PHAZAR

A phase Ib study to assess the safety and tolerability of oral Ruxolitinib in combination with 5-azacitidine in patients with advanced phase myeloproliferative neoplasms (MPN), including myelodysplastic syndromes (MDS) or acute myeloid leukaemia (AML) arising from MPN.

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Sponsor:	**University of Birmingham**
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TAP From Leukaemia & Lymphoma Research

Cancer Research UK Clinical Trials Unit @CRCTU

UNIVERSITY OF BIRMINGHAM

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SIGNATURE PAGE

Phazar Trial Protocol version 5.0a 15-Aug-2018

This protocol has been approved by:

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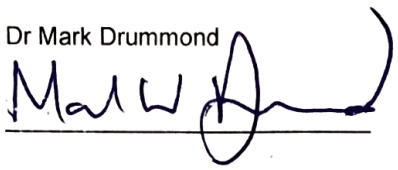
Signature:  **Date**: 9/10/2018

This protocol describes the PHAZAR trial and provides information about procedures for patients taking part in the PHAZAR trial. The protocol should not be used as a guide for treatment of patients not taking part in the PHAZAR trial.

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
2	18-Jun-2015	3.0	Substantial	Update to eligibility criteria Introduction of the collection of concomitant medication Details regarding eCRF added Collection of transfusion data updated Minor amendments for clarity and consistency
3	14-Oct-2016	4.0	Substantial	Clarification of outcome measures Update to eligibility criteria Modification of trial design Update to schedule of assessments Clarification of dose modification rules Update to concomitant medications Clarification of adverse event reporting for observational patients Clarification of statistical analyses Minor changes for clarity and consistency
6	23-Apr-2018	5.0	Substantial	Update to recruitment period Update to concomitant medications Minor update to schedule of assessments
N/A	15-Aug-2018	5.0a	Notification	Change in Data Protection Regulations

TRIAL SYNOPSIS

Title

A phase Ib study to assess the safety and tolerability of oral ruxolitinib in combination with 5-azacitidine in patients with advanced phase myeloproliferative neoplasms (MPN), including myelodysplastic syndromes (MDS) or acute myeloid leukaemia (AML) arising from MPNs.

Trial Design

A continual reassessment method (CRM) trial design to evaluate the Maximum Tolerated Dose (MTD) of ruxolitinib in combination with 5-azacitidine in patients with advanced phase MPN, including MDS or AML arising from MPNs.

In addition, 30 patients that are unable or unwilling to enter the interventional component of the trial will be entered to a parallel observational component focussed on collecting information on patient demographics and outcomes.

Objectives

Primary objective

- To establish the MTD and safety of ruxolitinib in combination with 5-azacitidine.

Secondary objectives
- To investigate the clinical activity of the combination of ruxolitinib in combination with 5-azacitidine.
- To investigate the outcome and treatment in an observational component of this patient group.

Outcome Measures

Interventional Component

Primary

To determine the MTD of ruxolitinib in combination with 5-azacitidine in patients with advanced phase MPNs, including MDS or AML arising from MPNs using the CRM with a predefined target DLT probability of 25% within cycle 1 (days 1 - 28).

Secondary
- Best response following 3 and 6 cycles of treatment.
  Assessment will be made according to the following criteria:
  - "Proposed criteria for response assessment in patients treated in clinical trials for MPNs in blast phase (MPN-BP): Formal recommendations from the post-MPN acute myeloid leukaemia consortium" (for patients with ≥20% bone marrow blasts at baseline)[1]
  - International Working Group (IWG) response criteria in myelodysplasia (for patients with <20% bone marrow blasts at baseline)[2]
- Change in the proportion of patients who require transfusion of red cells or platelets after completion of cycles 3 and 6.
- Achievement of red blood cell (RBC) transfusion independence after completion of cycles 3 and 6.
- Achievement of platelet transfusion independence after completion of cycles 3 and 6.
- Change in palpable splenomegaly or hepatomegaly
- Duration of Complete Response (CR) or Partial Response (PR)
- 12 months Progression-free survival (PFS)
- 12 months Leukaemia-free survival (LFS)
- 12 months Overall survival (OS)
- Duration of trial treatment
- Clinical improvement in haemoglobin level
- Clinical improvement in platelet count
- Quality of life measured by the MPN SAF; EQ-5D-5L and EORTC QLQ-C30 (Cycles 1, 2, 4 and 6)

Observational Component

- To determine treatment and outcome of Accelerated Phase MPN (MPN-AP) and Blast Phase MPN (MPN-BP) patients
- Quality of life as measured by the MPN SAF; EQ-5D-5L and EORTC QLQ-C30 (at registration, 3 months and 6 months)

Exploratory (both components)
- Change in clonal marker (e.g. JAK2 or CALR allele burden) (to be centrally assessed)

Patient Population

Patients with advanced phase MPNs, including MDS or AML arising from MPN, that meet the eligibility criteria.

Sample Size

A maximum of 34 patients to be recruited to the interventional component over 36 months.

Up to 30 patients will enter the observational component.

Main Inclusion and Exclusion Criteria

Inclusion Criteria:

Interventional component:

- Age ≥16 years old
- A prior diagnosis of Essential Thrombocythaemia (ET), Polycythaemia Vera (PV) or Myelofibrosis (MF) with one of the following:
  - 10-19% bone marrow blasts with or without dysplastic changes (MPN-AP) at baseline
  - ≥20% bone marrow Blasts (MPN-BP) at baseline
- In need of treatment in the opinion of the investigator
- Eastern Cooperative Oncology Group (ECOG) performance status 0-3
- Adequate liver and renal function, defined as:
  - Liver transaminases ≤3 × ULN (AST/SGOT or ALT/SGPT)
  - Bilirubin <4 x ULN (Patients with elevated bilirubin due to Gilbert's syndrome are eligible)
  - GFR ≥40 ml/min
- Willingness to undergo and ability to tolerate assessments during the study including bone marrow assessments and symptom assessments using patient reported outcome instruments
- Able to give valid informed consent

Observational Component

- Age ≥16 years old
- A prior diagnosis of ET, PV or MF with one of the following:
  - ≥10% blasts in blood or bone marrow with or without dysplastic changes (MPN-AP) at baseline
  - ≥20% blasts in blood or bone marrow (MPN-BP) at baseline
- Patients who are unwilling/unable to enter the interventional component and/or fail the interventional component entry criteria. This can include patients previously treated post transformation into MPN-AP/MPN-BP, or entered into studies with more aggressive therapy such as AML 17/19 as well as those receiving palliation only.
- Able to give valid informed consent

Exclusion Criteria:
Interventional Component:

- Any co-morbidity that could limit compliance with the trial or any other condition (including laboratory abnormalities) that in the Investigators opinion will affect the patient's participation in this trial
- New York Heart Association Class II, III, or IV congestive heart failure
- On-going cardiac dysrhythmias of grade 3, QTc prolongation >480 ms, or other factors that increase the risk of QT interval prolongation (e.g. heart failure, hypokalemia defined as serum potassium <3.0 mEq/L, family history of long QT interval syndrome)
- Erythropoietic agent within 28 days prior to registration
- Thrombopoietic agent within 14 days prior to registration
- Potent CYP3A4 inhibitor within 7 days prior to registration
- Experimental treatment within 14 days prior to registration.
- Previous treatment for MPN-AP or MPN-BP, including stem cell transplant and low intensity AML chemotherapy
- Previously received 5-azacitidine. Ruxolitinib can be taken up until study entry at the pre-study dose. Hydroxycarbamide prescribed prior to study entry must be stopped before the first scheduled day of trial treatment
- Known contraindications to receiving 5-azacitidine or ruxolitinib
- Active infection ≥ grade 3 (CTCAE criteria) at trial entry
- Known HIV seropositivity
- Known to have active hepatitis A, B, or C

- Women who are pregnant or lactating. Patients of childbearing potential must have a negative pregnancy test prior to study entry
- Patients and partners of childbearing potential not willing to use effective contraception for the duration of the study treatment and for three months after the last dose

Observational Component:

No Exclusions planned.

Trial Duration

All patients on the interventional component will receive a minimum of 6 cycles of treatment and will be followed up for a further 6 months (total of 12 months from registration). Patients will continue therapy if they receive a clinical benefit at the discretion of the CI.

Patients on the observational component will be assessed over a 6 month period and will be followed up for survival data for a minimum of 1 year from the date of registration.

Recruitment will be over 36 months. Therefore the total trial duration will be 48 months.

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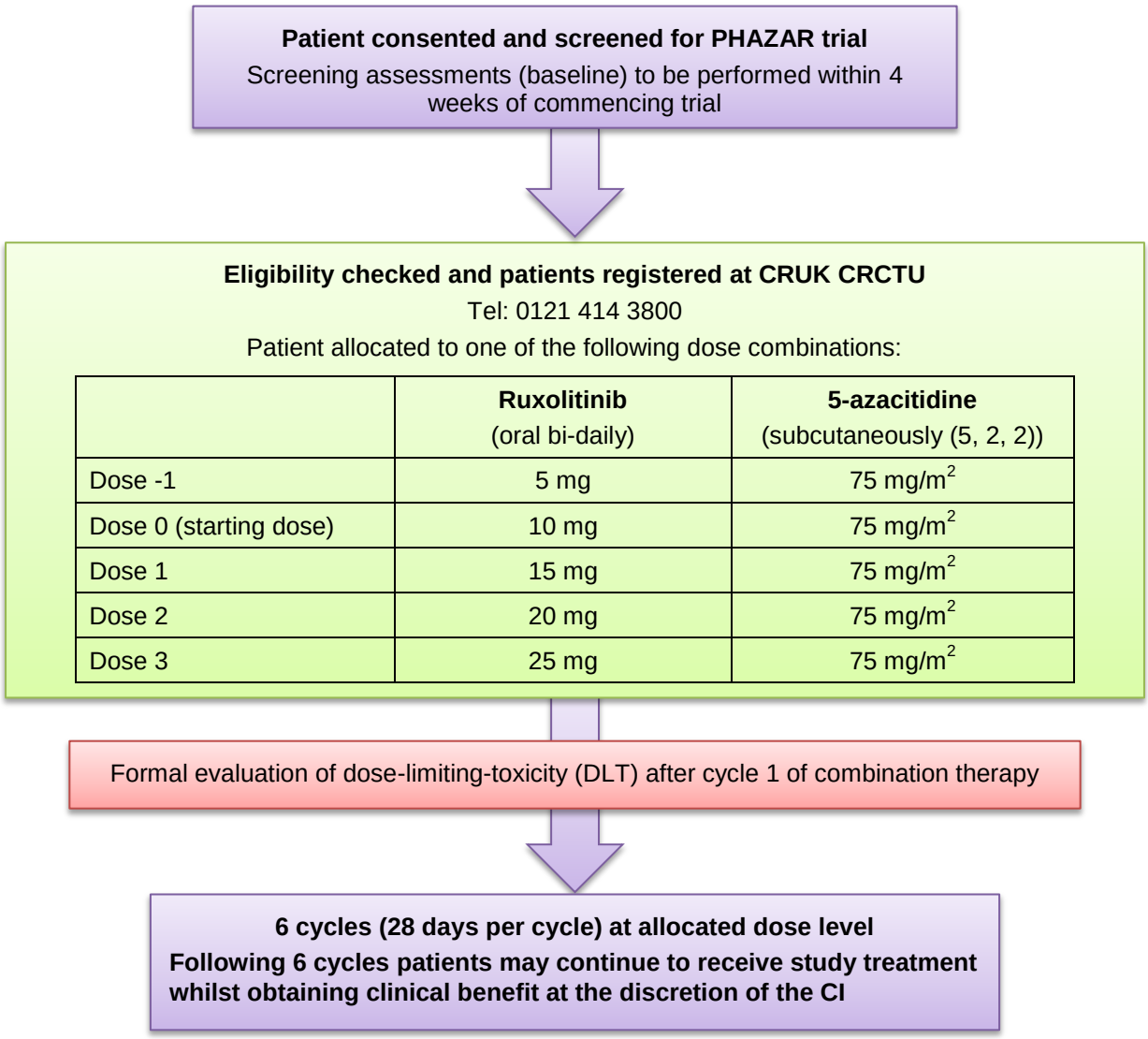
TRIAL SCHEMA



