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Clinical Development

INC424/Ruxolitinib/JAKAVI

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A randomized, double blind, placebo-controlled, multi-center, Phase III study investigating the efficacy and safety of ruxolitinib in Early Myelofibrosis patients with high molecular risk mutations

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List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BAT	Best available therapy
BCR-ABL	Breakpoint cluster region Abelson
BCS	Biopharmaceutical Classification System
BID	bis in diem/twice a day
BP	Blood pressure
BUN	Blood Urea Nitrogen
Clcr	Creatinine Clearance
CNS	Central Nervous System
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRP	C-Reactive Protein
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DIPSS	Dynamic International Prognostic Scoring System
DMC	Data Monitoring Committee
DS&E	Drug safety and epidemiology
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EOT	End Of Treatment
EQ-5D	EuroQol-5D-5L
ET	Essential Thrombocythemia
FA	Final Analysis
FAS	Full Analysis Set
GI	Gastrointestinal
Hb	Hemoglobin
hCG	Human chorionic gonadotropin
HDL	High Density Lipoprotein
hERG	human ether-à-go-go related gene
HIV	Human Immunodeficiency Virus
HMR	High Molecular Risk
HR	Hazard Ratio
IA	Interim Analysis
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IL	Interleukin
IN	Investigator notification

[redacted]

INR	International normalized ratio
IPSS	International Prognostic Scoring System
IRB	Institutional review board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IUD	Intrauterine device
IUS	Intrauterine system
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK	Janus kinase
JAK-STAT	Janus Kinase-Signal Transducer & Activator of Transcription
LC-MS	Liquid chromatography-tandem mass spectrometry
LDL	Low Density Lipoprotein
LLOQ	Lower limit of quantification
LMR	Lower molecular risk
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
MF	Myelofibrosis
MF-7	Myelofibrosis 7 Item Symptom Scale
MM	Multiple Myeloma
MPN	Myeloproliferative Neoplasm
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
PAS	Pharmacokinetic Analysis Set
PD	Progressive disease
PET-MF	Post-essential Thrombocythemia Myelofibrosis
PFS	Progression Free Survival
[redacted]	[redacted]
PHI	Protected health information
PK	Pharmacokinetic(s)
PLT	Platelet
PMF	Primary Myelofibrosis
PML	progressive multifocal leuko-encephalopathy
PPS	Per Protocol Set
PPV-MF	Post-polycythemia vera Myelofibrosis
PRO	Patient Reported Outcome
PT	Prothrombin Time
PTT	Partial Prothrombin Time
PV	Polycythemia Vera
QALY	Quality-adjusted life years
QoL	Quality of life
RA	Rheumatoid Arthritis
RAP	Report and Analysis Plan
RBC	Red Blood Cell
RDC	Remote data capture
REB	Research Ethics Board

[redacted]

RU	Resource Utilization
SAE	Serious Adverse Event
SAWP	Scientific advice working party
SC	Steering Committee
SEC	Safety Event Categories
SmPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
TNF-α	Tumor necrosis factor alpha
TTP	Time to progression
TTPPS	Time to progressive palpable splenomegaly
TTSP	Time to symptomatic progression
ULN	Upper Limit Normal
VAS	Visual analogue scale
WBC	White Blood Cell

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
One week	Equates to 7 calendar days
Control drug (Placebo)	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Baseline Period / Baseline Data Collection	The initial period /initial collection of data, prior to randomization and pre-dose, that serves as the reference for all statistical analyses investigating (potential) changes occurred while on study treatment.
Study treatment (ruxolitinib /Placebo)	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination.
INC424	Refers to ruxolitinib
HMR+ EMF	Early myelofibrosis patients positive for high molecular risk mutations
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
MF-7	Myelofibrosis 7 Item symptom scale
MF-7 score	Computed as the sum of the observed scores in the individual symptom items to achieve a 0-to-70 score
Subject Number	A unique identifying number assigned to each patient/subject/healthy volunteer who participates in the study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and End of Treatment visit should occur.
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Treatment Period 1	Period of treatment with blinded study treatment (ruxolitinib or placebo)
Treatment Period 2	Period of treatment with ruxolitinib (post progression on blinded treatment)
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

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Protocol summary:

Title	A randomized, double blind, placebo-controlled, multi-center, Phase III study investigating the efficacy and safety of ruxolitinib in Early Myelofibrosis patients with high molecular risk mutations
Brief title	Phase III study investigating the efficacy and safety of ruxolitinib in Early Myelofibrosis patients with high molecular risk mutations.
Sponsor and Clinical Phase	Novartis Phase 3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Myelofibrosis patients with high molecular risk mutations have an intrinsically aggressive disease with increased risk of leukemic transformation and reduced overall survival. As there are no therapies currently established in the subset of high molecular risk patients with early myelofibrosis, the study aims to evaluate ruxolitinib in this patient population.
Primary Objective	To evaluate the effect of ruxolitinib in delaying progression of MF from early disease to more advanced disease stages
Secondary Objectives	To evaluate time to disease progression of MF with or without ruxolitinib To evaluate the changes in spleen volume with or without ruxolitinib To assess the changes in symptoms using MF-7, EuroQol-5D-5L (EQ-5D) To assess the safety and tolerability of ruxolitinib To evaluate the effect of ruxolitinib on overall survival To assess the pharmacokinetics of ruxolitinib To evaluate the efficacy of ruxolitinib post progression
Study design	Randomized, double blinded, placebo controlled (1:1) study with treatment until disease progression or patient discontinuation.
Population	Patients must have a confirmed diagnosis of MF; exhibit minimally symptomatic early MF disease and should also be positive for the HMR mutational status
Inclusion criteria	● Confirmed diagnosis of MF with bone marrow fibrosis of at least Grade 1; irrespective of JAK2 mutational status ● Patients with at least one mutation in one of the five HMR genes (ASXL1, EZH2, SRSF2 and IDH1/2) ● Patients with non-palpable spleen or spleen palpable ≤ 5 cm from the left costal margin to the point of greatest splenic protrusion ● Patients with MF-7 score of ≤ 15, with each individual symptom score of ≤ 3
Exclusion criteria	● Patients with prior treatment with ruxolitinib or other JAK inhibitors.

[redacted]

Investigational and reference therapy	Ruxolitinib or Placebo
Efficacy assessments	● Spleen volume determination by MRI/CT ● Laboratory assessments confirming disease progression (Hb decrease, WBC count and peripheral blood blast count) ● Bone marrow biopsy and aspirate for leukemic transformation ● Symptom assessment using MF-7, EQ-5D
Safety assessments	Physical examination, laboratory assessments, ECG
Other assessments	[redacted] ● Assessment and characterization of the pharmacokinetics of ruxolitinib [redacted]
Data analysis	An interim analysis will be performed once 45 PFS-1 events are documented. The primary analysis of study data will be conducted once 90 PFS-1 events are documented.
Key words	Ruxolitinib; INC424; early myelofibrosis; High molecular risk mutations; HMR.

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Myelofibrosis (MF) is a clonal hematologic neoplastic disease characterized by the presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin and/or collagen fibrosis (Tefferi 2008), splenomegaly, anemia, and debilitating constitutional symptoms that include fatigue, weight loss, pruritus, night sweats, fever, and bone, muscle, or abdominal pain (Mesa et al 2007, Abdel-Wahab, Levine 2009). MF can either be primary in origin (primary myelofibrosis, or PMF) or result from progression of polycythemia vera or essential thrombocythemia vera (Tefferi 2008). The median age at diagnosis of MF is approximately 65 years. Patients with myelofibrosis have shortened survival that ranges from a median of approximately 2 years to 11 years depending on the presence of certain risk factors that define their risk category including age, anemia, leukocytosis, etc.

Several prognostic risk scores that are based on survival outcomes have been developed in MF to better define treatment choices for physicians and therefore improve patient management. The International Prognostic Scoring System (IPSS) was developed by the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) (Cervantes et al 2009). The IPSS is used at diagnosis and employs five hematologic and clinical variables (age, leukocytosis, anemia, peripheral blood blasts and constitutional symptoms) to stratify patients in a low, intermediate-1, intermediate-2 and high-risk category. The dynamic IPSS (DIPSS) was subsequently developed to be used for patients evaluated after MF diagnosis (Gangat et al 2011). The DIPSS relies upon the same five variables as IPSS but utilizes the predictive value of selected cytogenetic abnormalities. These scoring systems are expected to facilitate categorizing patients to different risk groups, and thus assist physicians in recommending optimal treatment management plans.

All currently available pharmacologic treatments are either directed towards the management of MF-originated anemia or the treatment of MF-symptoms including splenomegaly. As these treatments do not cure or modify the disease progression of MF, they are mostly used to treat patients in the higher risk categories. MF patients in the lower risk categories (IPSS Low and Int-1), by virtue of a relatively asymptomatic disease and an indolent disease course, are managed through active surveillance or a ‘watch and wait’ approach until appearance of bothersome symptoms or the definitive progression to the higher risk groups. Allogeneic stem cell transplantation is the only curative option, but it is often associated with a high rate of mortality and morbidity (Kroger 2008). Other available treatments include splenectomy, involved field radiotherapy, erythropoiesis stimulating agents, androgen preparations, thalidomide and its analogs, hydroxyurea. More recent advancements in MF treatment include the discovery of ruxolitinib, a Janus Kinase (JAK)1 and JAK2 inhibitor. Ruxolitinib is one of the first treatments in MF that has demonstrated rapid and durable reductions in MF- related splenomegaly, improvement in disease-related symptoms and offers a distinct survival benefit (Vannucchi et al 2015).

[redacted]

The recent years have witnessed major advances in the molecular understanding of MF, first with the identification of *JAK2* and *MPL* mutations (Kilpivaara, Levine 2008) and more recently the calreticulin (*CALR*) gene (Klampfl T et al 2013), all of which are associated with an activation of the Janus Kinase-Signal Transducer & Activator of Transcription (JAK-STAT) pathway. In addition, as also shown in other myeloid malignancies, mutations in a multiplicity of other genes involved in the epigenetic and spliceosome regulatory machineries have been reported in MF across IPSS risk categories and shown to have a negative prognostic impact.

A recent study evaluated 879 PMF patients to determine the individual and combinatorial prognostic relevance of somatic mutations. Analysis was performed in 483 European patients and the seminal observations were validated in 396 Mayo Clinic patients. Samples from the European cohort, collected at the time of diagnosis, were analyzed for mutations in *ASXL1*, *SRSF2*, *EZH2*, *TET2*, *DNMT3A*, *CBL*, *IDH1*, *IDH2*, *MPL* and *JAK2* (Vannucchi et al 2013a). A specific sub-group of mutations were identified (*ASXL1, EZH2, SRSF2* and *IDH)* that may be predictive of PMF patients who are at risk for premature death or leukemic transformation. These mutations are classified as the 'high molecular risk' category (HMR) in PMF based on the presence of at least one of the five prognostically detrimental mutated genes.

