Erythromycin
Felodipine
Itraconazole
Ketoconazole
Lopinavir & Ritonavir
Quercetin
Quinidine
Ranolazine
Ticagrelor
Verapamil