SCHEDULE OF ASSESSMENTS – INTERVENTIONAL COMPONENT

	Baseline		Cycle 1				Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			Subsequent cycles		End of Study[10]
Study schedule[1]	Within **28** days of registration	Within **7** days of registration	**1**	**8**	**15**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**22**	**28 days after last treatment**
Informed consent	x																							
Medical history & demographics	x																							
Physical examination and vital signs		x				x[2]			x[2]			x[2]			x[2]			x[2]			x[2]		x[2]	x
ECG		x	x	x	x	x	<< as clinically indicated >>																	
Pregnancy test[3]		x																						
Haematology and biochemistry		x	x	x	x	x[7]	x	x	x[7]	x	x	x[7]	x	x	x[7]	x	x	x[7]	x	x	x[7]	x	x[7]	x
Peripheral blood smear (blast assessment)	x					x[2]			x[2]			x[2]			x[2]			x[2]			x[2]		x[2]	
Bone marrow inc. cytogenetics	x[5]											x[4,5]									x[4,5]		x[6]	
Disease assessment												x									x		x[6]	
Bone marrow for biobanking	x[5]											x[4,5]									x[4,5]			
Blood Samples for biobanking	x[5]											x[4,5]									x[4,5]			
Nail clippings and/or saliva collection for germline DNA	x																							
Transfusion assessment		x	Throughout Study																					

	Baseline		Cycle 1				Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			Subsequent cycles		End of Study[10]
Study schedule[1]	Within **28** days of registration	Within **7** days of registration	**1**	**8**	**15**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**22**	**28 days after last treatment**
Quality of life assessment			**x**				**x**						**x**						**x**					
Adverse event reporting			Throughout study																					**x**
Concomitant medication		**x**	Throughout study																					
Ruxolitinib			Daily				Daily throughout study[8]															**x[9]**		
5-Azacitidine			6 cycles in 5-2-2 schedule																			**x[9]**		

1. Every effort should be made for patients to attend on the scheduled visit days. However, if a patient is unable to attend on the specified day, assessments may be scheduled for +/- 3 days
2. The physical examination and peripheral blood smear may be performed from day 22 of the preceding cycle to the start of the next cycle at local discretion
3. Women of child bearing potential only
4. Or earlier when there is evidence of remission or progression in the peripheral blood
5. Research samples should be taken between days 22-25 (or on a Monday – Thursday at baseline) so that they can be received by the biobank. Both research samples (bone marrow and blood samples) should be collected on the same day
6. For patients continuing trial treatment beyond cycle 6, bone marrow aspirate, trephine and disease assessments are recommended every 3 months and at progression/relapse. Patients will have a final disease assessment when the additional treatment stops using the information of the most recent previous bone marrow obtained
7. The haematology and biochemistry assessments can be performed between days 22-25 to coincide with the collection of research blood and bone marrow samples or safety bloods
8. Dose modifications permitted in accordance with section 7.8 of the protocol after cycle 1
9. Administered at Chief Investigator's discretion following 6 cycles of combination treatment if patient obtaining clinical benefit
10. Patients will be followed up for a minimum of 12 months from study entry for survival and outcome data

SCHEDULE OF ASSESSMENTS – OBSERVATIONAL COMPONENT

Study schedule[1]	At registration	End of Month 3	End of Month 6	End of Month 12
Informed consent	x			
Medical History & Demographics	x			
Information on further treatment		x	x	x
Collection of routine full blood count results	x	x	x	x
Collection of routine peripheral blood smear results (blast assessment)	**Results to be collected if assessment performed as part of routine clinical practice**			
Disease Assessment		x	x	x
Quality of Life Assessment (optional)	x	x	x	
Blood Samples for Biobanking (optional)	x	x	x	
Bone marrow for Biobanking (optional)	**Sample to be collected if assessment performed as part of routine clinical practice**			
Nail clippings and/or saliva collection for germline DNA (optional)	x			

1. Efforts should be made to perform assessments during patient's routine visits rather than asking the patients to attend clinic for extra visits. Assessments should be performed as closely as possible to the schedule outlined above.

ABBREVIATIONS

ABPI	ASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY
AE	ADVERSE EVENT
ALP	ALKALINE PHOSPHATASE
ALT	ALANINE TRANSAMINASE
AML	ACUTE MYELOID LEUKAEMIA
AR	ADVERSE REACTION
AST	ASPARTATE TRANSAMINASE
BD	TWICE DAILY
BP	BLOOD PRESSURE
BSA	BODY SURFACE AREA
CI	CHIEF INVESTIGATOR
CR	COMPLETE RESPONSE
CRCTU	CANCER RESEARCH UK CLINICAL TRIALS UNIT (UNIVERSITY OF BIRMINGHAM)
CRF	CASE REPORT FORM
CRM	CONTINUAL REASSESSMENT METHOD
CTCAE	COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS
CV	CURRICULUM VITAE
DCF	DATA CLARIFATION FORM
DLT	DOSE LIMITING TOXICITY
DNA	DEOXYRIBOSE NUCLEIC ACID
ECOG	EASTERN COOPERATIVE ONCOLOGY GROUP
ECG	ELECTROCARDIOGRAM
EORTC	EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER
ET	ESSENTIAL THROMBOCYTHAEMIA
GCP	GOOD CLINICAL PRACTICE
GFM	GROUPE FRANCOPHONE DES MYELODYSPLASIES
GFR	GLOMERULAR FILTRATION RATE
GMP	GOOD MANUFACTURING PRACTICE
GP	GENERAL PRACTITIONER
HDAC	HISTONE DEACETYLASE
HIV	HUMAN IMMUNODEFICIENCY VIRUS
ICF	INFORMED CONSENT FORM
ISF	INVESTIGATOR SITE FILE
IMF	IDIOPATHIC MYELOFIBROSIS
IMP	INVESTIGATIONAL MEDICINAL PRODUCT
ISRCTN	INTERNATIONAL STANDARD RANDOMISED CLINICAL TRIAL NUMBER
IWG	INTERNATIONAL WORKING GROUP
LDH	LACTATE DEHYDROGENASE
LFS	LEUKAEMIA FREE SURVIVAL
MDS	MYELODYSPLASTIC SYNDROME

MF	MYELOFIBROSIS
MHRA	MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY
ML	MILILITRE
MPN	MYELOPROLIFERATIVE NEOPLASM
MPN-AP	MYELOPROLIFERATIVE NEOPLASM – ACCELERATED PHASE
MPN-BP	MYELOPROLIFERATIVE NEOPLASM – BLAST PHASE
MPN-SAF	MYELOPROLIFERATIVE NEOPLASM – SELF ASSESSMENT FORM
MS	MILLISECOND
MTD	MAXIMUM TOLERATED DOSE
NCI	NATIONAL CANCER INSTITUTE
OS	OVERALL SURVIVAL
PFS	PROGRESSION FREE SURVIVAL
PI	PRINCIPAL INVESTIGATOR
PIS	PATIENT INFORMATION SHEET
PR	PARTIAL RESPONSE
PV	POLYCYTHAEMIA VERA
QOL	QUALITY OF LIFE
RBC	RED BLOOD CELL
REC	RESEARCH ETHICS COMMITTEE
SAE	SERIOUS ADVERSE EVENT
SAR	SERIOUS ADVERSE REACTION
SC	SUBCUTANEOUS
SGOT	SERUM GLUTAMIC OXALOACETIC TRANSAMINASE
SGPT	SERUM GLUTAMIC PYRUVIC TRANSAMINASE
SPC	SUMMARY OF PRODUCT CHARACTERISTICS
SUSAR	SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION
TAP	TRIALS ACCELERATION PROGRAMME
TMG	TRIAL MANAGEMENT GROUP
TSC	TRIAL STEERING COMMITTEE
ULN	UPPER LIMIT OF NORMAL

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

1.1 Background

Blast phase myeloproliferative neoplasm (MPN-BP) has a dismal prognosis with non-transplant therapy. Therapeutic options are limited and may include supportive care only, low dose chemotherapy or conventional acute myeloid leukaemia (AML)-type induction therapy. Even with the latter, remission rates are <50%[3] and responses are not durable; median survival was 6 months with intensive induction therapy in one study and all patients were projected to have died from their disease by 3 years. Furthermore, these poor results were near identical to those achieved with a low-dose chemotherapy approach [3]. While stem cell transplant may be associated with long-term survival, the advanced median age of this patient group (64 years and 68.5 years in two large cohorts respectively [3, 4]) precludes this as a treatment for most patients.

JAK2 inhibitors are now licensed and approved for use in Myelofibrosis (MF), with treatment shown to reduce spleen size, improve symptoms and, tantalizingly, perhaps increase survival (reviewed in [5]), and for polycythaemia vera resistant/intolerant to hydroxyurea. There is little published data however, on their use in advanced phase MPNs. A recent study documented a 16% CR rate (3 of 18 patients) with AML secondary to preceding MPN treated with ruxolitinib, using a large starting dose of 25 mg BD[6]. Haematological toxicity was modest and the drug was well tolerated, allowing for continued therapy of responders. This modest (although encouraging) activity as well as its good tolerability suggests that it would be a useful component of any combination strategy.

5-azacitidine is licensed and approved for treatment of adult patients who are not eligible for HSCT with high risk myelodyplastic syndromes (MDS), where it has been documented to improve survival [7]; low-blast count (20-30%) AML; and AML with >30% marrow blasts. There are few reports of its use in MPNs however (either chronic phase or advanced phase). Considerable haematological toxicity was noted in a Phase 2 study of 5-azacitidine in MF at the standard licensed dose (75 mg/m2 for 7 days every 4 weeks, with 29% grade 3/4 neutropenia). Responses were seen in 24% of patients, however no CRs were reported, and no impact on marrow fibrosis was observed [8]. Median time to response was 5 months, in keeping with treatment results in MDS where prolonged therapy is necessary. Interestingly global DNA-hypomethylation was documented in sequential patient samples. Hypermethylation of promoter regions of tumour-related genes is however rare in early-phase MF suggesting that methylation of cell-cycle control genes is unlikely to drive the pathogenesis of the disease at diagnosis. However, hypermethylation of the P15INK4b and P16INK4a genes in MF in transformation to AML has been frequently observed, and might be a legitimate therapeutic target [9]. Furthermore, sequential treatment with demethylating agents (decitabine) followed by HDAC inhibitors has been shown to eliminate JAK2+ marrow repopulating cells in NOD/SCID mice[10]. A recent historical treatment cohort from the Groupe Francophone des Myelodysplasies (GFM) (54 patients) describes the efficacy of 5-azacitidine in advanced phase MPN or AML secondary to MPN [4]. An overall response rate of 54% was observed, with 24% CR rate. Higher responses were seen in advanced phase than established AML (36% CR vs. 14% CR respectively). Small series of patients treated with decitabine have also been described (in both chronic phase IMF and advanced phase), including 2 of 4 patients with blast crisis MPN who achieved CR [11, 12]. These data are certainly encouraging for further studies.

It is clear from the limited clinical data available thus far that monotherapy of advanced phase MPNs / secondary AML with either of these agents is unlikely to produce significant and durable responses for a majority of patients. Combination therapy is attractive to fully exploit their differing mechanisms of action. There are currently very few therapeutic options available for this patient group.

Aside from successful transplant in a small number of patients, MPN-BP is universally fatal. Progress continues to be made in managing 'chronic-phase' disease, however blast phase disease represents a significant unmet need and has been relatively neglected by clinical researchers thus far.

If the combination is shown to be safe and tolerable, this could be taken forward into a phase II trial to assess activity.