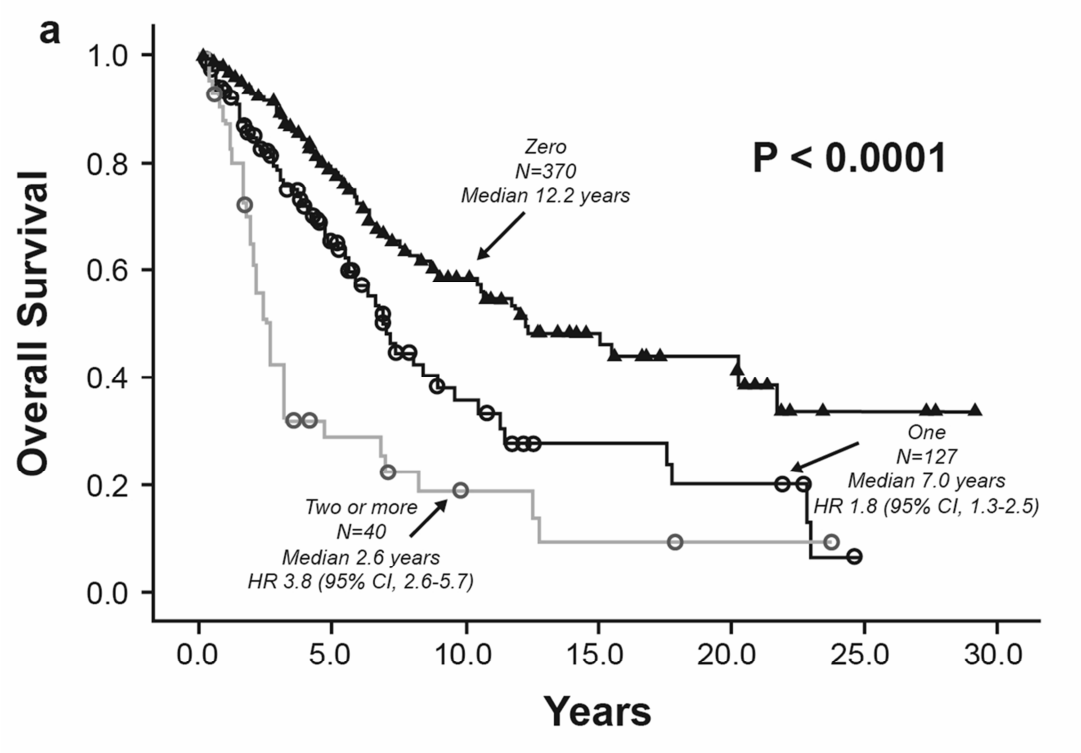
[Guglielmelli et al.] further evaluated the additional prognostic value of the number of mutated genes. A total of 797 patients were recruited from Europe (n=537) and the Mayo Clinic (n=260). In the European cohort, 167 (31%) patients were categorized as HMR: 127 (23.6%) had one and 40 (7.4%) had two or more mutated genes. The presence of two or more mutations predicted the worst survival: median 2.6 years (hazard ratio (HR) 3.8, 95% confidence interval (CI) 2.6‑5.7) vs 7.0 years (HR 1.9, 95% CI 1.4‑2.6) for one mutation vs 12.3 years for no mutations (Figure 1-1, Ref – Guglielmelli et al 2014a). The presence of two or more mutations was also associated with shortened leukemia-free survival (HR 6.2, 95% CI 3.5‑10.7). Overall, the recent studies demonstrate that patients with PMF harboring mutations in any one of the five prognostically detrimental genes (*ASXL1*, *EZH2*, *SRSF2* and *IDH1/2*) constitute an IPSS/DIPSS-plus independent HMR category with shorter survival and greater risk of acute myeloid leukemia (AML) progression compared with the low molecular risk (LMR) patients. These findings therefore identify a clinically relevant subgroup of MF patients with HMR mutations, who despite being minimally symptomatic (including less severe splenomegaly) and thus categorized to harbor a lower risk disease through the IPSS or DIPSS scoring systems, may require earlier intervention with treatments that would prevent or delay their disease progression and leukemic transformation and potentially improve their survival. The majority of HMR positive patients with minimally symptomatic disease (Early MF) are currently not treated until symptoms present more aggressively. These HMR positive early MF (HMR+ EMF) patients are in need of therapy that can delay progression and therefore have an unmet medical need.

Currently, ruxolitinib is the only treatment that has shown evidence through prospective randomized trials to not only reduce symptom burden and splenomegaly but also confer a longer term survival advantage and delay time to leukemia transformation (Vannucchi et al 2015). A retrospective analysis conducted by Guglielmelli et al in the COMFORT II study, showed that HMR status did not affect the likelihood of obtaining a treatment benefit with ruxolitinib, suggesting that the clinical efficacy and survival

[redacted]

improvement observed with ruxolitinib in MF patients may occur independently of the underlying molecular pattern. These observations were however confined to patients in the higher risk categories (IPSS Int-2 and High) and therefore currently not established in the lower risk categories. This study will investigate the effect of JAK inhibition with ruxolitinib in a patient population with earlier MF disease harboring HMR mutations. It is to be noted that the selection of patients with HMR mutations is solely intended to identify a subset of patients with an intrinsically aggressive MF disease, with poor prognosis and hence an unmet medical need for appropriate therapeutic intervention. The HMR test in the study is not intended for preselecting patients who are more likely to respond to ruxolitinib or tolerate the treatment.

Figure 1-1 Prognostically detrimental 'HMR' mutations and survival in PMF: Kaplan Meier Plots



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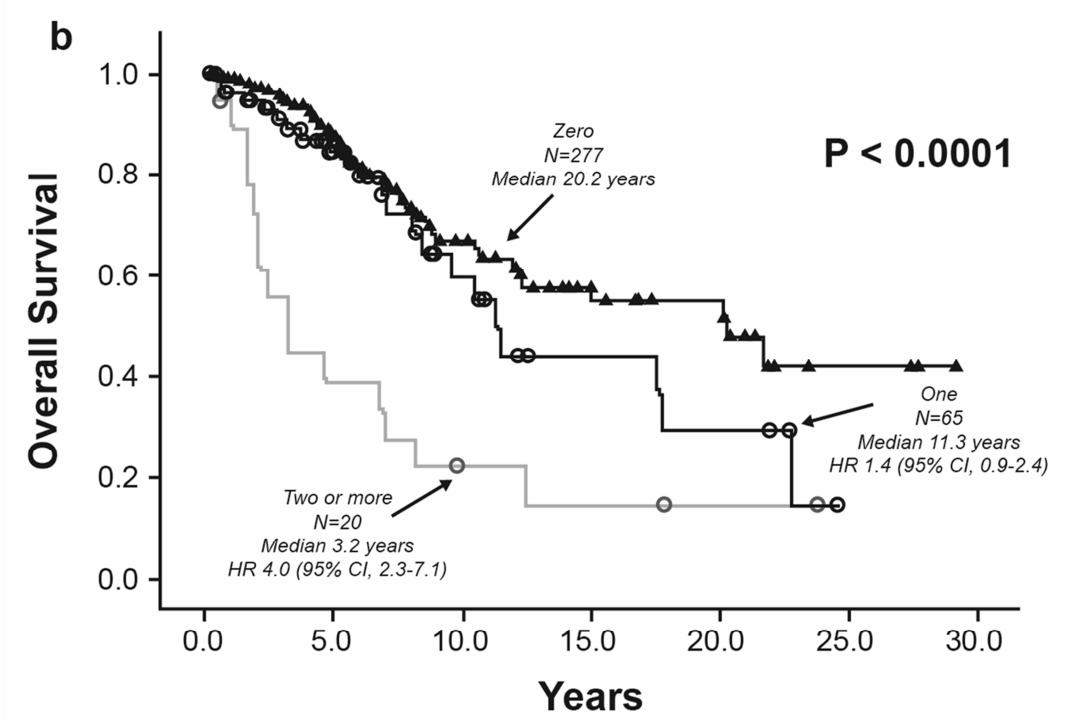
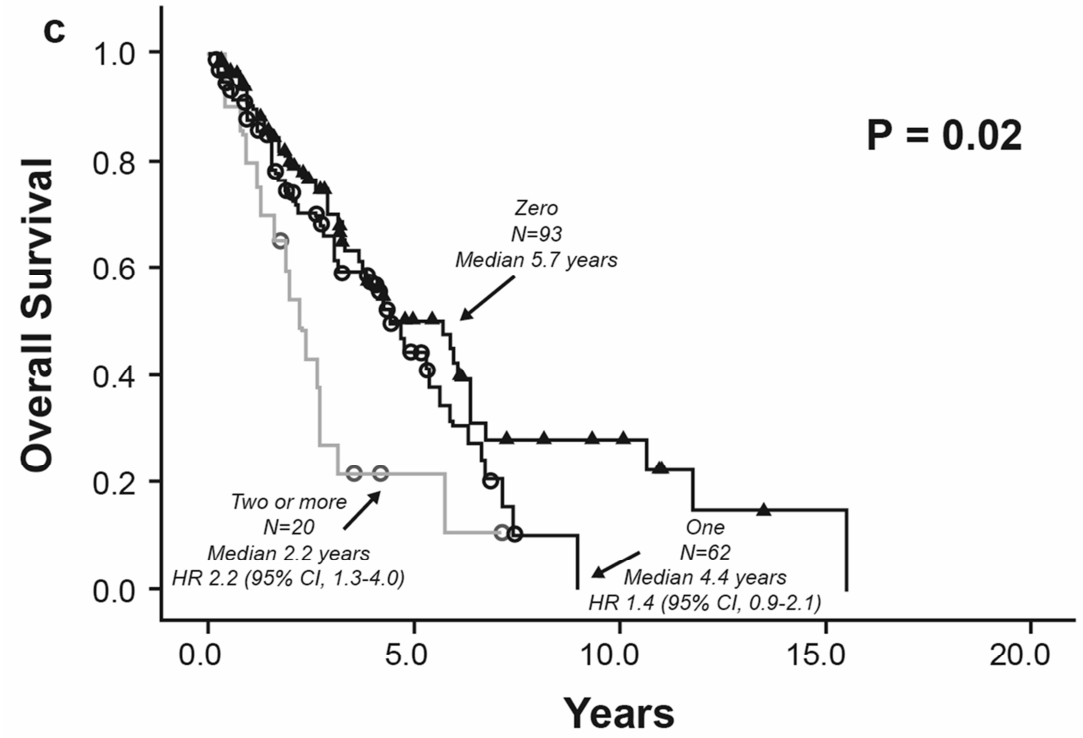




a – Overall survival stratified by zero, one and two/more prognostically detrimental mutations (HMR).

b – Overall survival for IPSS low risk categories (Low and intermediate-1) stratified by number of HMR mutations.

c - Overall survival for IPSS high risk categories (intermediate-2 and high) stratified by number of HMR mutations.

[redacted]

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of ruxolitinib

Dysregulated JAK-STAT signaling, via upregulation of JAK1 and JAK2 or gain of function mutations such as JAK2V617F, have been implicated as drivers of Breakpoint Cluster Region Abelson (BCR-ABL)-negative Myeloproliferative neoplasms (MPN), namely myelofibrosis, polycythemia vera (PV) and essential thrombocythemia (ET). Ruxolitinib, which is jointly developed in Hematology and Oncology indications by Novartis Pharma AG (Switzerland) and Incyte Corporation (USA) specifically binds to and inhibits JAK1, as well as JAK2 and mutated JAK2V617F, leading to inhibition of growth factor-mediated cell signaling and tumor cell proliferation. [redacted]

Ruxolitinib is currently approved under the trade name of 'Jakavi' in over 90 countries for the treatment of disease-related splenomegaly or symptoms in adult patients with (primary myelofibrosis) PMF, post-polycythemia vera myelofibrosis (PPV-MF) and post-essential thrombocythemia myelofibrosis (PET-MF). The use of ruxolitinib to treat polycythemia vera (PV) patients who are resistant to or intolerant of hydroxyurea is currently under regulatory review worldwide based on the results from the RESPONSE study. So far approval in this second indication was granted in more than 45 countries including EU and Switzerland. Ruxolitinib is also approved in the USA under the trade name of 'Jakafi' and is indicated for the treatment of patients with intermediate or high risk myelofibrosis, including PMF, PPV-MF and PET-MF and for the treatment of PV patients who have had an inadequate response to or are intolerant of hydroxyurea.

1.2.1.1 Non-clinical experience

Ruxolitinib was evaluated in non-clinical investigations in pharmacology, safety pharmacology, repeat-dose toxicity, genotoxicity, reproductive toxicity studies and carcinogenicity studies. Ruxolitinib was efficacious in mouse models of Philadelphia chromosome negative MPNs and in additional preclinical tumor models representing both hematological and solid tumors expressing wild-type JAKs or a clinically relevant constitutively active mutant JAK2. Efficacy was also observed in rodent models of cytokine-dependent inflammation. Effects noted in multiple-dose toxicity studies in mice, rats, and dogs were primarily those associated with the mechanism of action of ruxolitinib, a potent and reversible inhibitor of JAK/STAT signaling. In these studies, expected consequences of the pharmacology of JAK inhibition, were noted. In a respiratory safety pharmacology study, an adverse decrease in minute volume was noted in female but not in male rats at the highest dose, 150 mg/kg. In a cardiovascular evaluation of ruxolitinib in dogs, electrocardiogram (ECG) parameters were unaffected at all doses. Administration of ruxolitinib at the highest dose evaluated (30 mg/kg) resulted in an adverse lowering of blood pressure along with an increase in heart rate compared to vehicle control. The IC50 for the human ether-à-go-go related gene (hERG) ion channel was determined to be 131.6 µM. Ruxolitinib was not

[redacted]

mutagenic, clastogenic or teratogenic, nor did it demonstrate potential for carcinogenicity or in studies involving animal models and embryo-fetal assessments. Increases in post-implantation loss were noted at the higher doses. In a pre- and post-natal development and maternal function study in rats there were no adverse findings for fertility indices or for maternal and embryo-fetal survival, growth, and developmental parameters. Ruxolitinib passed into the milk of lactating rats with an exposure that was 13-fold higher than maternal plasma exposure.