1.2 Trial Rationale

1.2.1 Justification for patient population

This study will recruit patients with advanced phase MPNs, MDS or AML after MPNs. These are rare conditions which are associated with high mortality and for which standard treatment has yet to be established. Challenges exist as patients have often had their pre-existing disease for many years and may be elderly with other co-morbidities. Younger patients may elect to undergo intensive chemotherapy and stem cell transplant but this is not an option for the majority of patients. Hence alternative treatment strategies need to be evaluated.

1.2.2 Justification for design

Outcomes and treatments used for patients with MDS and AML after MPN are not well described. We have therefore included an observational arm for patients not entering the interventional component. Patients in the observational component can receive treatment at the discretion of the investigator and will only contribute to the biobanking and outcome aspect of the trial with no scheduled study visits.

The interventional aspect of the study involves testing the combination of 5-azacitidine and ruxolitinib in a phase I dose finding study. 5-azacitidine has a well-established dose and well-described toxicity in MDS / AML patients but there is much less information regarding ruxolitinib and only a recent small series of patients describing the two agents in combination.

The aim of this study is to define the maximum tolerated dose (MTD) for ruxolitinib in combination with 5-azacitidine via a Continual Reassessment Method (CRM). The CRM offers several advantages over a standard 3+3 design, including more accurate determination of the MTD, ability to expose fewer patients to potentially toxic doses and allocating more patients to the MTD. Successive cohorts of patients will be enrolled at a fixed dose of 5-azacitidine in combination with varying ruxolitinib doses and evaluated for dose limiting toxicities as described in section 3 until the MTD is established.

1.2.3 Choice of treatment

The JAK1/2 inhibitor ruxolitinib is approved for use in MF, where it has been shown to reduce spleen size and symptoms and prolong survival, and for polycythaemia vera resistant/intolerant to hydroxyurea. It is also being evaluated in other MPN. Transformation to AML is a rare event and it has not been possible to assess the benefit of ruxolitinib in affecting the likely occurrence of this complication. Efficacy of this agent in AML secondary to prior MPN has also been demonstrated as discussed above[13]. 5-azacitidine has been documented to improve survival in one of its licensed indications (high risk MDS). It is therefore a logical progression to study these two agents in combination, since monotherapy is unlikely to produce responses in patients with secondary MDS or AML and given that the mode of action of these drugs is complimentary. In fact, preliminary experience from the treatment of three patients with AML after preceding MPN with the combination of ruxolitinib and 5-azacitidine was recently reported[13]. Here the regime was well tolerated with minimal haematological toxicity and stable disease.

2. AIMS, OBJECTIVES AND OUTCOME MEASURES

2.1 Aims and Objectives

Primary objective

- To establish the MTD and safety of ruxolitinib in combination with 5-azacitidine

Secondary objectives

- To investigate the clinical activity of the combination of ruxolitinib in combination with 5-azacitidine
- To investigate the outcome and treatment in an observational arm of this patient group

2.2 Outcome Measures

Interventional Component
Primary

MTD of ruxolitinib in combination with 5-azacitidine in patients with advanced phase MPNs, including MDS or AML arising from MPN as determined by the CRM with a predefined target DLT probability of 25% within cycle 1 (days 1 - 28).

Dose limiting toxicity (DLT) is defined as:

- Grade 3 or 4 non-haematological toxicity with the exception of the following:
  - Febrile neutropenia - a disorder characterised by a neutrophil count of $<1.0 \times 10^9$/L and a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour
  - Fever - a disorder characterised by elevation of the body's temperature above the upper limit of normal
  - Sepsis – a disorder characterised by the presence of pathogenic microorganisms in the blood stream and that can cause a rapidly progressing systemic reaction that may lead to shock
  - Other infections – any grade 3 or 4 adverse events listed in the infections and infestations section of the NCI CTCAE criteria version 4.0

Events meeting the definition above will only be classed as a DLT if they meet all of the following criteria:

- Occur within the first cycle of therapy
- Considered clinically significant
- Considered related to the trial medication as assessed by the treating clinician.

DLTs must be reported to the trial coordinator by faxing a copy of the Adverse Event Form as soon as they are detected.

Any patients meeting the definition of a DLT must promptly discontinue the trial medication considered to be related to the event: 5-azacitidine must be immediately discontinued, whereas the dose of ruxolitinib should be tapered by 5 mg decrements, to be completed over a 10-14 day period. The unrelated study drug may be continued as per section 7.8. If the DLT cannot be directly attributable to only one of the study drugs both should be discontinued.

Patients who are not evaluable for DLT assessment at the end of cycle 1 (e.g. for death considered unrelated to trial treatment, withdrawal etc.) will be replaced.

Secondary

- Best response following 3 and 6 cycles of treatment
  - Assessment will be made according to the following criteria:
    - "Proposed criteria for response assessment in patients treated in clinical trials for MPNs in blast phase (MPN-BP): Formal recommendations from the post-MPN acute myeloid leukaemia consortium" (for patients with ≥20% bone marrow blasts at baseline)[1]
    - International Working Group (IWG) response criteria in myelodysplasia (for patients with <20% bone marrow blasts at baseline)[2]
- Change in the proportion of patients who require transfusion of red cells or platelets after completion of cycles 3 and 6
- Achievement of red blood cell (RBC) transfusion independence after completion of cycles 3 and 6.
- Achievement of platelet transfusion independence after completion of cycles 3 and 6.
- Change in palpable splenomegaly or hepatomegaly after completion of cycles 3 and 6.
- Duration of Complete Response (CR) or Partial Response (PR)
- 12 months Progression-free survival (PFS)
- 12 months Leukaemia-free survival (LFS)

- 12 months Overall survival (OS)
- Duration of trial treatment
- Clinical improvement in haemoglobin level
- Clinical improvement in platelet count
- Quality of life as measured by the MPN SAF; EQ-5D-5L and EORTC QLQ-C30 (baseline and cycles 1, 2, 4 and 6)

Observational Component

- To determine treatment and outcome of Accelerated Phase MPN (MPN-AP) and Blast Phase MPN (MPN-BP) patients who enter the observation component
- Quality of life as measured by the MPN SAF; EQ-5D-5L and EORTC QLQ-C30 (at registration, 3 months and 6 months)

Exploratory (both components)

- Change in clonal marker (e.g. JAK2 or CALR allele burden) (to be centrally assessed)

3. TRIAL DESIGN

3.1 Interventional Component

This is a single arm, multicentre, phase I dose finding study of ruxolitinib combined with 5-azacitidine in patients with advanced phase MPNs, including MDS or AML arising from MPNs.

The aim of this study is to define the MTD for ruxolitinib in combination with 5-azacitidine using a restricted two-stage Bayesian CRM. The MTD is defined as the dose level with an associated DLT probability over the first cycle of treatment (28 days) that is closest to the target DLT rate of 25%.

The dose levels of ruxolitinib are 5 mg, 10 mg, 15 mg, 20 mg and 25 mg twice daily. 5-azacitidine is given at a fixed dose of 75 mg/m^2 at each dose level. Patients will be assigned to the dose levels in cohorts of up to 5. The prior estimation of MTD is at dose level 3, however to exercise caution, dose level 0 is defined as the starting dose.

In the first stage, the first cohort of 3-5 patients will be enrolled at dose level 0. If none experiences a DLT, the next cohort of 3-5 patients will be recruited at the next level, (i.e. dose level 1). This process continues until the first DLT is observed in a cohort. Once there is a DLT, the second stage which comprises of the model based CRM begins.

In the second stage, the recommended dose for each new cohort of up to 5 patients will be made using the CRM taking into account all the previous data observed including the first stage. This would be the dose with estimated DLT probability closest to the target of 25%. Subsequent cohorts will be assigned a dose level in the same way using all previous data observed until the MTD is declared or the maximum sample size is reached.

See Section 12 on Statistical Considerations for more model details.

Table 1: Five dose levels of combination of ruxolitinib and 5-azacitidine

Dose Level	**Ruxolitinib dose** (oral bi-daily)	**5-azacitidine dose** (subcutaneously (5, 2, 2))
Dose -1	5 mg	75 mg/m^2
Dose 0 (starting dose)	10 mg	75 mg/m^2
Dose 1	15 mg	75 mg/m^2
Dose 2	20 mg	75 mg/m^2
Dose 3	25 mg	75 mg/m^2

All patients will receive 6 cycles (28 days per cycle) of combination treatment. Following 6 cycles patients may continue to receive study treatment whilst obtaining clinical benefit, in the view of the local investigator. Typically this will be appropriate for patients in CR, PR or exhibiting stable disease.

Once the MTD is declared, patients recruited at a lower dose may receive the MTD for any subsequent cycles of treatment at the discretion of the treating Investigator and the Chief Investigator.

Bone marrow examinations will take place at baseline and after 3 and 6 cycles of treatment or where there is evidence of remission or progression in the peripheral blood (according to Investigator discretion).

3.2 Observational Component

Patients who are unwilling or unable to enter the interventional component may participate in an observational component which will recruit alongside the main study (max 30 patients). These patients will be monitored to record their treatments and outcomes and they will also have the option of contributing samples for biobanking over a 6 month period. No direct comparison will be made between the two arms in terms of outcome measures.

4. ELIGIBILITY

4.1 Inclusion Criteria

Interventional component:

- Age ≥16 years old
- A prior diagnosis of Essential Thrombocythaemia (ET), Polycythaemia Vera (PV) or Myelofibrosis (MF) with one of the following:
    - 10-19% bone marrow blasts with or without dysplastic changes (MPN-AP) at baseline
    - ≥20% bone marrow blasts (MPN-BP) at baseline
- In need of treatment in the opinion of the investigator
- Eastern Cooperative Oncology Group (ECOG) performance status 0-3
- Adequate liver and renal function, defined as:
    - liver transaminases ≤3 × ULN (AST/SGOT or ALT/SGPT)
    - bilirubin <4 x ULN (Patients with elevated bilirubin due to Gilbert's syndrome are eligible)
    - GFR ≥40 ml/min
- Willingness to undergo and ability to tolerate assessments during the study including bone marrow assessments and symptom assessments using patient reported outcome instruments
- Able to give valid informed consent

Observational Component

- Age ≥16 years old
- A prior diagnosis of ET, PV or MF with one of the following:
    - ≥10% blasts in blood or bone marrow with or without dysplastic changes (MPN-AP) at baseline
    - ≥20% blasts in blood or bone marrow (MPN-BP) at baseline
- Patients who are unwilling/unable to enter the interventional component and/or fail the interventional component entry criteria. This can include patients previously treated post transformation into MPN-AP/MPN-BP, or entered into studies with more aggressive therapy such as AML 17/19 as well as those receiving palliation only.
- Able to give valid informed consent

4.2 Exclusion Criteria

Interventional Component:

- Any co-morbidity that could limit compliance with the trial or any other condition (including laboratory abnormalities) that in the Investigators opinion will affect the patient's participation in this trial
- New York Heart Association Class II, III, or IV congestive heart failure

- On-going cardiac dysrhythmias of grade 3, QTc prolongation >480 ms, or other factors that increase the risk of QT interval prolongation (e.g. heart failure, hypokalemia defined as serum potassium <3.0 mEq/L, family history of long QT interval syndrome)
- Erythropoietic agent within 28 days prior to registration
- Thrombopoietic agent within 14 days prior to registration
- Potent CYP3A4 inhibitor within 7 days prior to registration
- Experimental treatment within 14 days prior to registration
- Previous treatment for MPN-AP or MPN-BP, including stem cell transplant and low intensity AML chemotherapy
- Previously received 5-azacitidine. Ruxolitinib can be taken up until study entry at the pre-study dose. Hydroxycarbamide prescribed prior to study entry must be stopped before the first scheduled day of trial treatment
- Known contraindications to receiving 5-azacitidine or ruxolitinib
- Active infection ≥ grade 3 (CTCAE criteria) at trial entry
- Known HIV seropositivity
- Known to have active hepatitis A, B, or C
- Women who are pregnant or lactating. Patients of childbearing potential must have a negative pregnancy test prior to study entry
- Patients and partners of childbearing potential not willing to use effective contraception for the duration of the study treatment and for three months after the last dose

Observational Component:

No Exclusions planned.

5. SCREENING AND CONSENT

5.1 Screening

Investigators will be expected to maintain a Screening Log of all potential study candidates. This Log will include limited information about the potential candidate (e.g. date of birth and gender), the date and outcome of the screening process (e.g. enrolled into study, reason for ineligibility, or refused to participate).

For patients who appear to meet the criteria for participation in the study, the Investigator will provide information to allow them to make an informed decision regarding their participation. If informed consent is given (see section 5.2), the Investigator will conduct a full screening evaluation to ensure that the patient satisfies all inclusion and exclusion criteria. A patient who gives written informed consent and who satisfies all the inclusion and exclusion criteria may be registered onto the study. Note that assessments conducted as standard of care do not require informed consent and may be provided as screening data if conducted within the stipulated number of weeks prior to registration. Assessments required in screening are listed in the schedule of assessments and detailed in section 7.5 for the Interventional component and 7.6 for the Observational component.

5.2 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent for each patient prior to performing any trial related procedure. Two Patient Information Sheets are provided to facilitate this process, one for the Interventional component and one for the Observational Component. Investigators must ensure that they adequately explain the relevant aims, trial treatments (if applicable), anticipated benefits and potential hazards of taking part in either component to the patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time. The patient should be given ample time (e.g. 24 hours) to read the Patient Information Sheet and to discuss their participation with others outside of the site research team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

If the patient expresses an interest in participating in the trial they should be asked to sign and date the latest version of the relevant Informed Consent Form. The Investigator must then sign and date the form. A copy of the Informed Consent Form should be given to the patient, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once the patient is entered into the trial the patient's trial number should be entered on the Informed Consent Form maintained in the ISF. In addition, if the patient has given explicit consent a copy of the signed Informed Consent Form must be sent in the post to the Trials Office for review.

Details of the informed consent discussions should be recorded in the patient's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the Patient Information Sheet and Informed Consent Form. Throughout the trial the patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient in which case the process above should be followed and the patient's right to withdraw from the trial respected. Patients are permitted to re-consent at the same visit that new information is provided if they wish to do so.

To avoid the need for repeat sampling, Investigators may collect and send baseline research bone marrow samples to the Central Laboratory at the same time as local diagnostic procedures are performed. Patients must consent to this on the 'Research Tissue Consent Form' provided by the Trials Office or using a standard NHS consent form for investigations or treatment (provided that this permits the collection, storage and transfer of material for research purposes). The Central Laboratory will process and store the sample but no investigations will be performed until the patient consents to the PHAZAR trial agreeing to the collection, storage and analysis of samples. Stored samples may also be used for future ethically approved medical research if the patient gives explicit consent for this purpose.

Electronic copies of the Patient Information Sheet and Informed Consent Form are available from the Trials Office and should be printed or photocopied onto the headed paper of the local institution.

Details of all patients approached about the trial should be recorded on the Patient Screening/Enrolment Log and with the patient's prior consent their General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.

6. TRIAL ENTRY

Interventional Component

A treatment slot must be reserved for a cohort prior to providing potential patients with a Patient Information Sheet (PIS). This should be done by contacting the Trials Office. If a treatment slot is available and if consent is provided, a peripheral blood smear should be obtained in the first instance to assess whether patient is expected to fulfil the bone marrow blasts eligibility criterion and its result reported to the Trial Office in order to confirm the booked treatment slot. If the patient satisfies the remaining eligibility criteria, including bone marrow blasts ≥10%, the patient may be registered to the PHAZAR study.

Patients on the interventional component will be registered to the trial via the Cancer Research UK Clinical Trials Unit (CRCTU).

☎: 0121 371 7866; 9am-5pm Monday to Friday.

Observational Component

All patients who meet the entry criteria for the observational component may be registered to PHAZAR. Registration for the observational component will be conducted by logging on to:

https://www.cancertrials.bham.ac.uk/PHAZARLive

Login details will be provided by the trials office as part of site initiation.

An eligibility checklist and registration form (found in the ISF) should be completed prior to registration by the Investigator or designee. The patient trial number and dose allocation (for those enrolled on the interventional component) will be given over the telephone, followed by a fax confirmation. The patient's trial number for patients on the observational component will be provided by the online system. A report can be printed as confirmation.

7. TREATMENT DETAILS

7.1 Trial Treatment – Interventional Component

Both 5-azacitidine and ruxolitinib are considered Investigational Medicinal Products (IMPs) for the purpose of the trial.

5-azacitidine

Subcutaneous 5-azacitidine will be provided free of charge for the trial by Celgene for the duration of the study period. Patients will receive 5-azacitidine by subcutaneous (SC) injection on seven consecutive days (excluding weekends), starting day 1 of 28-day cycles, for up to 6 cycles. It is recommended that this is delivered in a 5-2-2 schedule. Cycles should commence on a Monday whenever possible. Every effort should be made to attend on the scheduled visit days, however if not possible administration visits may be arranged for +/- 3 days.

Patients who continue to gain a clinical benefit (in the opinion of the local investigator) will be permitted to continue with therapy beyond 6 cycles at the discretion of the CI.

5-azacitidine will be supplied as a lyophilised powder in 100 mg single-use vials. The IMPs will be packaged and labelled in accordance with local regulations and Good Manufacturing Practice (GMP), stating that the drug is for clinical trial use only and to keep it out of the reach of children. For further details on supply and labelling, refer to the pharmacy manual.

Method of 5-azacitidine administration: The 5-azacitidine should be reconstituted as per the SPC. Reconstituted 5-azacitidine should be injected subcutaneously into the upper arm, thigh or abdomen. Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.

Ruxolitinib

Ruxolitinib will be provided free of charge for the trial by Novartis, in the form of 5 mg, 15 mg or 20 mg strength tablets. The allocated dose will be administered bd for up to 6 x 28-day cycles. Patients who continue to gain a clinical benefit (in the opinion of the local investigator) will be permitted to continue with therapy beyond 6 cycles at the discretion of the CI.

If patients are taking ruxolitinib at the point of study entry, they should continue to take the medication at their pre-study dose until the day prior to day 1 of cycle 1, at which point the dose will be changed to the appropriate study dose.

At the end of the patient's treatment, the dose of ruxolitinib should be tapered by 5 mg decrements to be completed over a 10-14 day period.

Medication labels will be in English. They will include storage conditions for the drug and the medication number but no information about the patient other than the trial number which will be added at the point of dispensing.

7.2 Trial Treatment – Observational Component

Patients on the observational component will not receive any trial treatment.

7.3 Treatment Schedule – Interventional Component

	Baseline		Cycle 1				Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			Subsequent cycles		End of Study[10]
Study schedule[1]	Within **28** days of registration	Within **7** days of registration	**1**	**8**	**15**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**22**	**28 days after last treatment**
Informed consent	x																							
Medical history & demographics	x																							
Physical examination and vital signs		x				x[2]			x[2]			x[2]			x[2]			x[2]			x[2]		x[2]	x
ECG		x	x	x	x	x	<< as clinically indicated >>																	
Pregnancy test[3]		x																						
Haematology and biochemistry		x	x	x	x	x[7]	x	x	x[7]	x	x	x[7]	x	x	x[7]	x	x	x[7]	x	x	x[7]	x	x[7]	x
Peripheral blood smear (blast assessment)	x					x[2]			x[2]			x[2]			x[2]			x[2]			x[2]		x[2]	
Bone marrow inc. cytogenetics	x[5]											x[4,5]									x[4,5]		x[6]	
Disease assessment												x									x		x[6]	
Bone marrow for biobanking	x[5]											x[4,5]									x[4,5]			
Blood Samples for biobanking	x[5]											x[4,5]									x[4,5]			
Nail clippings and/or saliva collection for germline DNA	x																							
Transfusion assessment		x	Throughout Study																					

	Baseline		Cycle 1				Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6			Subsequent cycles		End of Study[10]
Study schedule[1]	Within **28** days of registration	Within **7** days of registration	**1**	**8**	**15**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**8**	**22**	**1**	**22**	**28 days after last treatment**
Quality of life assessment			**x**				**x**						**x**						**x**					
Adverse event reporting			Throughout study																					**x**
Concomitant Medication		**x**	Throughout study																					
Ruxolitinib			Daily				Daily throughout study [8]															**x[9]**		
5-Azacitidine			6 cycles in 5-2-2 schedule																			**x[9]**		

1. Every effort should be made for patients to attend on the scheduled visit days. However, if a patient is unable to attend on the specified day, assessments may be scheduled for +/- 3 days.
2. The physical examination and peripheral blood smear may be performed from day 22 of the preceding cycle to the start of the next cycle at local discretion
3. Women of child bearing potential only
4. Or earlier when there is evidence of remission or progression in the peripheral blood
5. Research samples should be taken between days 22-25 (or on a Monday – Thursday at baseline) so that they can be received by the biobank. Both research samples (bone marrow and blood samples) should be collected on the same day
6. For patients continuing trial treatment beyond cycle 6, bone marrow aspirate, trephine and disease assessments are recommended every 3 months and at progression/relapse. Patients will have a final disease assessment when the additional treatment stops using the information of the most recent previous bone marrow obtained
7. The haematology and biochemistry assessments can be performed between days 22-25 to coincide with the collection of research blood and bone marrow samples or safety bloods
8. Dose modifications permitted in accordance with section 7.8 of the protocol after cycle 1
9. Administered at Chief Investigator's discretion following 6 cycles of combination treatment if patient obtaining clinical benefit
10. Patients will be followed up for a minimum of 12 months from study entry for survival and outcome data

7.4 Assessment Schedule – Observational Component

Study schedule[1]	At registration	End of Month 3	End of Month 6	End of Month 12
Informed consent	x			
Medical History & Demographics	x			
Information of further treatment		x	x	x
Collection of routine full blood count results	x	x	x	x
Collection of routine peripheral blood smear results (blast assessment)	**Results to be collected if assessment performed as part of routine clinical practice**			
Disease Assessment		x	x	x
Quality of Life Assessment (optional)	x	x	x	
Blood Samples for Biobanking (optional)	x	x	x	
Bone marrow for Biobanking (optional)	**Sample to be collected if assessment performed as part of routine clinical practice**			
Nail clippings and/or saliva collection for germline DNA (optional)	x			

1. Efforts should be made to perform assessments during patient's routine visits rather than asking the patients to attend clinic for extra visits. Assessments should be performed as closely as possible to the schedule outlined above.

7.5 Assessments – Interventional Component

7.5.1 Medical History and Demographics

A medical history and the patient's demographics will be taken within 28 days of registration including the following:

- Age
- Sex
- Disease type (current and prior)
- Disease status
- Previous medical conditions
- Previous treatments
- Cytogenetic status

7.5.2 Physical examination/symptom assessment

A physical examination and symptom assessment will be assessed within 7 days prior to registration, within 7 days of the start of each cycle of treatment and following treatment discontinuation and will include:

- ECOG performance status
- Blood pressure
- Pulse
- Height (baseline only)
- Weight
- BSA (prior to prescription)
- Transfusion assessment
- Palpation of spleen and liver

7.5.3 ECGs

ECG's will be conducted within 7 days prior to registration, weekly during the first cycle and as clinically indicated in subsequent cycles. ECG's should be considered more frequently for patients with a history of significant cardiovascular disease or patients taking medicines which are associated with significant QT prolongation or anti-arrhythmic medications.

7.5.4 Pregnancy testing and contraception

A pregnancy test (serum/urine) for females of child bearing potential must be performed within 7 days prior to registration.

Females of childbearing potential: Must have a negative pregnancy test and should not be breast-feeding. Females must agree to use a reliable form of contraception during the trial and for at least three months after treatment has finished.

Males (whose partner may become pregnant): Must agree to use a reliable form of contraception or during the trial and for three months after treatment has finished.

7.5.5 Haematology

A full blood count will be conducted within 7 days prior to registration, weekly in the first cycle, on day 1, 8 and 22 of cycles 2-6 and at the end of study visit. If the patient continues treatment beyond cycle 6, a full blood count will be performed on day 1 and 22 of all subsequent cycles. Day 22 assessment can be performed during days 22-25 to coincide with the collection of research blood and bone marrow samples or safety bloods.