Please refer to the [Investigator Brochure] for further information.

1.2.1.2 Clinical experience

Ruxolitinib has been administered to approximately 430 healthy volunteers as single, repeat single, or multiple doses for up to 10 days' duration, 32 subjects with various degrees of renal impairment, and 24 subjects with various degrees of hepatic impairment. Up to 22 February 2015, ruxolitinib has been administered to approximately 8240 subjects in Novartis and Incyte sponsored investigational trials and 5033 subjects in third party sponsored trials (Refer to [Investigator Brochure] for details).

1.2.1.2.1 Clinical Pharmacology

Fifteen Phase I, nine Phase II and three Phase III clinical studies (two in MF, one in PV) provided clinical pharmacology data on ruxolitinib in healthy volunteers and in patients with MF, ET, PV, as well as in subjects with renal or hepatic impairment, prostate cancer, pancreatic cancer, MM or RA. Oral absorption of ruxolitinib is rapid and nearly complete, with ≥95% absorption indicating high *in vivo* permeability in the human gastrointestinal tract, consistent with a Biopharmaceutical Classification System (BCS) Class I compound. Mean peak plasma concentrations (Cmax) is achieved 1-2 h post-dose.

The effect of food on ruxolitinib exposure is minimal and is not expected to be clinically significant; as a result, the drug may be administered either with or without food. Dose proportional exposure is observed between 5 and 200 mg dose range with linear pharmacokinetics (PK).

Plasma protein binding is approximately 97% *in vitro*. There is moderate distribution to organs and tissues with no long-term retention of drug-related material in preclinical species and limited drug penetration into the central nervous system (CNS) or across the blood-brain barrier. There is >95% [^{14}C] drug recovery in a mass balance study with 74% and 22% of the dose excreted in urine and feces of healthy subjects, respectively. Less than 1% of the administered dose is recovered in urine and feces as unchanged parent drug. The mean terminal elimination half-life (t1/2) is ~3 h with no appreciable accumulation of either parent or metabolites with twice daily dosing. Metabolism is predominantly via the cytochrome P450 isozyme CYP3A4 to yield oxygenated and subsequent conjugated metabolites. Oxidative metabolites of ruxolitinib retain pharmacological activity albeit with one half to one fifth of the activity of the parent compound. *Ex vivo* pharmacokinetic/pharmacodynamic analysis indicates that the total of 8 active metabolites contribute to 18% of the overall pharmacodynamics activity of ruxolitinib. When administering ruxolitinib with strong CYP3A4 inhibitors, the total daily dose should be reduced by approximately 50%. No dose adjustment is necessary when co-administering ruxolitinib with strong CYP3A4 inducers. No

[redacted]

dose adjustment is necessary when co-administering ruxolitinib with CYP3A4 substrates. Ruxolitinib did not decrease the exposure of a fixed dose oral contraceptive metabolized via the CYP3A4 pathway, thus demonstrating lack of CYP3A4 induction potential.

In patients with severe renal impairment [creatinine clearance (Clcr) < 30 mL/min], the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice a day. Patients on hemodialysis should initiate ruxolitinib with a single dose of 15 mg or 20 mg (or two doses of 10 mg given 12 hour apart) based on platelet counts on day of hemodialysis with subsequent doses only on hemodialysis days and following each hemodialysis session. Ruxolitinib doses should be titrated based on individual safety and efficacy.

In patients with mild, moderate or severe hepatic impairment, the recommended starting dose based on platelet count should be reduced by approximately 50% with subsequent dose titration based on individual safety and efficacy.

Ruxolitinib PK in healthy volunteers was largely comparable between Japanese, Chinese and Western subjects and did not lead to a conclusion of meaningful ethnic differences.

Baseline elevations in inflammatory markers such as tumor necrosis factor alpha (TNFα), interleukin (IL)-6, and C-reactive protein (CRP) noted in patients with MF were associated with constitutional symptoms such as fatigue, pruritus, and night sweats. Decreases were observed in these markers over the 24 weeks of treatment with ruxolitinib, with no evidence that patients became refractory to the effects of ruxolitinib treatment.

Please refer to the [Investigator Brochure] for additional details on pharmacokinetics and pharmacodynamics.

1.2.1.2.2 Summary of Clinical Efficacy data

The results from two Phase III studies in myelofibrosis (COMFORT-I, COMFORT-II) demonstrate the effectiveness of ruxolitinib in patients with PMF, PPV-MF and PET-MF. The results of these two studies were consistent, demonstrating statistically significant ($p < 0.0001$) differences in rates of ≥35% spleen volume reduction compared with either placebo or an investigator's selection of best available therapy (BAT). Although each study measures spleen volume reduction at different time points (Weeks 24 and 48 for COMFORT-I and COMFORT-II, respectively), the mean reduction in spleen volume is similar at Week 24 (31.6% vs. 29.2%, COMFORT-I and COMFORT-II, respectively).

Consistent with its activity in myelofibrosis, ruxolitinib demonstrated in the RESPONSE pivotal study its efficacy in polycythemia vera patients who are resistant to or intolerant of hydroxyurea. A significantly greater proportion of patients who were randomized to ruxolitinib met the primary endpoint of the study, which was a composite endpoint of hematocrit control in the absence of phlebotomy and spleen volume reduction ≥ 35% when compared to patients randomized to BAT (20.9% vs. 0.9%, $p < 0.0001$). Of the patients meeting the primary endpoint at Week 32, 94% maintained their response at Week 48.

[redacted]

1.2.1.2.3 Summary of Clinical safety data

In the randomized period of the two pivotal studies in MF, COMFORT-I and COMFORT-II discontinuation due to adverse events, regardless of causality was observed in 11.3% of patients. The most frequently reported adverse drug reactions were thrombocytopenia and anemia. Hematological adverse reactions (any Common Terminology Criteria for Adverse Events [CTCAE] Grade) included anemia (82.4%), thrombocytopenia (69.8%) and neutropenia (16.6 %). Anemia, thrombocytopenia and neutropenia are dose related effects. The three most frequent non-hematological adverse reactions were bruising (21.6%), dizziness (15.3%) and headache (14.0%). The three most frequent non-hematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (18.6%) and hypercholesterolemia (16.9%).

Long-term follow-up in patients with MF in the phase I/II study INCB 18424-251 and the COMFORT studies has shown that as expected, the numbers and proportions of adverse events (AEs) and serious adverse events (SAEs) have increased; however, no new safety signals have emerged. Additionally in patients with MF, the dose optimization strategy of dose reduction and occasional dose interruption for thrombocytopenia was successful in maintaining patients on therapy with only one patient on the ruxolitinib arm of each study discontinuing for thrombocytopenia; platelet transfusions occurred with low frequency, comparable to the control arms in the Phase III studies.

Overall, the safety profile of ruxolitinib in the PV population treated with ruxolitinib is generally consistent with what was observed in the MF population. Ruxolitinib was generally well tolerated in patients with PV and only a small proportion of patients discontinued ruxolitinib due to AEs (3.6%). Most of the AEs have been managed by dose adjustments. Hematological toxicities were less frequent and less severe in patients with PV as compared to those observed in patients with MF.

No new safety signals emerged from a study in pancreatic cancer in combination with capecitabine.

The AE profile of ruxolitinib has also been assessed in 198 healthy volunteers, subjects with various degrees of renal (n=32) or hepatic (n=24) impairment, and in patients with RA (n=59) receiving ruxolitinib: AEs were, in general, mild and resolved without interventions.

A thorough QT study was conducted in 50 healthy subjects. There was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up to a supra-therapeutic dose of 200 mg indicating that ruxolitinib has no effect on cardiac repolarization.

Please refer to the [Investigator Brochure] for further information.

[redacted]

2 Rationale

2.1 Study rationale and purpose

Ruxolitinib is currently indicated for the treatment of disease related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythemia vera myelofibrosis or post essential thrombocythemia myelofibrosis. This approval was based on the results of the COMFORT I & COMFORT II registration studies conducted in symptomatic MF patients and demonstrating significant improvements in MF related splenomegaly and symptoms, with acceptable safety and long term tolerability. Ruxolitinib was also shown to delay disease progression, time to leukemic transformation and prolong survival as compared to placebo and best available therapies (BAT) (Verstovsek – ASH 2013, Abstract 396; Cervantes, Blood 2013).

Recent advances in genetic profiling of MF and the discovery of high molecular risk (HMR) mutations have distinguished a biological sub-group of patients who, independently of their MF symptoms at presentation, have a more aggressive course of the disease. Genetic profiling of MF has led to the establishment of a set of genes, namely ASXL1, EZH2, SRSF2 and IDH1/ IDH2, mutations in one or more of which indicate an intrinsically aggressive MF disease (Guglielmelli et al, Leukemia 2014). The prognostic value of these mutations was evaluated based on data from 797 patients (inclusive of test and validation cohorts) and confirmed that patients harboring mutations in any one of these 'high molecular risk' (HMR) genes have shortened OS (Hazard ratio [HR] of 2.29; 95% confidence interval [CI] 1.65–3.19) and a higher risk of transformation to AML (HR of 2.96; 95% CI 1.85–4.76) compared with patients without the HMR genes. These findings are of significant clinical relevance as they allow the identification of a subgroup of patients with an intrinsically aggressive disease. Although patients without overt splenomegaly or disease related symptoms are currently not chosen for immediate commencement of active therapies, it is assessed, that the sub-group of patients with HMR status, by virtue of harboring a more aggressive disease, may be candidates requiring immediate therapeutic intervention.

Stem cell transplantation is the only intervention that has currently produced evidence for potential cure with prolongation of survival in MF. However, stem cell transplantation is limited by donor availabilities and is associated with considerable mortality and morbidity (Kroger 2008). This group of patients is therefore not currently considered as transplant candidate and is assessed to currently have an unmet medical need for therapies that would improve their clinical outcomes.

With ruxolitinib establishing its efficacy both in terms of alleviating disease symptoms, spleen burden and improving survival in advanced MF patients (IPSS int-2 and high risk patients), this study will investigate the benefits of ruxolitinib in patients with less advanced MF (patients with spleen $\leq$ 5 cm below left costal margin, hemoglobin (Hb) > 10 g/dl and symptoms by Myelofibrosis 7 Item symptom scale [MF-7] $\leq$ 15), who harbor at least one HMR mutation, and for whom ruxolitinib is currently not indicated for use or not actually used in countries with less restrictive labels.

[redacted]

2.2 Rationale for the study design

The study intends to investigate the potential of ruxolitinib in delaying progression of disease in MF patients with no/minimal splenomegaly or symptoms and harboring HMR mutations. The trial will consist of a double blind, placebo-controlled, randomized (1:1) study design with treatment administered until disease progression or premature discontinuation of patient (Section 6.1.5) (Figure 4-1). Given that ruxolitinib is currently indicated for the treatment of disease related splenomegaly or symptoms in adult patients with MF, patients who progress during the blinded study period due to splenomegaly or symptoms and are candidates for treatment with ruxolitinib (as per investigators decision) will be treated at the approved starting doses of 5mg, 15mg or 20 mg BID, based on platelet counts at the time of treatment initiation (Refer to Section 6.1).

The study will evaluate the primary endpoint of progression free survival as a primary efficacy measure. The study is designed in line with IWG-MRT group recommendation of using a 'time to event' endpoint in phase III studies investigating treatment options in early MF (Barosi 2014). The study will primarily investigate the potential of ruxolitinib in delaying progression of MF from the less advanced stages (Early MF) to more advanced stages. Assessment of disease progression will be performed utilizing criteria for clinical responses recommended by the IWG-MRT in MPN patients (Tefferi et al 2013). This will be based on events including progressive splenomegaly, emergence or worsening of cytopenia, blasts in the peripheral blood, deterioration in the severity of disease symptoms, leukemic transformation and death. Additionally, the study will evaluate longer term treatment benefits with ruxolitinib through evaluation of [redacted] overall survival as efficacy measures. Furthermore, the study will include the assessment of second progression (i.e. following progression of disease into advanced MF) on subsequent treatment with currently approved doses of ruxolitinib. The study will include an interim analysis for futility.

Disease progression in the blinded treatment Period 1 will be referred to as progression free survival-1 (PFS-1) event; while progression in the ruxolitinib treatment Period 2 will be referred to as progression free survival-2 (PFS-2) event.

2.3 Rationale for dose and regimen selection

The dose of ruxolitinib at 10 mg BID (twice a day) to be used in this study was selected based on assessment of data from COMFORT studies and the disease severity in the target population, alongside consultation with experts in the MF disease area.