Full blood counts include:

- Red blood cells
- Haemoglobin
- White blood cells
- Platelets
- Haematocrit
- Absolute neutrophil count
- Lymphocytes

In the event of permanent azacitidine discontinuation occurring after completion of the first cycle of treatment, haematology assessments will only be required on a monthly basis as a minimum at the investigator's discretion. These assessments should be performed on Day 1 of each month. Frequent monitoring of haematology parameters is still required when ruxolitinib is co-administered with strong

CYP3A4 inhibitors, dual inhibitors of CYP2C9 and CYP3A4 enzymes; refer to section 7.11 for further information.

A peripheral blood smear including percentage blasts should be performed in the first instance during screening (within 28 days prior to registration) to assess whether patient is expected to fulfil the bone marrow blasts eligibility criterion and its result reported to the Trial Office in order to confirm the booked treatment slot. Additional peripheral blood smears should be done once per cycle between day 22 and day 1 of the next cycle.

7.5.6 Blood chemistry

Biochemistry tests will be conducted within 7 days prior to registration, weekly in the first cycle, on day 1, 8 and 22 of cycles 2-6 and at the end of study visit. If the patient continues treatment beyond cycle 6, biochemistry tests will be performed on day 1 and 22 of all subsequent cycles. Day 22 assessment can be performed during days 22-25 to coincide with the collection of research blood and bone marrow samples or safety bloods.

Biochemistry tests will include*:

- Sodium
- Potassium
- Magnesium
- Calcium
- Urea
- Creatinine
- Total Protein
- Albumin
- Bilirubin
- LDH‡
- ALP
- ALT/AST
- eGFR

*Biochemistry to include bicarbonate if clinically indicated (see section 7.8).

‡Treatment with Ruxolitinib has been associated with increases in lipid parameters including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Lipid monitoring and treatment of dyslipidaemia according to current clinical guidelines is therefore recommended.

7.5.7 Bone Marrow

A bone marrow aspirate and trephine must be conducted within 28 days prior to registration to assess patient eligibility (blasts ≥10%), stratify the patient into MPN-AP or MPN-BP and determine the response assessment criteria to be used during the trial. The baseline bone marrow assessments recorded on the Baseline Form should be consistent with the stratification reported on the Eligibility Form.

A further bone marrow should be performed during days 22-25 of cycle 3 and cycle 6 or sooner if there is evidence of remission or progression in the peripheral blood. If the patient continues treatment beyond cycle 6, a bone marrow aspirate and trephine should be performed 3-monthly at the investigators discretion and at the time of relapse/progression. Morphological, immunophenotypic and cytogenetic characterisation and assessment of fibrosis, according to the WHO grading [14], should be performed locally using these samples to determine response to therapy.

7.5.8 Disease Assessment

Patients will have their disease assessed at the end of cycle 3 and 6. If patients continue treatment beyond 6 cycles, disease assessment is recommended every 3 cycles. Patients will have a final disease assessment when the additional treatment stops using the information of the most recent previous bone marrow obtained. During these disease assessments, patients will be evaluated for response using the following criteria:

- **Patients with ≥20% bone marrow blasts at baseline** will be analysed using the "proposed criteria for response assessment in patients treated in clinical trials for MPNs in blast phase (MPN-BP): Formal recommendations from the post-MPN acute myeloid leukaemia consortium"[1]
- **Patients with <20% bone marrow blasts at baseline** will be analysed using the IWG response criteria for MDS patients [2]

Both criteria can be found in Appendix 1.

7.5.9 Transfusion Assessment

All transfusions (red blood cells and platelets) that the patient receives from 8 weeks prior to registration until the end of the study should be recorded at every visit.

7.5.10 Quality of Life Assessment

All patients in PHAZAR will be asked to complete QoL questionnaires.

The EORTC QLQ-C30, EQ-5D and Myeloproliferative Neoplasm Self-Assessment Form (MPN-SAF) questionnaires (see Appendix 6) will be used to assess QoL and health outcome on Day 1 of cycle 1, cycle 2, cycle 4 and cycle 6 (before dosing).

- The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, pain, and nausea and vomiting) a global health status/QoL scale, and six single items.
- The EQ-5D is a standardised instrument for use as a measure of health outcome. The EQ-5D-5L descriptive system comprises of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).
- The MPN-SAF was created to function as a single instrument of patient-reported symptoms for the entire spectrum of patients with MPN. It is comprehensive and reliable and concisely assesses the prevalence and severity of symptoms of MF, PV, and ET, not captured in other instruments.

The three questionnaires are to be administered at the clinic under the supervision of study staff.

7.6 Assessments – Observational Component

7.6.1 Medical History & Demographics

A medical history and the patient's demographics will be taken within 28 days of registration including the following:

- Age
- Sex
- Disease type (current and prior)
- Disease status
- Previous medical conditions
- Previous treatments
- Cytogenetic status

7.6.2 Disease Assessment

The blast count from the most recent available routine bone marrow or blood test performed prior to registration will be used to assess patient eligibility (blasts ≥10%), stratify the patient into MPN-AP or MPN-BP at baseline and determine the response criteria to be used during the trial. The bone marrow blast assessments recorded on the Baseline Form should be consistent with the stratification reported on the Eligibility Form.

Patients will have their disease assessed after 3, 6 and 12 months on the study according to the following criteria (using patient's most recent available routine bone marrow):

- **Patients with ≥20% bone marrow blasts at baseline (MPN-BP)** will be analysed using the "proposed criteria for response assessment in patients treated in clinical trials for MPNs in blast phase (MPN-BP): Formal recommendations from the post-MPN acute myeloid leukaemia consortium"[1]
- **Patients with <20% bone marrow blasts at baseline (MPN-AP)** will be analysed using the IWG criteria for MDS patients [2]

Both criteria can be found in Appendix 1.

Information on any treatments received by the patient will also be collected at 3, 6 and 12 month follow-up visits.

7.6.3 Haematology

The results of full blood counts obtained during routine visits at registration and after 3, 6 and 12 months on the study should be recorded on the relevant CRF.

Full blood counts include:

- Red blood cells
- Haemoglobin
- White blood cells
- Platelets
- Haematocrit
- Absolute neutrophil count
- Lymphocytes

Blast assessments on peripheral blood smears performed as part of routine clinical practice at registration and after 3, 6 and 12 months on the study should be recorded on the relevant CRF.

7.6.4 Quality of Life Assessment

All patients in PHAZAR will be asked to complete QoL questionnaires.
The EORTC QLQ-C30, EQ-5D and Myeloproliferative Neoplasm Self-Assessment Form (MPN-SAF) questionnaires (see Appendix 6) will be used to assess QoL and health outcome at registration and after 3 and 6 months.

- The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, pain, and nausea and vomiting) a global health status/QoL scale, and six single items.
- The EQ-5D is a standardised instrument for use as a measure of health outcome. The EQ-5D-5L descriptive system comprises of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).
- The MPN-SAF was created to function as a single instrument of patient-reported symptoms for the entire spectrum of patients with MPN. It is a comprehensive and reliable and concisely assesses the prevalence and severity of symptoms of MF, PV, and ET, not captured in other instruments.

The three questionnaires are to be administered at the clinic under the supervision of study staff.

7.7 Sample Collection

7.7.1 Samples from patients on the interventional component

Samples are compulsory for patients on the interventional arm.

Germline Samples

Patients will have toe nail clippings and/or saliva collected within 28 days prior to registration.

Blood Samples

20 ml blood samples will be collected within 28 days prior to registration, during days 22-25 of cycles 3 and 6 (and on the same day as the bone marrow samples) or sooner if there is evidence of remission or progression in the peripheral blood. N.B. samples must be taken Monday to Thursday only to allow for processing at the biobank. Allele burden will be analysed at baseline, at 3 months and at 6 months at the Weatherall Institute of Molecular Medicine (Oxford).

Bone Marrow Aspirate and Trephine Samples

Up to 10 ml of bone marrow aspirate and a bone marrow trephine sample will be collected when trial bone marrow assessments are performed (within 28 days prior to registration and during days 22-25 of cycles 3 and 6 or sooner if there is evidence of remission or progression in the peripheral blood). For patients continuing trial treatment beyond cycle 6, bone marrow aspirate and trephine samples are

recommended every 3 months N.B. samples must be taken Monday to Thursday only to allow for processing at the biobank.

Optional Historic Bone Marrow Trephine Samples

With consent and if obtainable, approximately 15 historic unstained bone marrow trephine sections prepared during the chronic phase of the patient's disease will be requested at study entry.

7.7.2 Samples from patients on the observational component

All samples are optional for patients on the observational arm.

Germline Samples

Patients will be asked to consent to have toe nail clippings and/or saliva collected at the time of registration.

Blood Samples

Patients will be asked to consent to a 20 ml blood sample being collected at the time of registration, after 3 months and after 6 months. Allele burden will be analysed at baseline and at 3 and 6 months at the Weatherall Institute of Molecular Medicine (Oxford).

Bone Marrow Aspirate and Trephine Samples

Patients will be asked to consent to an additional 10 ml of bone marrow aspirate and a bone marrow trephine sample being collected and sent to the Weatherall Institute of Molecular Medicine from any routine bone marrow assessments conducted during the 6 month study period.

Historic Bone Marrow Trephine Samples

With consent and if obtainable, approximately 15 historic unstained bone marrow trephine sections prepared during the chronic phase of the patient's disease will be requested at study entry.

7.7.3 Sample processing

All samples should be sent to the Weatherall Institute of Molecular Medicine at the following address:

Tissue Bank Technician
MDSBio Study
Room 326 Molecular Haematology Unit
Weatherall Institute of Molecular Medicine
John Radcliffe Hospital
Headley Way
Oxford OX3 9DS

Address labels for the Weatherall Institute of Molecular Medicine will be provided in the Investigator Site file. Samples should be packaged and posted as per the table below:

Sample	Collection
Toe nails	Specimen Pot
Saliva	Oragene saliva kit
20 ml blood sample	EDTA tube(s)
10 ml Bone Marrow Aspirate	EDTA tube(s)
Bone Marrow Trephine	Slide box

Special delivery boxes, first class boxes, specimen pots, Oragene saliva kits and slide boxes will be provided by the trials unit.

7.8 Dose Modifications – Interventional Component

7.8.1 During the DLT assessment period

No dose modifications will be permitted in the first cycle of treatment. If a DLT is experienced, the trial medication considered to be related to the event must be promptly discontinued: 5-azacitidine must be suspended immediately, whereas the dose of ruxolitinib should be tapered by 5 mg decrements, to be completed over a 10-14 day period. The unrelated study drug may be continued at the discretion of the treating Investigator and the CI. If the DLT cannot be directly attributable to only one of the study drugs, both should be discontinued.

7.8.2 Following completion of the DLT assessment period

Once the DLT assessment period has completed, patients may receive dose modifications on ruxolitinib and/or 5-azacitidine. Any change in dose should be recorded on the relevant CRF.

Dose reductions of ruxolitinib and/or 5-azacitidine are allowed in the event of unacceptable toxicity as per the SPC at the local investigator discretion.

Cycles of therapy may be delayed by up to 4 weeks in patients that experience toxicities. Cycle delays for reasons other than toxicities may be considered if clinically indicated and must be discussed and agreed previously with the CI via the Trials Office. If a patient experiences a delay of a new cycle for more than 4 weeks or experiences 3 successive cycle delays, treatment with ruxolitinib and/or 5-azacitidine will be permanently discontinued.

After completion of the first cycle, ruxolitinib dose escalations are allowed in the event of inadequate efficacy. For patients receiving ruxolitinib alone (e.g. following azacitidine interruption due to unacceptable toxicity), dose escalations will be conducted as per SPC at the discretion of the treating Investigator.

For patients receiving combination therapy, ruxolitinib dose escalations are allowed in the event of inadequate efficacy in the absence of unacceptable toxicities after completion of 3 cycles of treatment. The dose limit for ruxolitinib will be set at the highest dose level which previously received a positive assessment from the TSC (highest dose level with reported DLT rate not exceeding the target toxicity rate of 25%). Dose increments should also follow SPC guidelines prior to these limits being reached.