Observations from the two pivotal COMFORT studies indicated that the incidence of hematological AEs were relatively lower and less severe at ruxolitinib 10 mg BID as compared to the higher dose of 15 mg BID. The ruxolitinib starting dose of 10 mg BID has also been shown to be well tolerated in patients with lower platelet counts (75,000 to 100,000/µL) than those originally enrolled in COMFORT studies (>100,000/µL) (Boekhorst et al, ASH 2014). Although relatively better spleen responses were observed in patients with higher dose intensities, the 10 mg BID dose was able to provide improvements in MF related symptoms that are significant and comparable to the higher doses. In the current study, eligible patients are expected to have an indolent MF disease at its earliest stages with

[redacted]

minimal or no splenomegaly and symptoms. Since large reductions in spleen sizes is not the mainstay of the expected benefit from treatment in the study target population, 10 mg BID dose was assessed to adequately maintain the small spleen size and minimal symptom burden, alongside a relatively better tolerability profile. The 10 mg BID dose is also consistent with the dose used in studies investigating ruxolitinib in other less severe MPNs such as PV.

Treatment with ruxolitinib following the first progression will be at the currently approved doses of 5 mg, 15 mg or 20 mg BID, depending on platelet counts at treatment initiation (Section 6.1).

2.4 Rationale for choice of comparators drugs

There is no standard therapy established in the management of patients with HMR positive early MF that is proven to delay their disease progression. Stem cell transplantation is the only intervention that is currently available for such patients but is very rarely used due to limited donor availabilities and the associated mortality and morbidity. As such, placebo will be used as the comparator of choice in the blinded period (Treatment Period 1), which will also ensure that there is no bias introduced in the assessment of the primary endpoint.

There will be no comparator used during Treatment Period 2.

2.5 Risks and Benefits

As the study is placebo-controlled and is conducted in a patient population that currently has no established treatment options, associated risks and benefits are limited to the use of ruxolitinib.

Dose-dependent, reversible thrombocytopenia and anemia are primary adverse effects that are observed with ruxolitinib. A theoretical risk of neutropenia exists, although only a few examples of Grade 3 or 4 neutropenia have been observed in MF patients in previous studies, generally in subjects who entered the study with baseline ANC levels near the lower limit of laboratory normal. Commonly occurring adverse events besides thrombocytopenia, anemia and neutropenia include bruising, urinary tract infection, hypercholesterolemia or hypertriglyceridemia, dizziness, headache, weight gain and abnormal liver function tests. The above events could increase the risk of infection, including pneumonia and bronchitis, possibility of developing anemia, bleeding, fatigue, and/or shortness of breath. Common toxicities in patients (affecting between 1 and 10 in every 100 patients) with myelofibrosis include herpes zoster, flatulence, constipation and hypertension which may also be the cause of dizziness and headache. Tuberculosis has been infrequently reported in patients receiving ruxolitinib to treat myelofibrosis (<1/100 patients). The symptoms of tuberculosis include chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. There may be risks associated with rapid discontinuation of ruxolitinib. Patients with myelofibrosis, particularly those who have stopped taking ruxolitinib suddenly, have reported symptoms that are associated with inflammation, including anxiety, insomnia or weakness, and recurrence of the signs and symptoms of myelofibrosis.

The effect of ruxolitinib on viral replication in patients with chronic hepatitis B virus is unknown. A rare disease called progressive multifocal leuko-encephalopathy (PML), has been reported in one patient treated with ruxolitinib. It is important to note that PML and infections

[redacted]

are complications associated with MF that has been previously described in the absence of ruxolitib. Additionally, non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and a rare and aggressive type of skin cancer called Merkel Cell Carcinoma has been reported in patients who took ruxolitinib, it is unknown whether this was due to ruxolitinib treatment.

Ruxolitinib has previously demonstrated marked reductions in disease related spleen sizes and symptom improvements in patients with advanced MF. Although the inclusive population in the current study have relatively early disease with minimal or no splenomegaly or disease related symptoms, it is hypothesized that ruxolitinib would delay progression of underlying disease and therefore benefit patients by delaying the time to acquiring these bothersome disease related events. It is anticipated that ruxolitinib will also be associated with reductions in inflammatory cytokine levels.

In summary, while early institution of treatment in the studied population and the expectant duration of treatment may increase the likelihood of some adverse events, the lower dose of ruxolitinib used in the study, the relatively better general physical status of the patients at study entry and the anticipated benefit of maintaining this status over prolonged periods, is expected to confer participating patients with an overall therapeutic advantage with acceptable tolerability.

Please refer to the study-specific informed consent form for further information.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To evaluate the effect of ruxolitinib in delaying progression of MF from early disease to advanced disease	Progression free survival (PFS-1) from date of randomization until the occurrence of any of the criteria for disease progression (See Section 10.4.1 for details on criteria and required confirmation): ● Progressive splenomegaly ● Circulating peripheral blast counts > 10% ● Leukemic transformation ● Hb < 10g/dl with absolute decrease of at least 3 g/dl from baseline ● White blood cell (WBC) counts > 25 x 10^3/ µL ● MF-7 score ≥ 30 ● Death from any cause	Refer to Section 10.4.1
Secondary		Refer to Section 10.5
To evaluate time to disease progression of MF with or without ruxolitinib	Time to primary progression	
To evaluate the changes in spleen volume with or without ruxolitinib	Time to first progressive splenomegaly as determined by spleen volume (by MRI/CT) Change in spleen volume (by MRI/CT) from baseline	
To assess the changes in symptoms using MF-7, EuroQol-5D-5L (EQ-5D)	Time to first symptomatic progression as determined by MF-7 Quality-adjusted life years using EQ-5D Changes in symptoms using MF-7 and EQ-5D from baseline	
To assess the safety and tolerability of ruxolitinib	Monitoring the frequency, duration, and severity of adverse events including abnormalities in vital signs, laboratory parameters and ECG data	
To evaluate the effect of ruxolitinib on overall survival	Overall survival	
To assess the pharmacokinetics (PK) of ruxolitinib	Plasma ruxolitinib concentrations. Characterize PK by utilizing a Population PK approach	
To evaluate the efficacy of ruxolitinib post PFS-1	Progression free survival (PFS-2) assessed by 25% increase over new baseline of PFS-1 in any of the following (See Section 10.5.1 for details): ● Progressive splenomegaly ● 25 % increase in MF-7 score with absolute score ≥ 30	

[redacted]

Objective	Endpoint	Analysis
[redacted]		

4 Study design

4.1 Description of study design

This is a double blind, randomized placebo-controlled study of ruxolitinib in patients with HMR positive early MF (HMR+ EMF). The study consists of a screening period, Treatment Period 1 and Treatment Period 2.

Screening:

Patients will be pre-screened for the determination of HMR mutation status after obtaining the molecular pre-screening informed consent. Only patients who are centrally confirmed to be HMR+ will be eligible to enter the screening phase. Patients should be consented to the main study informed consent as soon as HMR positivity is confirmed (recommended within 28 days). Patients will be randomized in a 1:1 ratio to ruxolitinib or placebo on Day 1 following confirmation of eligibility, including confirmed bone marrow fibrosis grading during the 40 day screening period.

Treatment Period 1

Blinded study treatment will begin on Day 1 following randomization. Visits will be every 4 weeks up to Week 24 to monitor tolerability and efficacy with the study treatment. After Week 24, visits will be every 8 weeks until Week 48, and then every 12 weeks thereafter. Blinded study treatment will be administered until disease progression or patient discontinuation. A 30-day safety follow up visit will be done after the last dose of blinded study drug (except if entering Treatment Period 2). Patients who discontinue for reasons other than disease progression will enter the post treatment follow up. Patients will be followed for survival after end of Treatment Period 1 or post-treatment follow up every 3 months until the termination of study by the sponsor.

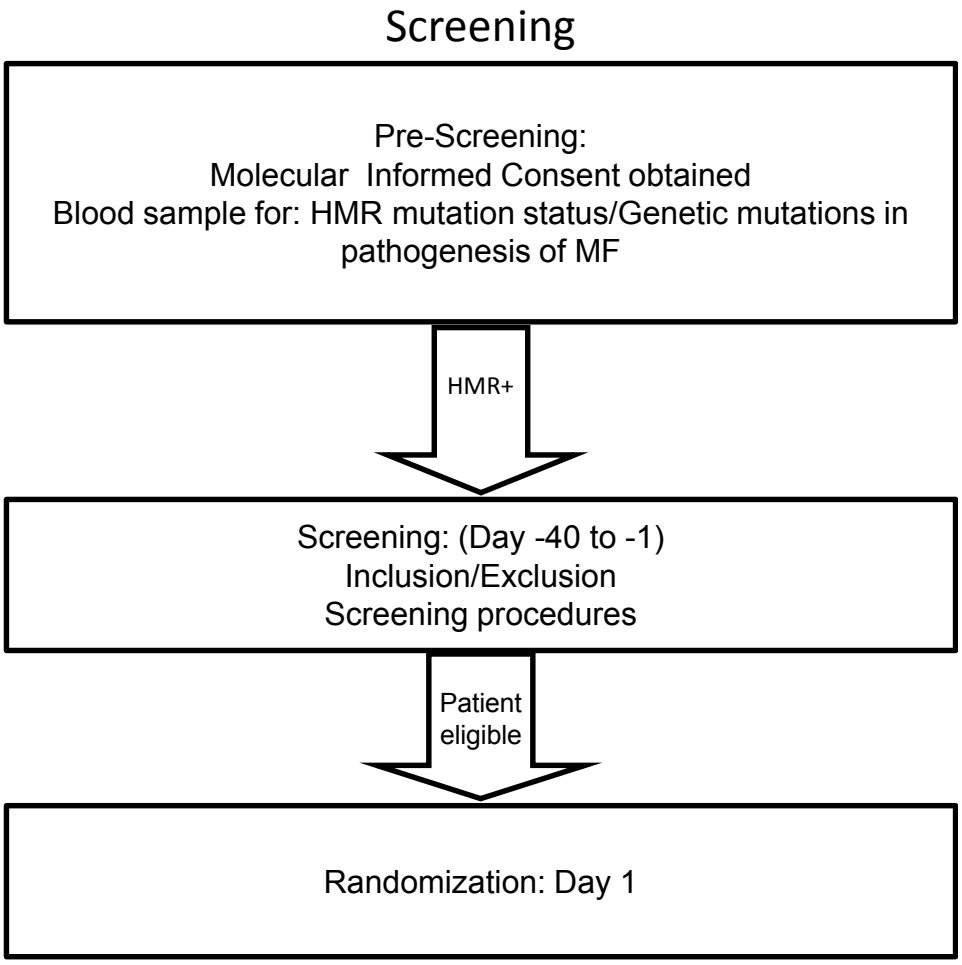
Treatment Period 2

Patients who progress due to splenomegaly or symptoms and are candidates for treatment with currently approved doses of ruxolitinib (as per investigators decision) will be treated with ruxolitinib at 5mg, 15mg or 20 mg BID, based on platelet counts at the time of treatment initiation (Section 6.1). These patients will continue on the same schedule of assessments as in 'Treatment Period 1' (Table 7-1). A 30-day safety follow up visit will be performed after the last dose of study drug. Patients will be followed for survival after end of Treatment Period 2 every 3 months until the termination of study by the sponsor (Figure 4-1).

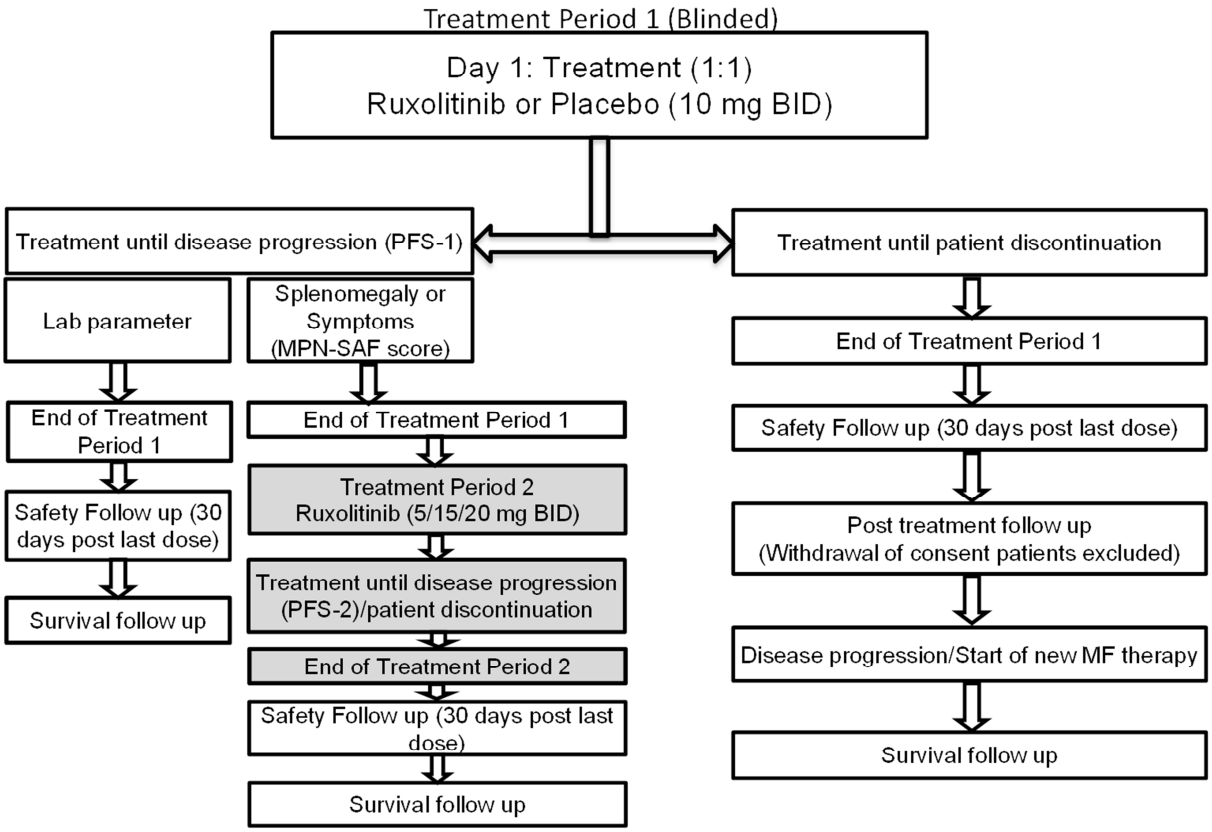
[redacted]

Figure 4-1 Schematic study design

A) Screening



B) Treatment Period



4.2 Timing of interim analyses and design adaptations

The study will have one interim analysis (IA) and one final analysis (FA). The intent of the interim analysis is to stop for futility. It is planned once at least 45 PFS-1 events are documented.

4.3 Definition of end of the study

The End of Study will occur after approximately 1 year after the 90th PFS-1 event on blinded study treatment has been confirmed & the primary analysis reported (estimated study duration 5.5 - 6 years). Following the primary analysis, if the primary objective is met and a need for longer term follow up of patients is assessed, the study may continue for an extended period of up to 5 years from LPFV. Patients will be discontinued at the end of study including any follow up for post treatment assessments and survival.

At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to patients who in the opinion of the Investigator are still deriving clinical benefit.

[redacted]

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis or by a regulatory authority based on the occurrence of any of the following.

- New side effects unknown in respect to their nature, severity, and duration or the unexpected incidence of known side effects
- Medical or ethical reasons that affect the continued performance of the study
- Further development of the study drug has been permanently discontinued due to safety reasons
- Data from interim analyses demonstrating futility (Refer to Section 4.2)
- Other reasons that are not known at this time

Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.5 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing institutional review boards (IRB) and/or ethics committees (EC) of the early termination of the trial.

5 Population

5.1 Patient population

Patient population will include approximately 320 male or female adults (age 18 or over) with a confirmed diagnosis of MF. Patients must exhibit minimally symptomatic early MF disease and must also be positive for the HMR mutational status. Patients will be pre-screened after obtaining a molecular screening consent for HMR status. The determination of HMR status will be performed at a Novartis accredited central laboratory with a targeted next generation sequencing assay. Those subjects harboring one or more mutations in the following genes; *ASXL1*, *EZH2*, *SRSF2* and *IDH1*/ *IDH2* will be determined HMR positive. Only patients with a centrally confirmed HMR positive mutational status should sign the main informed consent form and enter the main screening period (Section 7).

The investigator or designee must ensure that only patients who meet all of the following inclusion and none of the exclusion criteria at screening are randomized to receive treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria at screening:

Written informed consent must be obtained prior to any screening procedures.

1. Male or Female aged 18 or over.
2. Confirmed diagnosis of MF with bone marrow fibrosis of at least Grade 1 (Appendix 2); irrespective of JAK2 mutational status.

[redacted]

3. Patients with at least one mutation in one of the five HMR genes (ASXL1, EZH2, SRSF2 and IDH1/2).
4. Patients with non-palpable spleen or spleen palpable ≤ 5 cm from the left costal margin to the point of greatest splenic protrusion.
5. Patients with MF-7 score of ≤ 15, with each individual symptom score of ≤ 3.
6. Patients with a peripheral blood blast count percentage of < 1%.
7. Patients with Hemoglobin > 10g/dL.
8. Patients with platelet counts ≥ 75,000/μL.
9. Patients with Absolute neutrophil count (ANC) ≥ 1000/μL.
10. Patients with WBC ≤ 15 x 10^3/ μL.
11. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria at screening:

1. Patients with prior treatment with ruxolitinib or other JAK inhibitors.
2. Patients with known hypersensitivity to ruxolitinib or any of its excipients.
3. Patients with inadequate liver function defined by any of these:
   Total bilirubin ≥ 2.5 x ULN and subsequent determination of direct bilirubin ≥ 2.5 x ULN; Alanine aminotransferase (ALT) > 2.5 x ULN; Aspartate aminotransferase (AST) > 2.5 x ULN.
4. Patients with severely impaired renal function defined by:
   Serum creatinine > 2 mg/dL.
5. Patients with active bacterial, fungal, parasitic, or viral infection which requires therapy.
6. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of ruxolitinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
7. Known history of human immunodeficiency virus (HIV) infection or other immunodeficiency syndromes such as X-linked agammaglobulinemia and common variable immune deficiency.
8. Active hepatitis A, B or C infection, which requires treatment.
9. History of progressive multifocal leuko-encephalopathy (PML).
10. History or current diagnosis of uncontrolled or significant cardiac disease, including any of the following:
    - Myocardial infarction within last 6 months
    - Uncontrolled congestive heart failure
    - Unstable angina within last 6 months
    - Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker)

[redacted]

11. Significant concurrent, uncontrolled medical condition, which in the investigator's opinion would jeopardize the safety of the patient or compliance with the protocol.
12. Patients being treated concurrently with a strong (potent) systemic inhibitor or inducer of CYP3A4 (Appendix 1) at the time of Screening.
13. Patients under ongoing treatment with another investigational medication or having been treated with an investigational medication within 30 days or 5 half-lives (whichever is longer) prior to the first dose of study treatment.
14. Patients with a history of malignancy in the past 3 years, except for well-controlled early stage squamous or basal cell carcinoma in situ.
15. Patients eligible for stem cell transplantation.
16. Pregnant or nursing (lactating) women.
17. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception throughout the study duration inclusive of 30 day safety follow up. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before screening. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject.
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before screening.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
18. Subjects who are unable to comprehend or are unwilling to sign an informed consent form (ICF).

[redacted]

6 Treatment

6.1 Study treatment

Treatment Period1:

The study treatment will consist of INC424 (ruxolitinib) or matching placebo administered in a blinded manner following randomization of the patient on study Day 1.

Treatment Period 2:

INC424 (ruxolitinib) administered as per Table 6-1.

Table 6-1 Starting Doses of INC424 based on platelet counts (Treatment Period 2)

INC424	Platelet count (x 10^9/L)
5 mg BID	50 – <100
15 mg BID	100 – 200
20 mg BID	>200

6.1.1 Dosing regimen

Table 6-2 Dose and treatment schedule

Treatment Period 1 (INC424/Placebo - Blinded)

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
INC424/ Placebo	Tablet for oral use	10 mg BID (2 tablets of INC424 5mg/placebo BID)	Daily

Study treatment will be administered orally twice per day at a dose of 10 mg BID, given as 2 tablets of INC424 5mg / placebo (Table 6-2). Study treatment should be taken orally twice daily, approximately 12 hours apart (morning and night) without regards to food. Study treatment will be self-administered by the patient in an outpatient setting, and each investigator should instruct the patient to take the study drug as per protocol. All dosages taken by the patient must be recorded on the Dosage Administration Record case report form (CRF).

Patients should be instructed not to take study treatment at Week 12, Week 24 and Week 48 visit (and every 12 weeks thereafter) on the day of the scheduled pre-dose blood collection (Section 7). Dosing will be administered post blood collection at these visits.

[redacted]

Treatment Period 2 (INC424)

Once the patient progresses in Treatment Period 1 by splenomegaly or symptoms, the patient will start treatment with INC424 (ruxolitinib) 5/15/20 mg BID based on platelet count as per approved label (Table 6-1 and Table 6-3).

Table 6-3 Dose and treatment schedule

Treatment Period 2 (INC424)

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
INC424	Tablet for oral use	5/15/20 mg BID	Daily

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

Refer to Section 6.3 on dose modifications and follow up for toxicities for guidelines for continuation of treatment.

6.1.5 Treatment duration

Patient may continue treatment with the study drug until patient experiences unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or patient.

6.2 Dose escalation guidelines

Not applicable.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

6.3.1.1 Dose modification for hematologic toxicity

Treatment Period 1

Dose reductions or interruptions for hematological changes are permitted in order to allow the patient to continue on the study treatment. The maximum allowed doses for different ranges of cytopenia is described in Table 6-4. The objective of the dose adjustment rules is to optimize treatment response for each individual patient while avoiding significant cytopenia. Dosing may be restarted or increased following recovery of the hematologic parameter(s) to acceptable levels. Any patient requiring dose interruption continuously for more than 4 weeks

[redacted]

due to decreases in ANC or platelet (PLT) counts must be permanently discontinued from treatment. Hb levels decreasing below 8g/dL with an absolute drop of 3g/dL from baseline, will constitute a marker of progressive MF disease, if Hb levels fail to recover ≥ 8g/dL following treatment interruption for two consecutive weeks. Such patients must permanently discontinue study treatment.

Table 6-4 Dose reductions and interruptions due to hematological changes – Treatment Period 1

Current Hb (g/dL)	**Maximum allowable dose**
< 8	Interrupt dosing (HOLD)
8 to < 10	Reduce total daily dose to 5 mg BID
Current PLT (x 10^9/L)	
< 50	Interrupt dosing (HOLD)
50 to < 75	Reduce total daily dose to 5 mg BID
Current ANC (x 10^9/L)	
< 0.5	Interrupt dosing (HOLD)
0.5 to < 0.75	Reduce total daily dose to 5 mg BID

All dose changes must be recorded on the Dosage Administration Record CRF.

Patients whose dose has been interrupted for more than 4 weeks for any reason are recommended to be permanently discontinued from study treatment.

Treatment Period 2

Dose reductions and interruptions for ruxolitinib treatment during 'Treatment Period 2' can be performed in accordance with the local label requirements. In countries where ruxolitinib is not currently approved, treatment should be discontinued for platelet counts less than 50 x 10^9/L or absolute neutrophil counts less than 0.5 x 10^9/L. After recovery of blood counts above these levels, dosing may be re-started at 5 mg twice daily and gradually increased based on careful monitoring of complete blood cell count, including a white blood cell count differential.

6.3.1.2 Dose modification for non-hematological toxicity (Treatment Period 1 and 2)

Study drug MUST be permanently discontinued upon the occurrence of a clinically significant Grade 3 or Grade 4 laboratory or non-laboratory abnormality attributed to ruxolitinib if it fails to resolve to Grade 2 or better within 8 weeks or if a lower re-start dose or administration schedule is either not available or likely to be clinically ineffective. Specific recommendations that are to be followed in the event of abnormal liver function tests are provided in Table 6-5.

[redacted]

Table 6-5 Dose modifications for abnormal liver function tests

Isolated Elevation of Total Bilirubin	
> ULN – 1.5 x ULN	Maintain dose level
>1.5x baseline AND > 1.5 - 3.0 x ULN	Omit dose with weekly monitoring of LFTs[a], or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline levels - If resolved in ≤ 14 days, then maintain dose level - If resolved in > 14 days, then ↓ 1 dose level[d]
> 3.0 - 10.0 x ULN	Omit dose with weekly monitoring of LFTs[a], or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline levels - If resolved in ≤ 14 days, then ↓ 1 dose level[d] - If resolved > 14 days, discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline levels or have remained stable over 4 weeks.
> 10.0 x ULN	Discontinue patient from study drug treatment. The patient should be monitored weekly (including LFTs[a]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline levels or have remained stable over 4 weeks.