Once the MTD is declared, patients recruited at a lower dose may receive the MTD for any subsequent cycles of treatment at the discretion of the treating Investigator and the Chief Investigator.

Cytopenias

Cytopenias will not be an indication for dose delay. MPN-BP is often associated with profound peripheral cytopenia (neutropenia, thrombocytopenia or anaemia). Patients who have these features at baseline or who develop these whilst on treatment may receive supportive care in the form of red cell or platelet transfusion or growth factor support at the local Investigator's discretion.
5-azacitidine and ruxolitinib are associated with cytopenias and bone marrow suppression and dose modifications are not scheduled for these events. In the event of severe bone marrow suppression or cytopenias following acquisition of a clinical response and not considered disease related, the CI must be informed to decide an appropriate course of action. Complete blood counts will be performed as per the above schedule, and at other time-points according to investigator discretion.

Renal toxicities

The kidney plays a significant role in the excretion of 5-azacitidine and ruxolitinib and the effects on renal function should be carefully monitored before the start of each cycle according to local protocols. If eGFR falls to between 30-39ml/min whilst the patient is receiving treatment with azacitidine,

bicarbonate levels should be measured at the time of serum biochemistry and patient should receive dose reductions according to SPC as applicable.

In the event of worsening kidney function (eGFR<30ml/min, grade 3 chronic kidney disease), the current azacitidine cycle should be interrupted and the next cycle delayed until the eGFR resolves to ≥30ml/min.

Other non-haematological toxicities

Cycles may be delayed up to 4 weeks at the Investigator's discretion for non-haematological toxicities greater than grade 2 occurring after completion of cycle 1.

7.9 Treatment Compliance – Interventional Component

Non-compliance is not expected for 5-azacitidine as patients must attend hospital to receive sub-cutaneous injections.

Ruxolitinib compliance will be measured in two ways. The local trial pharmacist will be responsible for maintaining and updating the drug accountability log in the PHAZAR pharmacy file. All unfinished bottles of ruxolitinib will be returned to the trial pharmacist who will count and document any unused medication. All IMPs can then be destroyed in accordance with local pharmacy practice and this will be documented on the drug destruction log in the hospital pharmacy file. In addition, patients will be issued with a Patient Diary which they will be asked to complete each day, recording the time that each dose was taken, and whether any doses were missed. The diary also includes a section where the patient can record any relevant information such as side effects suffered or reasons for missed doses. The completed diary will be collected by the centre at clinic visits and returned to the PHAZAR Study Office.

7.10 Supportive Treatment

Interventional Component

As ruxolitinib is associated with the development and reactivation of bacterial, fungal and viral infections, patients should be monitored for symptoms at protocol visits and use of antibiotic, antiviral and antifungal prophylaxis are advised as per local protocols. Special attention should be paid to the possibility of reactivation of tuberculosis and Herpes Zoster. Patients should be educated about the early symptoms of Herpes Zoster to enable them to notify the research team and receive treatment as soon as possible.

Patients may also receive treatment with G-CSF/GM-CSF and / or blood transfusions (red blood cells and platelets) as applicable. EPO and TPO are prohibited throughout the trial.

Observational Component

All supportive treatment permitted.

7.11 Concomitant Medication

Interventional Component

The metabolism of Ruxolitinib is affected by CYP3A4 inducers and inhibitors. Strict attention to this detail is required.

<u>CYP3A4 inhibitors:</u>

Potent CYP3A4 inhibitors

Patients should not take any potent inhibitors of the CYP3A4 family of metabolising enzymes during the first cycle of treatment. Following completion of the DLT assessment period, potent CYP3A4 inhibitors are permitted but their use is strongly discouraged, however the dose of ruxolitinib may need to be adjusted.

Azole antifungals commonly used for fungal prophylaxis are potent inhibitors of the CYP3A4 pathway. Their use is therefore prohibited during the first cycle of treatment and discouraged from cycle 2

onwards. Alternatives permitted throughout the trial include Isavuconazole, Amphotericin B and Micafungin.

Isoniazid is also expected to affect ruxolitinib bioavailability. Therefore, alternatives should be discussed with the local infectious disease team if tuberculosis prophylaxis is needed. Active tuberculosis will mandate discontinuation of trial treatment.

When ruxolitinib is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole), the dose of ruxolitinib should be reduced by approximately 50%, to be administered twice daily. Concomitant use of ruxolitinib with fluconazole doses greater than 200 mg daily should be avoided. More frequent monitoring (e.g. twice a week) of haematology parameters to detect cytopenias and of clinical signs and symptoms of ruxolitinib-related adverse drug reactions is recommended while strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes and ruxolitinib are co-administered.

Mild or moderate CYP3A4 inhibitors

No dose adjustment is recommended when ruxolitinib is co-administered with mild or moderate CYP3A4 inhibitors. However, patients should be closely monitored for cytopenias when initiating therapy with a moderate CYP3A4 inhibitor.

CYP3A4 inducers:

Patients taking potent CYP3A4 inducers should be monitored proactively whilst on ruxolitinib and the dose titrated based on safety and efficacy. Where possible, an alternative therapy should be administered.

Other prohibited concomitant medications:

Patients should not receive any chemotherapy, anticancer immunotherapy, other investigational therapy or other JAK2 inhibitors whilst on trial treatment. Cytoreductive treatment is also prohibited throughout the trial with the exception of hydroxycarbamide and anagrelide, which can be used to control blood cell counts or manage aggressive disease following consultation with the Chief Investigator for a period not exceeding 28 days. Hydroxycarbamide or anagrelide prescribed prior to study entry must be stopped before the first scheduled day of trial treatment.

Splenic irradiation is prohibited throughout the trial. Sites are requested to obtain prior CI approval via the trials office before administering any other radiotherapy treatment.

Prohibited foods:

Grapefruit products (including juice) and Seville oranges (including marmalade) should be avoided for the duration of the trial.

Please refer to the prohibited concomitant medication list as detailed in Appendix 5.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances for which prohibited therapies are administered.

Observational Component

All concomitant medication is permitted.

7.12 Patient Follow Up

Interventional Component

Patients who are gaining clinical benefit at the end of 6 cycles may continue to receive therapy with 5-azacitidine and/or ruxolitinib at the discretion of the CI until loss of response or unacceptable toxicity. Patients that have to discontinue the combination therapy due to a toxicity that is clearly related to just

one of the trial treatments may continue to take the alternative medication as long as they continue to obtain a clinical benefit in the view of the local investigator and the Chief Investigator (section 7.8.1).

Patients will be followed-up for survival data for a minimum of 1 year from the date of start of treatment.

All patients must have a final assessment 28 days after the last dose of trial medication.

Observational Component

After the 6 month study period patients will be followed up for data on further treatments and response and survival data for a minimum of 1 year from the date of registration.

7.13 Treatment Discontinuation and Patient Withdrawal

In the event of discontinuation of study treatment, e.g. unacceptable toxicity or patient choice, full details of the reason/s for discontinuation should be recorded on the CRF.

All patients, including non-compliant subjects, should be followed up according to the protocol unless they withdraw specific consent.

In the event of a patient's decision to withdraw from the trial, the Investigator should ascertain from which aspects of the trial the patient wishes to withdraw and record the details on the appropriate CRF. All information and blood/tissue samples collected up until the point of retraction will be retained and analysed. If a patient chooses to withdraw from treatment only (interventional arm only), the patient should discontinue treatment and continue to be assessed in accordance with the protocol. If a patient wishes to withdraw from the trial (i.e. including trial specific assessments), but is willing for further data to be supplied to the Trials Office, then further routine 'follow-up' data (e.g. toxicity data) will continue to be supplied by the Investigator to the Trials Office.

Interventional Component

Patients who stop treatment due to adverse experiences (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the CRF.

The following are justifiable reasons for the Investigator to stop study treatment:

- Unforeseen events: any event which in the judgement of the Investigator makes further treatment inadvisable
- Serious violation of the trial protocol (including persistent patient non-attendance and persistent non-compliance)
- Stopping by the Investigator for clinical reasons not related to the study drug treatment

Patients must stop study treatment in the event of:

- Occurrence of a DLT
- Unacceptable toxicity
- SAE requiring permanent discontinuation of treatment
- Occurrence of pregnancy in female participant

8. ADVERSE EVENT REPORTING

The collection and reporting of AEs will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 3. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the SPC.

8.1 Reporting Requirements – Interventional Component

8.1.1 Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 3 for definition) should be reported. Please note this does not include abnormal laboratory findings. An abnormal laboratory value is only considered to be an AE if the abnormality:

- Results in early discontinuation from the study treatment and/or
- Requires study drug dose modification or interruption, any other therapeutic intervention or is judged to be of significant clinical importance

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded.

Pre-existing conditions should only be reported if the condition worsens by at least 1 CTCAE grade. Details of all AEs experienced by the patient should be recorded in the hospital notes.

8.1.2 Serious Adverse Advents

Investigators should report AEs that meet the definition of a Serious Adverse Event (SAE) (see Appendix 3 for definition) and are not excluded from the reporting process as described below.

8.1.2.1 Events that do not require reporting on a Serious Adverse Event Form

The following events should not be reported on an SAE Form:

- Hospitalisations for:
  - Pre-planned elective procedures unless the condition worsens

8.1.2.2 Monitoring pregnancies for potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data in the case of congenital anomalies or birth defects.

In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the Trials Office as soon as possible. If it is the patient who is pregnant provide outcome data on a follow-up Pregnancy Notification Form. Where the patient's partner is pregnant consent must first be obtained and the patient should be given a pregnancy release of information form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the pregnancy release of information form. Once consent has been obtained provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form. If appropriate also complete an SAE Form as detailed below.

8.1.3 Reporting period

Details of all AEs and SAEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 28 days after the administration of the last treatment. SAEs that are judged to be at least possibly related to any of the trial IMPs must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

8.2 Reporting Requirements – Observational Component

8.2.1 Serious Adverse Advents

For patients recruited to the observational component, Investigators should only report AEs that meet the definition of a Serious Adverse Event (SAE) (see Appendix 3 for definition) and are at least possibly related to a trial specific procedure. Any AE related to the patient's current disease or treatment is explicitly excluded from the reporting process.

8.2.2 Reporting period

SAEs related to trial specific procedures will be documented and reported from the date of registration until 28 days after completion of the last protocol assessment.

8.3 Reporting Procedure

8.3.1 Site

8.3.1.1 Adverse Events

AEs should be reported on an AE Form (and where applicable on an SAE Form). An AE Form should be completed at each visit and returned to the Trials Office.

AEs will be reviewed using the CTCAE, version 4.0 (see Appendix 4). Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

8.3.1.2 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in the ISF.

AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 8.1 or 8.2 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.0.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the Trials Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, either e-mail or fax the SAE Form with an SAE Fax Cover Sheet to:

0121 371 7874 or 0121 371 4398

Or Phazar@trials.bham.ac.uk

On receipt the Trials Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed/e-mailed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the Trials Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the Trials Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Trials Office in the post and a copy kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.

8.3.1.3 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

8.3.2 Trials Office

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Summary of Product Characteristics) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

8.3.3 Reporting to the Competent Authority and main Research Ethics Committee

8.3.3.1 Suspected Unexpected Serious Adverse Reactions

The Trials Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and main Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days.

8.3.3.2 Serious Adverse Reactions

The Trials Office will report details of all SARs (including SUSARs) to the MHRA and main REC annually from the date of the Clinical Trial Authorisation, in the form of a development safety update report (DSUR).

8.3.3.3 Adverse Events

Details of all AEs will be reported to the MHRA on request.

8.3.3.4 Other safety issues identified during the course of the trial

The MHRA and main REC will be notified immediately if a significant safety issue is identified during the course of the trial.

8.3.4 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

8.3.5 Trial Steering Committee

The independent Trial Steering Committee (TSC) will review all SAEs.