[redacted]

Isolated AST or ALT elevation	
> ULN - 3.0 x ULN	Maintain dose level
> 3.0 - 5.0 x ULN	Maintain dose level. Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN
> 5.0 - 10.0 x ULN ● For patients with baseline value ≤ 3.0 x ULN	Omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN Then - If resolved in ≤ 14 days, maintain dose level - If resolved in > 14 days, ↓ 1 dose level
● For patients with baseline value > 3.0 -5.0 x ULN	Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b], weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 x ULN
> 10.0 - 20.0 x ULN	Omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ baseline. Then↓ 1 dose level.
> 20.0 x ULN	Discontinue patient from study drug treatment AND Repeat LFTs[a] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[a] weekly, or more frequently if clinically indicated, until resolved to baseline levels or have remained stable over 4 weeks.

Combined[b] elevations of AST or ALT and total bilirubin	
For patients with normal baseline ALT or AST or total bilirubin value: AST or ALT >3.0xULN combined with total bilirubin >2.0 x ULN without evidence of cholestasis[c] OR [AST or ALT>2x baseline AND > 3.0 xULN] OR [AST or ALT > 8.0 xULN], whichever is lower, combined with [total bilirubin >2x baseline AND >2.0 xULN without evidence of cholestasis[c]	Permanently discontinue patient from study drug treatment; AND Repeat LFTs[a] as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[a]), or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or have remained stable over 4 weeks. Refer to Section 6.3.2.1 for additional follow-up evaluations as applicable.
a. Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.) b. "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction c. "Cholestasis" defined as: ALP elevation (>2xULN and R value <2) in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis Note : The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury d. Total daily dose 10 mg (5 mg BID) lower than the previous dose	

[redacted]

6.3.1.3 Optional dose tapering strategy in the event of study treatment discontinuation

Following interruption or discontinuation of ruxolitinib, symptoms of myelofibrosis may return over a period of approximately one week. There have been cases of patients discontinuing ruxolitinib who sustained more severe events, particularly in the presence of acute intercurrent illness. It has not been established whether abrupt discontinuation of ruxolitinib contributed to these events. Unless abrupt discontinuation is required, gradual tapering of the study treatment dose may be considered, although the utility of the tapering is unproven.

6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of study treatment.

6.3.2.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT or AST or TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as: ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury)

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed

history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
- A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
- Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g., biliary tract) may be warranted.
- Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
- Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria as well as specific dose modification and stopping rules are included in this protocol. Refer to preclinical toxicity and/or clinical data found in the [Investigator's Brochure].

6.4 Concomitant medications

All concomitant medications and treatments must be recorded on the appropriate eCRF. Any prior medication received up to 30 days prior to the first dose of study drug will be recorded in the CRF. Any prior anti-neoplastic medications used to treat hematological disease will also be recorded.

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without consultation with the investigator.

6.4.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies CRF.

[redacted]

6.4.2 Permitted concomitant therapy requiring caution and/or action

The following medications have restrictions on use, dose, or require changes to the way in which study treatment is administered during the study:

- Systemic corticosteroid doses greater than the equivalent of 10 mg prednisolone per day are prohibited at any time during the study until treatment discontinuation.
- Inducers or inhibitors of the metabolizing enzyme CYP3A4 (Appendix 1):
  - When concomitant administration of a strong (potent) systemic inhibitor of CYP3A4 metabolizing enzymes or dual CYP2C9/CYP3A4 inhibitors (see Appendix 1) is required for patient management, the dose of study treatment must be reduced by approximately 50% to be administered twice daily by decreasing the twice daily dose or by decreasing the frequency of dosing to the corresponding once daily dose when twice daily dosing is not practical.

    Note: No dose adjustment of study treatment is needed for use with topical ketoconazole.

    Note: More frequent monitoring of hematology parameters and clinical signs and symptoms of ruxolitinib related adverse reactions is recommended upon initiation of a strong (potent) CYP3A4 inhibitor.
  - No dose adjustment will be made when moderate CYP3A4 inducers (See Appendix 1) are co-administered with study treatment.
- Granulocyte growth factors are not allowed while study treatment is being administered but may be used for severe neutropenia at the Investigator's discretion while study medication is being withheld.

6.4.3 Prohibited concomitant therapy

The following therapies are prohibited at any time during the study until treatment discontinuation:

- Concomitant use of another JAK inhibitor.
- Any investigational medication (other than study treatment) that is not approved for any indication. Use of such medications within 30 days or 5 half-lives, whichever is longer, prior to the first dose of study treatment and until treatment discontinuation is prohibited.
- Any use of known drugs treating the investigated underlying disease is not permitted at any time during the study until treatment discontinuation.
- Use of strong (potent) systemic CYP3A4 inducers is prohibited (See Appendix 1).
- Aspirin in doses exceeding 150 mg per day is prohibited unless medically indicated.
- Stem cell transplantation is prohibited.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for molecular pre-screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No.

[redacted]

consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

At molecular pre-screening, the patient will be assigned a subject number (as assigned by Novartis to the investigative site). Once the subject enters the screening phase, the investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized the reason will be entered into the Screening Disposition page and indicated in the Interactive Response Technology (IRT) system.

6.5.2 Treatment assignment or randomization

Treatment Period 1

Patients will be assigned to one of the *"2"* treatment arms (Section 4.1 and Section 6.1) in a ratio of 1:1 (ruxolitinib or placebo).

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

Treatment Period 2

Patients entering Treatment Period 2 will be assigned to receive ruxolitinib by the IRT. Sites must enter all required information including dosage (5/15/20 mg) in the IRT to ensure ruxolitinib medication assignment.

6.5.3 Treatment blinding

This is a double-blind study in Treatment Period 1. Patients, investigator, site personnel, and data analysts will remain blinded to the identity of the treatment administered in Treatment Period 1 from the time of randomization until database lock. There will be no unblinding of Treatment Period 1 even as patients enter Treatment Period 2. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else

involved in the study. This information will not be accessible with the following exceptions: bio analyst and pharmacokineticist to avoid the unnecessary analysis of placebo samples, independent biostatistician who will perform the interim analysis. The identity of the treatments will be concealed by the use of study treatments that are all identical in packaging, labeling, schedule of administration, appearance.

Unblinding will only occur in the case of patient emergencies (Section 8.3), at the time of the interim analysis (see Section 10.7), by designated personnel for a data monitoring committee (DMC) (Section 8.6), for regulatory reporting purposes and at the conclusion of the study.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.6.1 Study drug packaging and labeling

Treatment Period 1

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label. Responsible site personnel will identify the study treatment package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the medication number but no information about the patient.

Treatment Period 2

The study medication will have the same labeling and dispensing procedure as described for Treatment Period 1. The medication will be assigned appropriately by the IRT and dispensed to the patient.

Table 6-6 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
INC424 or placebo	Tablets in HDPE bottles	INC424/placebo (BID)

[redacted]

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the **study treatment** should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

No CRF will be used as a source document.

(S) is defined as 'source' and (D) as 'data based'.

Assessments noted as (D) in the category column will remain in the clinical database, except the following which will be part of the central database – 1) Eligibility checklist in IRT and 2) contact IRT system.

[redacted]

Table 7-1 Visit evaluation schedule

A) Treatment Period 1 (Blinded)

Visit Name	Category	Protocol Section	Molecular Pre-screening	Screening	Treatment Period 1 (Blinded)											End of treatment (EOT)	Progressive disease (PD) confirmation	Safety Follow up 30 days after last dose	Post treatment follow up (See Section 7.1.7)	Survival Follow up (Every 3 months)
					Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 36 (MRI / CT)	Week 40	Week 48+ (every 12 weeks until EOT)					
Day				-40 to -1	1	28	56	84	112	140	168	224	252	280	336+					
Visit window (Study day)						+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7					
Obtain Molecular pre-screening ICF	D	7.1.1	x																	
Blood collection (Genetic mutations impacting pathogenesis of MF including HMR)	D	7.2.4	x								x				x (every 24 weeks)	x				
Obtain Informed Consent	D	7.1.2		x (centrally confirmed HMR+ status)																

[redacted]

Visit Name	Category	Protocol Section	Molecular Pre-screening	Screening	Treatment Period 1 (Blinded)											End of treatment (EOT)	Progressive disease (PD) confirmation	Safety Follow up 30 days after last dose	Post treatment follow up (See Section 7.1.7)	Survival Follow up (Every 3 months)
					Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 36 (MRI / CT)	Week 40	Week 48+ (every 12 weeks until EOT)					
Day				**-40 to -1**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**224**	**252**	**280**	**336+**					
Visit window (Study day)						**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**					
Inclusion/Exclusion	D	5		x																
Eligibility checklist in IRT	D	7.1.2.1			x															
Patient history		7.1.2																		
Demography	D			x																
Medical History	D			x																
Disease diagnosis	D			x																
Prior Anti-neoplastic therapy medication (Hematologic disease)	D			x																
Prior/concomitant medications	D			x	x (at every visit)															

[redacted]

Visit Name	Category	Protocol Section	Molecular Pre-screening	Screening	Treatment Period 1 (Blinded)											End of treatment (EOT)	Progressive disease (PD) confirmation	Safety Follow up 30 days after last dose	Post treatment follow up (See Section 7.1.7)	Survival Follow up (Every 3 months)
					Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 36 (MRI / CT)	Week 40	Week 48+ (every 12 weeks until EOT)					
Day				-40 to -1	1	28	56	84	112	140	168	224	252	280	336+					
Visit window (Study day)						+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7					
Physical examination	S	7.2.2.1		x	x	x	x	x	x	x	x	x		x	x	x				
Performance status	D	7.2.2.4		x	x	x	x	x	x	x	x	x		x	x	x				
Height	D	7.2.2.3		x																
Weight	D	7.2.2.3		x	x	x	x	x	x	x	x	x		x	x	x				
Vital signs	D	7.2.2.2		x	x	x	x	x	x	x	x	x		x	x	x				
Spleen measurement (length)	D	7.2.2.1		x	x	x	x	x	x	x	x	x		x	x	x				
Laboratory assessments		7.2.2.5																		
Hematology	D	7.2.2.5.1		x	x	x	x	x	x	x	x	x		x	x	x	x (Refer to PD guidance)		x	
Chemistry	D	7.2.2.5.2		x	x	x	x	x	x	x	x	x		x	x	x				

[redacted]

Visit Name	Category	Protocol Section	Molecular Pre-screening	Screening	Treatment Period 1 (Blinded)											End of treatment (EOT)	Progressive disease (PD) confirmation	Safety Follow up 30 days after last dose	Post treatment follow up (See Section 7.1.7)	Survival Follow up (Every 3 months)
					Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 36 (MRI / CT)	Week 40	Week 48+ (every 12 weeks until EOT)					
Day				**-40 to -1**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**224**	**252**	**280**	**336+**					
Visit window (Study day)						**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**					
Coagulation	D	7.2.2.5.4		x	x (To be performed as clinically indicated)											x				
Urinalysis	D	7.2.2.5.3		x												x				
Pregnancy test	D	7.2.2.5.5		x	x	x	x	x	x	x	x	x		x	x	x				
Hepatitis test	D	7.2.2.5		x																
Imaging		7.2.1																		
ECG	D	7.2.2.6.1		x	x (Every 48 weeks)											x				
MRI/CT	D	7.2.1		x (-7 to -1)				x			x		x		x	x			x	
Safety		7.2.2																		
Adverse events	D			x	x (at every visit)															

[redacted]

Visit Name	Category	Protocol Section	Molecular Pre-screening	Screening	Treatment Period 1 (Blinded)											End of treatment (EOT)	Progressive disease (PD) confirmation	Safety Follow up 30 days after last dose	Post treatment follow up (See Section 7.1.7)	Survival Follow up (Every 3 months)
					Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 36 (MRI / CT)	Week 40	Week 48+ (every 12 weeks until EOT)					
Day				-40 to -1	1	28	56	84	112	140	168	224	252	280	336+					
Visit window (Study day)						+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7					
[redacted]																				
Bone Marrow biopsy and aspirate	D	7.2.1		x	x (every 2 years)											x			x	

[redacted]

Visit Name	Category	Protocol Section	Molecular Pre-screening	Screening	Treatment Period 1 (Blinded)											End of treatment (EOT)	Progressive disease (PD) confirmation	Safety Follow up 30 days after last dose	Post treatment follow up (See Section 7.1.7)	Survival Follow up (Every 3 months)
					Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 36 (MRI / CT)	Week 40	Week 48+ (every 12 weeks until EOT)					
Day				**-40 to -1**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**224**	**252**	**280**	**336+**					
Visit window (Study day)						**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**					
Patient reported Outcomes (PRO)		7.2.5																		
MF-7	D			x	x	x	x	x	x	x	x	x		x	x	x	x (Refer to PD guidance)	x	x	
EQ-5D	D			x	x	x	x	x	x	x	x	x		x	x	x		x		
[redacted]																				
Study Drug administration	D	6.1			x	x	x	x	x	x	x	x		x	x					
PK sampling		7.2.3						x			x									
Contact IRT system	D			x	x (at every dispensing visit)											x	x			
Survival	D	7.1.7																		x

[redacted]

Visit Name	Category	Protocol Section	Molecular Pre-screening	Screening	Treatment Period 1 (Blinded)											End of treatment (EOT)	Progressive disease (PD) confirmation	Safety Follow up 30 days after last dose	Post treatment follow up (See Section 7.1.7)	Survival Follow up (Every 3 months)
					Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 36 (MRI / CT)	Week 40	Week 48+ (every 12 weeks until EOT)					
Day				-40 to -1	1	28	56	84	112	140	168	224	252	280	336+					
Visit window (Study day)						+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7					
Leukemic transformation	D	7.1.7																		x
Anti-neoplastic therapy after discontinuation of study treatment	D	7.1.7																x	x	x

[redacted]

B) Treatment Period 2 (Ruxolitinib) for patients progressing due to splenomegaly or symptoms (MF-7 score)

Visit Name	Category	Protocol Section	Treatment Period 2 (Ruxolitinib)											End of treatment (EOT)	Progressive disease (PD) confirmation	Safety Follow up 30 days after last dose	Survival Follow up (Every 3 months)
			First dose – Ruxolitinib	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 36 (MRI / CT)	Week 40	Week 48+ (every 12 weeks until EOT)				
Day				28	56	84	112	140	168	224	252	280	336+				
Visit window (Study day)				+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7				
Prior/concomitant medications	D		x (at every visit)														
Physical examination	S	7.2.2.1		x	x	x	x	x	x	x		x	x	x			
Performance status	D	7.2.2.4		x	x	x	x	x	x	x		x	x	x			
Weight	D	7.2.2.3		x	x	x	x	x	x	x		x	x	x			
Vital signs	D	7.2.2.2		x	x	x	x	x	x	x		x	x	x			
Spleen measurement (length)	D	7.2.2.1		x	x	x	x	x	x	x		x	x	x			

[redacted]

Visit Name	Category	Protocol Section	Treatment Period 2 (Ruxolitinib)											End of treatment (EOT)	Progressive disease (PD) confirmation	Safety Follow up 30 days after last dose	Survival Follow up (Every 3 months)
			First dose – Ruxolitinib	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 36 (MRI / CT)	Week 40	Week 48+ (every 12 weeks until EOT)				
Day				28	56	84	112	140	168	224	252	280	336+				
Visit window (Study day)				+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7				
Laboratory assessments		7.2.2.5															
Hematology	D	7.2.2.5.1		x	x	x	x	x	x	x		x	x	x			
Chemistry	D	7.2.2.5.2		x	x	x	x	x	x	x		x	x	x			
Coagulation	D	7.2.2.5.4	(To be performed as clinically indicated)											x			
Urinalysis	D	7.2.2.5.3												x			
Pregnancy test	D	7.2.2.5.5		x	x	x	x	x	x	x		x	x	x			
Imaging		7.2.1															
ECG	D	7.2.2.6.1		x (Every 48 weeks)									x				
MRI/CT	D	7.2.1				x			x		x		x	x			
Safety		7.2.2															
Adverse events	D		x (at every visit)														

[redacted]

Visit Name	Category	Protocol Section	Treatment Period 2 (Ruxolitinib)											End of treatment (EOT)	Progressive disease (PD) confirmation	Safety Follow up 30 days after last dose	Survival Follow up (Every 3 months)
			First dose – Ruxolitinib	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 36 (MRI / CT)	Week 40	Week 48+ (every 12 weeks until EOT)				
Day				**28**	**56**	**84**	**112**	**140**	**168**	**224**	**252**	**280**	**336+**				
Visit window (Study day)				**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-7**	**+/-7**	**+/-7**	**+/-7**	**+/-7**				
Bone Marrow biopsy and aspirate	D	7.2.1	x (every 2 years)											x			
Patient reported Outcomes (PRO)		7.2.5															
MF-7	D			x	x	x	x	x	x	x		x	x	x	x (Refer to PD guidance)	x	
EQ-5D	D			x	x	x	x	x	x	x		x	x	x		x	
[redacted]																	
Study Drug administration	D	6.1	x	x	x	x	x	x	x	x		x	x				
Contact IRT system	D		x (at every dispensing visit)											x	x		

[redacted]

Visit Name	Category	Protocol Section	Treatment Period 2 (Ruxolitinib)											End of treatment (EOT)	Progressive disease (PD) confirmation	Safety Follow up 30 days after last dose	Survival Follow up (Every 3 months)
			First dose – Ruxolitinib	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 36 (MRI / CT)	Week 40	Week 48+ (every 12 weeks until EOT)				
Day				28	56	84	112	140	168	224	252	280	336+				
Visit window (Study day)				+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7				
Survival	D	7.1.7															x
Leukemic transformation	D	7.1.7															x
Anti-neoplastic therapy after discontinuation	D	7.1.7														x	x

[redacted]

7.1.1 Molecular pre-screening

Molecular pre-screening will be done for all patients after the molecular informed consent form is obtained. Subject will sign the molecular pre-screening informed consent form and will have blood sample tested for genetic mutations impacting pathogenesis of MF including HMR by a Novartis accredited central laboratory. Only subjects who show the presence of any of the HMR mutations will be eligible to enter screening and sign the main informed consent form. Molecular pre-screening is mandatory for all patients to enter into the screening phase.

7.1.2 Screening

Patients will be consented to the main study informed consent after obtaining a central confirmation of HMR positivity. There will be a 40 day screening period (Day -40 to –Day -1). Screening procedures are outlined in the visit evaluation schedule (Table 7-1 [A]).

Upon completion of all routine screening procedures and all other eligibility criteria including patient history, laboratory assessments, and symptom score assessments should be performed.

A bone marrow biopsy should be performed, unless adequate archival tissue is available for the patient from a procedure performed within the last 6 months prior to randomization. Biopsy specimen and marrow aspirate must be sent to a Novartis designated laboratory for central analysis. Upon receipt of the bone marrow biopsy grade confirming patient eligibility, the investigator must perform the MRI (or CT for applicable patients) scan and send to the central imaging laboratory for assessment the same day as the scan. MRI/CT should be performed within 7 days prior to randomization.

A patient who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated. These tests may be repeated as soon as the investigator believes the retest result is likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within 40 days of the original screening visit date. In this case, the subject will not be required to sign another ICF, and the original patient ID number assigned by the investigator will be used. In the event that the laboratory test(s) cannot be performed within 40 days of the original screening visit, or the retest(s) do not meet the entrance criteria or the patient's medical condition has change significantly during the screening phase so that the inclusion/exclusion criteria are no longer met, the patient is considered a screen failure.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed. The subject number will remain unchanged and patient will be entered in the IRT as re-screen. All required screening activities must be performed when the patient is rescreened for participation in the study. An individual patient may only be rescreened once for the study.

[redacted]

7.1.2.1 Eligibility screening

Patients must meet all inclusion and exclusion criteria at screening in order to be eligible to proceed to the Treatment Period of the study.

Investigative staff will capture patient eligibility within source documents maintained at the site. Additionally the sites will enter patient information into the eCRF. Eligibility information in source documents will be made available during planned interim monitoring visits and compared against the clinical database for accuracy. The site will also be asked to confirm eligibility with the IRT system. Following registering in IRT for screening, patient eligibility data will be verified once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual. Only when eligibility data has been confirmed with the IRT system will the IRT assign study treatment.

7.1.2.2 Information to be collected on screening failures

Subject who signed an Informed Consent Form but failed to be randomized for any reason will be considered a screen failure. Both subjects who signed a molecular pre-screening ICF but are considered ineligible after molecular pre-screening, as well as subjects who are found not eligible after signing the main study consent will be considered as screening failures, and data will be handled in the same manner.

The reason for not being started on treatment for molecular pre-screening failure or screening failure will be entered on the Screening Phase Disposition Page.

The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure subjects. Additionally, data for genetic mutations affecting MF pathogenesis including HMR will be available. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure will be reported.

If the patient in the screening phase fails to be randomized, the IRT should be notified.

7.1.2.3 Patient demographics and other baseline characteristics

Patients will have the following assessments performed at screening:

- Review of medical history, prior anti-neoplastic therapy related to hematologic disease, prior concomitant medications and adverse events
- Disease diagnosis confirmed by a Novartis designated laboratory (Section 7.1.2) using a bone marrow biopsy and aspirate
- Physical examination including height, weight, performance status, vital signs and measurement of spleen length by palpation (Section 7.2.2)
- Laboratory assessments – Hematology, serum chemistry, coagulation, urinalysis, pregnancy test (if applicable) and hepatitis test (Section 7.2.2)
- Patient reported outcomes – MF-7, EQ-5D and [redacted] questionnaires

[redacted]

- Electrocardiogram (ECG)
- MRI/CT of the spleen to determine spleen volume by central imaging laboratory

The investigator must confirm all the inclusion and exclusion criteria prior to contacting IRT for randomization of the patient. Once the patient's eligibility is confirmed, the patient must have baseline assessments performed on Day 1 prior to randomization and treatment initiation (Table 7-1).

7.1.3 Run-in period

Not applicable.

7.1.4 Treatment Period

Treatment Period 1

Blinded study treatment will be initiated on Day 1 after randomization and treatment assignment by IRT system. Day 1 is defined as the first day of study treatment. After day 1, visits will occur at the following frequency as specified in Table 7-1.

- Every 4 weeks until week 24 (+/- 3 days)
- Every 8 weeks until week 48 (+/- 7 days)
  Note: Week 36 visit is required only for MRI/CT of the spleen.
- Every 12 weeks until the end of treatment (+/- 7 days)

Blinded treatment will be administered until disease progression or patient discontinuation.

Treatment Period 2

Patients progressing due to splenomegaly or symptom (MF-7 score) in Treatment Period 1 will enter the ruxolitinib Treatment Period 2. All patients are required to have an End of Treatment Period 1 assessment prior to entering Treatment Period 2. All End of Treatment Period 1 assessments should be performed within 2 weeks prior to the first dose of ruxolitinib in Treatment Period 2. The End of treatment bone marrow biopsy and MRI/CT assessments should follow the schedule as per Section 7.2.1.1. The schedule of assessments for patients entering Treatment Period 2 will continue from when the patient discontinued in Treatment Period 1 (Table 7-1 [B]).

7.1.5 Discontinuation of Study Treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under the following circumstances:

[redacted]

- Disease progression in Treatment Period 1 (except if entering Treatment Period 2) (Refer to Section 10.4.1)
- Disease Progression in Treatment Period 2 (Refer to Section 10.5.1)
- Dose modifications to study treatment leading to discontinuation (Section 6.3)
- Protocol deviations that results in a significant risk to the patient's safety
- Pregnancy
- New therapy for study indication

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason. Refer to Section 8.3 on emergency unblinding.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for assessments as specified at the end of treatment visit in Table 7-1. The patients will then undergo safety follow up visit and then enter the follow-up period (Section 7.1.7). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.8. The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

Patients who permanently discontinue study treatment in Treatment Period 1 due to reasons other than progressive disease must continue to return for post-treatment follow up assessments as described in Section 7.1.7 until progressive disease is evident or a new therapy for MF is commenced. Upon progressive disease or starting a new therapy the patients will be followed for survival (Section 7.1.7).

7.1.5.1 Replacement policy

Patients who discontinue prematurely will not be replaced on this study. Enrollment of new patients will be considered if the PFS event rate is not met based on statistical assumptions.

7.1.6 Withdrawal of Consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

[redacted]

7.1.7 Follow up for Safety Evaluations

All patients must have a follow-up visit for safety evaluations 30 days following the last dose of study drug based on discontinuation from Treatment Period 1 or 2. At this visit adverse events and anti-neoplastic therapies after treatment discontinuation will be reviewed and patient reported outcomes will be collected. Refer to Table 7-1 for a complete list of assessments at the 30 day safety follow up visit.