8.3.6 Manufacturer of Investigational Medicinal Product

All SAEs will be reported to the manufacturer of the Investigational Medicinal Product within 24 hours by fax.

8.3.7 Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

9. DATA HANDLING AND RECORD KEEPING

9.1 Electronic Data Collection

The Case Report Form (CRF) will comprise a set of forms capturing details of eligibility, baseline characteristics, treatment and outcome details. There will be a separate CRF for the Interventional Component and the Observational Component.

This trial will use an electronic data capture (EDC) system which will be used for completion of CRFs.

Access to the EDC system will be granted to individuals via the Trials Office. SAE reporting and Notification of Pregnancy will be paper-based.

The CRF must be completed by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within specified timeframes (found in the eCRF completion guidelines). The exceptions to this are the SAE Form and Withdrawal Form which must be co-signed by the Investigator.

Entries on the paper CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The completed originals (of the paper forms) should be sent to the Trials Office and a copy filed in the Investigator Site File.

Trial forms may be amended by the Trials Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

9.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, ISFs, Pharmacy Files, patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 10 years after the end of the trial. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.

10. QUALITY MANAGEMENT

10.1 Site Set-up and Initiation

All sites will be required to sign a Clinical Study Site Agreement prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements e.g. registration forms and supply a current CV to the Trials Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the Trials Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trials Office must be informed immediately of any change in the site research team.

10.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the CRCTU Quality Management Plan. Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the Trials Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the PHAZAR trial staff access to source documents as requested.

10.3 Central Monitoring

Where a patient has given explicit consent sites are requested to send in copies of signed Informed Consent Forms for in-house review.

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms (DCFs) requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the main REC and the MHRA.

10.4 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the Trials Office of any MHRA inspections.

10.5 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

Sites are therefore requested to notify the Trials Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

11. END OF TRIAL DEFINITION

The end of trial will be 6 months after the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The Trials Office will notify the MHRA and main REC that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

12. STATISTICAL CONSIDERATIONS

12.1 Trial Design

Observational Component

Up to 30 patients will be recruited into an observational component. Data concerning their treatments and outcomes will be collected and they will also have the option of contributing samples for biobanking over a 6 month period. No direct comparison will be made between the two components in terms of outcome measures.

Interventional Component

The primary objective of the trial is to establish the MTD of ruxolitinib in combination with 5-azacitidine using a restricted 2-stage Bayesian CRM [15-17]. The target DLT probability for the trial combination therapy is 25%. The prior estimation of MTD is at dose level 3, however to exercise caution, dose level

0 is defined as the starting dose. Patients will be assigned to dose combinations in cohorts of up to 5 patients.

In the first stage, the first cohort will be enrolled at dose level 0. If none experiences a DLT, the next cohort will be recruited at the next higher level (i.e. dose level 1). This process continues until the first DLT is observed in a cohort. Once there is a DLT, the second stage which comprises of the model based CRM begins.

In the second stage, we will utilise an empiric dose-toxicity model, $F(x,\beta)$ given as

$F(x,\beta) = x^{\exp(\beta)}$ for $0 < x < 1$,

where the model parameter β is estimated using Bayesian analysis and x comprises of the initial guesses of probability of DLT at each dose level.

The recommended dose for the next cohort will be made using the CRM taking into account all the previous data observed including the first stage. This would be the dose with estimated DLT probability closest to the target of 25%. Subsequent cohorts will be assigned a dose level in the same way using all previous data observed until the MTD is declared or the maximum sample size is reached.

The five dose levels scheduled for a combination of ruxolitinib and azacitidine, together with the prior probabilities of DLT, are presented in Table 2. The prior guess of MTD is at dose level 3, but to exercise caution as this combination regimen has not been well studied in this patient population, dose level 0 (75 mg/m^2 azacitidine and 10 mg ruxolitinib bd) is defined as the starting dose. If the starting combination dose is too toxic, the design allows for de-escalation to dose -1. If the combination therapy is found to be tolerable, we would then escalate to higher doses of ruxolitinib.

Table 2: Dose levels with initial guesses of probability of DLT at each level

Dose Level	Azacitidine dose	Ruxolitinib dose (bd)	Prior Probability of DLT
-1	75mg/m^2	5 mg	0.05
0 (starting dose)	75mg/m^2	10 mg	0.10
1	75mg/m^2	15 mg	0.15
2	75mg/m^2	20 mg	0.20
3	75mg/m^2	25 mg	0.25

We will apply restrictions to avoid skipping dose levels in escalation, as well as to ensure no immediate escalation if observed toxicity at the current dose level is greater than the target toxicity level. A “look ahead” strategy will be implemented if the next recommended dose level by the CRM model is the same regardless of the outcome of the remaining patient(s) in the current cohort (DLT or no DLT). If that occurs, we could consider recruiting patients for the next cohort. By implementing this strategy, we enable the next cohort of patients to be recruited immediately before observing all the patients’ outcomes in the current cohort (whenever such a scenario occurs). This has the advantage of reducing waiting time between cohorts.

We plan to accrue 34 patients. Once recruitment is completed, the MTD will be declared as the combination dose with associated DLT rate closest to the target of 25%.

Criteria for Termination of the Trial

If there is a high probability that the posterior probability of DLT at the lowest dose is more than 10% greater than the target DLT rate, indicating that the lowest dose level is too toxic, the model will recommend the early termination of the trial. If this happens, the Trial Management Group and Trial

Steering Committee will be alerted and the latter, with support of any external evidence, will recommend if the trial should be stopped.

The TSC will be allowed to declare the MTD before the full recruitment of 34 patients is completed if 12 patients have already been allocated at the most current MTD, which would be the recommended dose level for the next cohort if the trial continues.

The performance of the proposed CRM design with 33 patients was assessed via simulations in terms of accuracy of selecting the true MTD, optimal allocation, and average percentage of patients being treated at an overdose. The design was found to perform well in various scenarios. More details of the operating characteristics of the proposed CRM design described above will be made available in the PHAZAR Statistical Analysis Plan.

12.2 Definition of Outcome Measures

12.2.1 Interventional Component

12.2.1.1 Primary outcome measures

MTD of ruxolitinib in combination with 5-azacitidine in patients with advanced phase MPNs as defined by the number of reported DLTs (as defined in section 2.2) occurring within the first cycle of treatment (first 28 days).

Safety of ruxolitinib in combination with 5-azacitidine will be assessed using the CTCAE v4.0 criteria.

12.2.1.2 Secondary outcome measures

The following will be analysed for patients in the interventional component:

- Best response following 3 and 6 cycles of treatment. Response will be assessed according to the following criteria:
  - Proposed criteria for response assessment in patients treated in clinical trials for MPNs in blast phase (MPN-BP): Formal recommendations from the post-MPN acute myeloid leukaemia consortium" (for patients with ≥20% bone marrow blasts at baseline)[1]
  - International Working Group (IWG) response criteria in myelodysplasia (for patients with <20% bone marrow blasts at baseline)[2]

  In order to assess disease response, bone marrow, peripheral blood and spleen/liver assessments should be performed during days 22-25 of cycle 3 and cycle 6.
- Achievement of RBC transfusion independence after completion of cycles 3 and 6 compared to baseline.

  RBC transfusion dependence is defined as transfusion of ≥2 RBC units in the 8 weeks prior to registration at baseline, and as transfusion of ≥2 RBC units in the 8 weeks prior to cycle 3-day 28 or cycle 6-day 28 for subsequent assessments.
- Achievement of platelet transfusion independence after completion of cycles 3 and 6 compared to baseline.

  Platelet transfusion dependence is defined as transfusion of ≥1 platelet units in the 4 weeks prior to registration at baseline, and as transfusion of ≥1 platelet units in the 4 weeks prior to cycle 3-day 28 or cycle 6-day 28 for subsequent assessments.
- Change in the proportion of RBC or platelet transfusion-dependent patients after completion of cycles 3 and 6 compared to baseline as defined above.
- Change in palpable splenomegaly or hepatomegaly after completion of cycles 3 and 6 compared to baseline

  Size of palpable spleens will be measured below the left costal margin and reported in cm

  Size of palpable livers will be measured below the right costal margin and reported in cm
- Duration of Complete Response (CR) or Partial Response (PR) according to established criteria [1] [2]
- 12 months Progression-free survival (PFS)
- 12 months Leukaemia-free survival (LFS)

- 12 months Overall survival (OS)
- Duration of trial treatment
- Mean change in haemoglobin level from baseline to end of cycles 3 and 6 (cycle 3-day 22-25 or cycle 6-day 22-25)
- Mean change in platelet count from baseline to end of cycles 3 and 6 6 (cycle 3-day 22-25 or cycle 6-day 22-25)
- Quality of life as measured by the MPN SAF; EQ-5D-5L and EORTC QLQ-C30 (at beginning of cycles 1, 2, 4 and 6)

12.2.2 Observational Component

The following will be analysed for patients in the observational component:

- The outcome and treatment of this patient group
- Quality of life as measured by the MPN SAF; EQ-5D-5L and EORTC QLQ-C30 at registration, 3 months and 6 months

12.2.3 Exploratory

The following will be analysed for all patients contributing to samples for in the interventional and observational component:

- Change in clonal marker (e.g., JAK2 or CALR allele burden) from baseline to end of cycles 3 and 6 (samples taken on day 22-25 of cycle 3 and cycle 6)

12.3 Analysis of Outcome Measures

Descriptive statistics will be reported for all patients recruited as described below.

Interventional component

Primary outcome measure

- The MTD, defined as the dose level with an associated DLT probability over the first cycle of treatment (28 days) closest to the target DLT rate of 25%, will be reported with its associated probability of DLT and 90% probability interval.

Secondary outcome measures

- Best response following 3 and 6 cycles of treatment will be reported as the number and proportion of patients in each response category and overall.
- DLTs and AEs (according to the CTCAE criteria version 4.0), records of blood and platelet transfusions, physical examinations to assess spleen and liver size, blood counts (including haemoglobin and platelet count, quality of life questionnaires and survival data) will be collected and reported in a descriptive manner.

Observational component

The analysis cohort will be all patients registered to this part of the trial.

No formal hypothesis testing is planned for the study. All analysis will be in the form of descriptive statistics only, with 95% Confidence Intervals given where appropriate.

12.4 Planned Analyses

An interim assessment by the TMG and TSC committees will take place after approximately 24-28 patients are recruited taking into account all safety and activity data available to decide if the CRM model is allowed to continue dose-recommendation until recruitment is completed or if the MTD should be declared earlier and the remaining patients recruited at the declared MTD.

The final analysis of the primary outcome will be performed when the MTD is determined according to the CRM or the maximum sample size is reached.

The final analysis of secondary and exploratory outcome measures is planned for one year after the final patient has enrolled on the study; this will allow enough time for the patient to receive all cycles of treatment and for data to be returned to the trials office.

13. TRIAL ORGANISATIONAL STRUCTURE

13.1 Sponsor

The trial is sponsored by the University of Birmingham.

13.2 Coordinating Centre

The trial is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham according to their local procedures.

13.3 Trial Management Group

The Trial Management Group (TMG) will consist of the Chief Investigator, Clinical coordinator, Statistical Consultant and the trials team at the CRCTU. The TMG will provide overall supervision of the trial; in particular clinical set-up, ongoing management, adherence to the protocol, consideration of new information and interpretation of the results. The TMG will meet every three months. An emergency meeting may be convened if a significant issue is identified.

13.4 Trial Steering Committee

A TSC will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC. The TSC will meet once each cohort of patients completes the first cycle of their combined treatment, or more often if required, to perform a formal assessment of DLT.

In each meeting, the TSC will be presented with recruitment and safety data. During the second stage, a statistical report for next dose recommendation will also be provided, and the TSC will decide whether to progress to the recommended dose as indicated by the CRM model.

If no DLTs have occurred, the TSC may review the data via correspondence.

13.5 Finance

This is a clinician-initiated and clinician-led trial funded by the Bloodwise Trials Acceleration Programme (TAP). Additional funding from Novartis Ltd and Celgene Ltd has also been provided for the management of the trial. Ruxolitinib and 5-azacitidine have been provided free of charge by Novartis Ltd and Celgene UK Ltd respectively.

No individual per patient payment will be made to NHS Trusts, Investigators or patients. This trial has been adopted into the NIHR CRN Portfolio.

14. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the General Data Protection Regulation and the Data Protection Act (2018) and Human Tissue Act 2008) and Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the main REC prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the Trials Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

15. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation and the Data Protection Act (2018). With the patient's consent, their full name and date of birth will be collected at trial entry. Patients will be identified using only their unique trial number, initials, and date of birth on the Case Report Form and correspondence between the Trials Office and the participating site. However patients are asked to give permission for the Trials Office to be sent a copy of their signed Informed Consent Form which will not be anonymised. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to the Trials Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The Trials Office will maintain the confidentiality of all patients' data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer. Representatives of the PHAZAR trial team may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

16. INSURANCE AND INDEMNITY

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

17. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the TMG and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of University of Birmingham. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

18. REFERENCE LIST

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APPENDIX 1 – RESPONSE ASSESSMENT

Proposed criteria for response assessment in patients treated in clinical trials for MPNs in blast phase (MPN-BP): Formal recommendations from the post-MPN acute myeloid leukaemia consortium - For patients with ≥20% bone marrow blasts at baseline

Myeloproliferative neoplasm in blast phase (MPN-BP) response categories.

Complete molecular response (CMR)	
Description	Complete remission of both leukemia and MPN without detectable molecular markers associated with either leukemia or MPN
Hematologic profile	ANC > 1000 Hemoglobin > 10 g/dL Platelets > 100 × 10^9/L Absence of leukoerythroblastosis[a]
Spleen	Non-palpable
Bone marrow	Cellularity appropriate for age Resolution of abnormal morphology Blasts ≤ 5%[b] ≤Grade 1 marrow fibrosis
Cytogenetics	Normal karyotype[c]
Molecular markers	Loss of any previously documented markers associated with either the leukemic or MPN clone[d]
Complete cytogenetic response (CCR)	
Description	Complete remission of both leukemia and MPN with detectable molecular markers associated with either leukemia or MPN
Hematologic profile	ANC > 1000 Hemoglobin > 10 g/dL Platelets > 100 × 10^9/L Absence of leukoerythroblastosis[a]
Spleen	Non-palpable
Bone marrow	Cellularity appropriate for age Resolution of abnormal morphology Blasts ≤ 5%[b] ≤Grade 1 marrow fibrosis
Cytogenetics	Normal karyotype[c]
Molecular markers	Residual expression of MPN/leukemia associated gene mutations (e.g. JAK2V617F, MPL515L/K)[d]
Acute leukemia response-complete (ALR-C)	
Description	Complete remission of leukemia with residual MPN features
Hematologic profile	Absence of blasts[a]
Spleen	<25% increase in spleen size by palpation or imaging if baseline spleen <10 cm or <50% if baseline spleen ≥10 cm
Bone marrow	Blasts ≤ 5%[b]
Cytogenetics	Loss of cytogenetic abnormality associated with leukemic clone, may have persistent abnormality associated with MPN
Molecular markers	Loss of any previously identified markers in leukemic clone, may have persistent molecular markers associated with MPN[d]
Acute leukemia response-partial (ALR-P)	
Description	Decrease in leukemic burden but without resolution of peripheral blood or bone marrow blasts and residual MPN features
Hematologic profile	>50% reduction in blasts
Spleen	<25% increase in spleen size by palpation or imaging if baseline spleen <10 cm or <50% if baseline spleen ≥10 cm
Bone marrow	>50% reduction in blasts
Cytogenetics	No new abnormalities
Molecular markers	No new abnormalities
Stable disease (SD)	
Description	Failure to achieve at least LR-P, but no evidence of progression for at least 8 weeks.
Progressive disease (PD)	
Description	Progression of leukemia and/orbackground MPN
Hematologic profile	For patients with 10-20% blasts: ≥50% increase to >20% blasts For patients with >20% blasts: ≥50% increase to >30% blasts
Spleen	>25% increase in spleen size by palpation or imaging if baseline spleen <10 cm and >50% if baseline spleen ≥10 cm
Bone marrow	For patients with 5–10% blasts: ≥50% increase to >10% blasts For patients with 10–20% blasts: ≥50% increase to >20% blasts For patients with >20% blasts: ≥50% increase to >30% blasts
Cytogenetics	Does not apply
Molecular markers	Does not apply

[a] Absence of peripheral blood blasts by morphologic review of the peripheral smear on two occasions separated by at least 2 weeks.
[b] Blast percentage can be assessed by morphologic review of aspirate and in cases of inaspirate marrows, immunohistochemical staining of the marrow for CD34+, CD117+ is acceptable.
[c] Normal karyotype by conventional cytogenetics in peripheral blood or bone marrow aspirate, if a cytogenetic abnormality is detected prior to treatment it must not be identified at time of assessment; if an abnormality is detected at baseline by FISH it must be absent by FISH at time of assessment.
[d] Absence or loss of evidence of mRNA transcript by quantitative PCR assay performed in a validated laboratory, this will also include any exploratory biomarkers determined to be positive prior to therapy.

Cheson criteria for MDS patients: Working Group (IWG) response criteria in myelodysplasia. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia - For patients with <20 % bone marrow blasts at baseline

Table 3. Proposed modified International Working Group response criteria for altering natural history of MDS[7]

Category	Response criteria (responses must last at least 4 wk)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines*
	Persistent dysplasia will be noted*†
	Peripheral blood‡
	Hgb ≥ 11 g/dL
	Platelets ≥ 100 × 10^9/L
	Neutrophils ≥ 1.0 × 10^9/L†
	Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except:
	Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5%
	Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment†
	Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following:
	Return to pretreatment bone marrow blast percentage
	Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets
	Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete
	Disappearance of the chromosomal abnormality without appearance of new ones
	Partial
	At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with:
	Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
	5%-10% blasts: ≥ 50% increase to > 10% blasts
	10%-20% blasts: ≥ 50% increase to > 20% blasts
	20%-30% blasts: ≥ 50% increase to > 30% blasts
	Any of the following:
	At least 50% decrement from maximum remission/response in granulocytes or platelets
	Reduction in Hgb by ≥ 2 g/dL
	Transfusion dependence
Survival	Endpoints:
	Overall: death from any cause
	Event free: failure or death from any cause
	PFS: disease progression or death from MDS
	DFS: time to relapse
	Cause-specific death: death related to MDS

Deletions to IWG response criteria are not shown.

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.

*Dysplastic changes should consider the normal range of dysplastic changes (modification).[41]

†Modification to IWG response criteria.

‡In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

APPENDIX 2 - WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians
in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

APPENDIX 3 - DEFINITION OF ADVERSE EVENTS

Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment:

An AE can therefore be any unfavourable and unintended sign (not including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Adverse Reaction

All untoward and unintended responses to an IMP related to any dose administered.

Comment:

An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event

Any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator***

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Serious Adverse Reaction

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

Suspected Unexpected Serious Adverse Reaction

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.

A SUSAR should meet the definition of an AR, UAR and SAR.

Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).

When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.

APPENDIX 4 - COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX 5 – MEDICATION AND FOOD INTERACTIONS - RUXOLITINIB

CYP3A4 inducers:

Patients taking potent CYP3A4 inducers should be monitored proactively whilst on ruxolitinib and the dose titrated based on safety and efficacy. Where possible, an alternative therapy should be administered.

Potent CYP3A4 inducers include, but are not limited to:

- Rifampin (rifampicin)
- St. John's wort (*Hypericum perforatum*)
- Barbiturates
- Carbamazepine
- Phenytoin
- Nevirapine
- Rifabutin
- Avasimibe
- Phenobarbital

CYP3A4 inhibitors:

Potent CYP3A4 inhibitors

Patients should not take any potent inhibitors of the CYP3A4 family of metabolizing enzymes during the first cycle of treatment. Beyond the first cycle such medication is discouraged but permitted, however the dose of ruxolitinib may need to be adjusted.

Potent inhibitors of the CYP3A4 include, but are not limited to:

- Clarithromycin
- Itraconazole
- Nefazodone
- Telithromycin
- Indinavir
- Ritonavir
- Cobicistat
- Troleandomycin
- Saquinavir
- Voriconazole
- Mibefradil
- Lopinavir
- Elvitegravir
- Posaconazole
- Nelfinavir
- Boceprevir
- Ketoconazole
- Telaprevir
- Fluconazole
- Isoniazid

Azole antifungals commonly used for fungal prophylaxis are potent inhibitors of the CYP3A4 pathway. Their use is therefore prohibited during the first cycle of treatment and discouraged from cycle 2 onwards. Alternatives permitted throughout the trial include Isavuconazole, Amphotericin B and Micafungin.

Isoniazid is also expected to affect ruxolitinib bioavailability. Therefore, alternatives should be discussed with the local infectious disease team if tuberculosis prophylaxis is needed. Active tuberculosis will mandate discontinuation of trial treatment.

When ruxolitinib is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole), the dose of ruxolitinib should be reduced by approximately 50%, to be administered twice daily. Concomitant use of ruxolitinib with fluconazole doses greater than 200 mg daily should be avoided. More frequent monitoring (e.g. twice a week) of haematology parameters to detect cytopenias and of clinical signs and symptoms of ruxolitinib-related adverse drug reactions is recommended while strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes and ruxolitinib are co-administered.

Mild or moderate CYP3A4 inhibitors

No dose adjustment is recommended when ruxolitinib is co-administered with mild or moderate CYP3A4 inhibitors. However, patients should be closely monitored for cytopenias when initiating therapy with a moderate CYP3A4 inhibitor.

Mild or moderate CYP3A4 inhibitors include, but are not limited to:

- Erythromycin
- Ciprofloxacin
- Amprenavir
- Atazanavir
- Diltiazem
- Cimetidine

Other prohibited concomitant medications:

Patients should not receive any chemotherapy, anticancer immunotherapy, other investigational therapy or other JAK2 inhibitors whilst on trial treatment.

Cytoreductive treatment is also prohibited throughout the trial with the exception of hydroxycarbamide and anagrelide, which can be used to control blood cell counts or manage aggressive disease following consultation with the Chief Investigator for a period not exceeding 28 days. Hydroxycarbamide or anagrelide prescribed prior to study entry must be stopped before the first scheduled day of trial treatment.

Splenic irradiation is prohibited throughout the trial. Sites are requested to obtain prior CI approval via the trials office before administering any other radiotherapy treatment.

Prohibited foods:

Patients should not consume the following food:

- Grapefruit products (including juice)
- Seville oranges (including marmalade)

APPENDIX 6 – QUALITY OF LIFE QUESTIONNAIRES

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

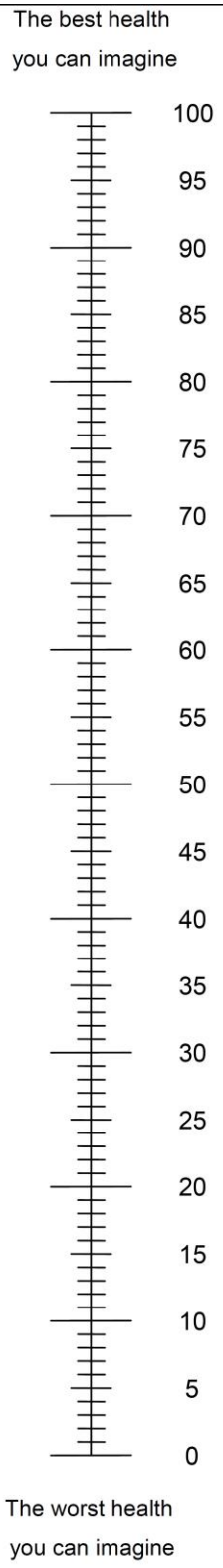
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) With 1-item Brief Fatigue Inventory

Instructions: Please fill out all questions, as best able, reflecting how these symptoms affected you over the **LAST WEEK** unless directed otherwise.

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 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 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 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)
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)

Date Completed:……..

1

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