7.1.7.1 Survival Follow up

Patients who discontinue study treatment due to disease progression (as outlined below) will be followed for survival every 3 months:

- Disease progression in Treatment Period 1 (except if entering Treatment Period 2)
- Disease progression in Treatment Period 2

Patients will be contacted by the site for information on survival, leukemic transformation and anti-neoplastic therapy after treatment discontinuation (Table 7-1). Data collected should be entered in the appropriate CRF.

7.1.7.2 Post Treatment Follow Up Assessments

Patients who permanently discontinue study treatment in Treatment Period 1 due to reasons other than progressive disease must continue to return for hematological laboratory assessments, spleen volume assessments via MRI/CT and MF-7 assessments. Data for new MF therapy after treatment discontinuation will also be collected. The assessments in the post-treatment follow up phase should follow the same visit schedule as described in Table 7-1 until progressive disease is evident or a new anti-neoplastic therapy is commenced. Upon progressive disease or starting a new therapy the patients will enter the survival follow up period.

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

[redacted]

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Assessments for primary efficacy endpoint (progression free survival – PFS-1)

The criteria for disease progression (PFS-1) will be assessed for determination of the primary endpoint of progression free survival in accordance with Section 10.4.1. For patients meeting the progressive disease criteria the Investigator must review according to the guidance below, and confirm the relevant criterion. The data should be entered in the appropriate CRF and IRT notified.

Guidance for progressive disease criterion assessment:

- Earliest confirmed single disease progression criterion should be entered.
- If more than one criterion are confirmed on the same date, time or visit (+ 14 days from the date of first confirmed criterion); progressive disease should be assessed using the single criterion based on the hierarchy below:
  1. Death
  2. Leukemic transformation
  3. Splenomegaly
  4. Symptom (MF-7 score)
  5. Hematologic criteria. Note: In the case of more than one hematologic criteria, the investigator should assess the key contributing criterion to declare disease progression

The following assessments will be utilized to assess and confirm disease progression.

1. Spleen volume determination by MRI/CT:

Evaluation of progressive splenomegaly will be performed by regular assessments of spleen volumes via Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) where MRI is contraindicated to ensure an objective and unbiased assessment. MRI (or CT) of the spleen will be performed at screening (within 7 days prior to randomization), every 12 weeks and at the end of treatment (Table 7-1). An end of treatment MRI (or CT) assessment is only required for patients who discontinue treatment due to disease progression if a MRI (or CT) scan was not performed within 6 weeks of study treatment discontinuation. Patients who enter the post treatment follow up phase after study treatment discontinuation for reasons other than disease progression should have their assessments performed as per the visit schedule at the time of discontinuation.

A designated central imaging laboratory will be used to collect all imaging data; perform quality check and provide read-out for the study. The scans from an individual patient will be read by a central reader upon transfer from the site radiologist. Results from the central evaluations will be used for primary analyses.

MRI is the preferred method for obtaining spleen volume data. However, CT scans may be performed at the visits where MRI would be conducted if the patient is not a candidate for MRI (because of the presence of metal clips in the body, or because of claustrophobia, for

[redacted]

example), or if MRI is unavailable to the study site. CT scans will be similarly processed by a Central Laboratory. Procedure specific training for scanning and image capture will be provided by the vendor. NOTE: Generally, the same method (MRI or CT) should be used for all visits for a given patient unless a new contraindication to the use of MRI (e.g., pacemaker insertion) occurs. Please contact the sponsor if a modality change is required.

2. Laboratory assessments confirming disease progression (Hb decrease, WBC count and peripheral blood blast count):

Assessments involving specific laboratory parameters should be confirmed in accordance with Section 10.4.1 if they meet criteria for progressive disease. Description of laboratory assessments is outlined in Section 7.2.2.5.

3. Bone marrow biopsy and aspirate for leukemic transformation and [redacted]:

Bone marrow fibrosis will be measured in grades (see Appendix 2) from samples obtained for patients at screening, every 2 years and at the end of treatment. An end of treatment biopsy and aspirate is not required if a biopsy from a previous assessment is within 6 months of study treatment discontinuation.

A paraffin embedded core bone marrow biopsy block (1/2 of the core biopsy sample) and 3 unstained bone marrow aspirate slides are required to be sent to a Novartis designated central lab for central analysis for all patients. If per local SOP the paraffin embedded core bone marrow biopsy block sample cannot be sent to the central lab, six unstained slides of the bone marrow biopsy block may be sent. Please refer to the vendor manual for additional instructions.

A centrally confirmed grading of bone marrow fibrosis is required for patient eligibility (Section 7.1.2). The central lab will notify the site of results at the time of screening and when results meet the protocol definition of progressive disease criteria for leukemic transformation (Section 10.4.1). Results from the central evaluations will be used for primary [redacted] analyses. [redacted]

4. Symptom assessment using MF-7:

MF-7 symptom score assessment will be used to determine the primary endpoint in accordance with Section 10.4.1. Details regarding the use of patient reported outcomes and specific time points are outlined in Section 7.2.5.

7.2.1.2 Assessments for secondary efficacy endpoints

Assessments for secondary endpoints will be done in accordance with Section 10.5.1.

1. Time to primary progression, time to first progressive splenomegaly and time to first symptomatic progression:

Refer to Section 10.5.1 for details on time to progression for specific parameters.

2. Changes in spleen volume by MRI/CT:

Refer to Section 7.2.1.1 for detailed description of assessments.

3. Changes in symptoms using MF-7, EQ-5D, Quality adjusted life years:

Assessments for patient reported outcomes as detailed in Section 7.2.5 will be used to determine the secondary endpoints.

[redacted]

4. Overall survival:

Survival follow up will be done as per Table 7-1 for all patients after study treatment discontinuation. Detailed description is outlined in Section 7.1.7.

5. Progression free survival -2 (PFS-2)

The criteria for disease progression (PFS-2) will be assessed in accordance with Section 10.5.1. For patients meeting the progressive disease criteria the Investigator must review according to the guidance below, confirm the relevant criterion and enter data in the appropriate e CRF and notify IRT.

Guidance for progressive disease criterion assessment:

If more than one criterion are confirmed on the same date, time or visit (+ 14 days from the date of first confirmed criterion); progressive disease should be assessed using the single criterion based on the hierarchy below:

1. Splenomegaly
2. Symptom (MF-7 score)

The following assessments will be utilized to assess and confirm disease progression.

a. Spleen volume determination by MRI/CT:

Refer to Section 7.2.1.1 for detailed description of assessments.

b. Symptom assessment using MF-7:

MF-7 symptom score assessment will be used to determine the secondary endpoint in accordance with Section 10.5.1. Details regarding the use of patient reported outcomes and specific time points are outlined in Section 7.2.5.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, laboratory assessments, ECG, PROs as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A physical exam as per local standard of care will be performed at screening and all scheduled study visits up to the end of treatment (Table 7-1). It will include the examination of general appearance and vital signs (blood pressure [BP], respiratory rate, temperature and pulse). Spleen size will be assessed by palpation and measured in centimeters using a soft ruler, from the coastal margin to the point of greatest splenic protrusion. [redacted]

Significant findings that were present prior to the signing of informed consent and any ongoing conditions must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

[redacted]

7.2.2.2 Vital signs

Vital signs (blood pressure, pulse, body temperature, and respiratory rate) will be collected as outlined in the Visit Schedule in Table 7-1. Vital signs will be taken with the patient in the sitting position after 5 minutes of rest. Body temperature may be measured orally or via ear.

7.2.2.3 Height and weight

Height in centimeters (cm) will be measured only at screening. Body weight in kilograms (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured according to Table 7-1. The CRFs include the following units e.g., height in cm or in and weight in kg or lb. and therefore, data may be collected in the units they are measured in.

7.2.2.4 Performance status

The performance status will be assessed per the schedule in Table 7-1 and according to the ECOG performance status scale (Appendix 3)

7.2.2.5 Laboratory evaluations

Table 7-2 Central Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Mean corpuscular volume (MCV), Platelets, Red blood cells (RBC), White blood cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), Absolute neutrophil count [with bands]
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Calcium, Creatinine, Total Bilirubin*, Blood Urea Nitrogen (BUN) or Urea Additionally, specified parameters are required at the following visits: At screening only - Direct Bilirubin, Indirect Bilirubin At screening, every 24 weeks and EOT - Total Cholesterol, Low density lipoprotein (LDL), High density lipoprotein (HDL), Total Protein, Triglycerides
Urinalysis	Macroscopic Panel** (Color, Bilirubin, Blood, Glucose, pH, Protein, Specific Gravity)
Coagulation	Prothrombin time (PT) or International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Pregnancy test	At screening and EOT – Serum pregnancy test All other time points – Urine pregnancy test
Hepatitis test	Screening only - Hepatitis A virus antibody; Hepatitis B surface antigen, Hepatitis B surface antigen antibody, Hepatitis B core antibody, Hepatitis C virus antibody
*Direct and indirect bilirubin tests may be performed centrally at any visit if clinically indicated. **Any clinically significant findings will be followed with a microscopic evaluation centrally. A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the [Laboratory Manual].	

7.2.2.5.1 Hematology

Hematocrit, hemoglobin, MCH, MCHC, MCV, platelet count, RBC count, WBC count with differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils) and Absolute neutrophil count [with bands] will be measured at screening, all scheduled visits during treatment and end of treatment as noted in Table 7-1.

[redacted]

7.2.2.5.2 Clinical chemistry

Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Calcium, Creatinine, Total Bilirubin and BUN or Urea will be measured at screening, all scheduled visits during treatment and end of treatment as noted in Table 7-1. Direct and indirect bilirubin will be measured only at screening. These tests may however be performed centrally at any visit if clinically indicated. Total Cholesterol, LDL, HDL, Total Protein and Triglycerides will be measured at screening, every 24 weeks and end of treatment.

7.2.2.5.3 Urinalysis

Urinalysis will be performed using macroscopic evaluation of color, bilirubin, blood, glucose, pH, protein, specific gravity. Any significant findings on the macroscopic panel will be followed up with a microscopic evaluation.

7.2.2.5.4 Coagulation

PT, INR, and aPTT will be measured at screening, all scheduled study visits during treatment and end of treatment.

7.2.2.5.5 Pregnancy and assessments of fertility

All pre-menopausal female patients, who are not surgically sterile must undergo a serum pregnancy test at screening to confirm eligibility in the trial, and at end of treatment. The patient will have urine pregnancy tests performed at all other scheduled visits as noted in Table 7-1.

A positive urine pregnancy test requires immediate interruption of study drug until serum hCG is performed and found to be negative. If positive, the patient must be discontinued from the study.

If local requirements mandate more frequent pregnancy testing, applicable sites must adhere to these requirements even if scheduled visits are less frequent. For women of child bearing potential, home pregnancy test kits should be provided by the site for the duration of study. The outcome of the home urinary test should be available at the site as part of the source documentation. The site must instruct the patient to contact the investigator immediately in case of a positive test.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at screening, every 48 weeks and at the end of treatment.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened

[redacted]

clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

7.2.3 Pharmacokinetics

Pharmacokinetic assessment is required only in Treatment Period 1 (Refer to Table 7-1 [A]). To explore PK characteristics of HMR positive Early MF patients, a subset of at least 80 (40 ruxolitinib) patients are required to have a sampling scheme as described in Table 7-3. All early enrolling patients (referred to as 'Group 1' with an estimate of first 100 patients) must have one pre-dose on Week 12 (Day 84) and Week 24 (Day 168) and three (3) post dose PK samples collected on Week 24 (Day 168) for ruxolitinib concentration determination (Refer to Table 7-3). Once this requirement is fulfilled all sites will be notified. Subsequent patients (referred to as 'Group 2') will have a total of two (2) pre-dose samples on Week 12 (Day 84) and Week 24 (Day 168) per Table 7-4.

Whole blood per sampling time as outlined in Table 7-3 and Table 7-4 will be obtained by either direct venipuncture or via an indwelling cannula from a peripheral vein into a tube containing di-potassium ethylenediaminetetraacetic acid (EDTA). Immediately after collection the tube should be inverted several times to prevent clotting. Blood samples should be kept in an ice water bath at approximately 4°C until centrifugation. The tubes should be centrifuged within 30 minutes of collection at approximately 2000 x g at 4°C for 15 minutes to yield plasma. The plasma should be decanted and transferred into a polypropylene screw-cap tube, the tube capped, and then immediately placed in a freezer at ≤ -60°C until shipment to sponsor and/or designated central laboratory. Refer to the [Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

All sampling is relative to the ingestion of ruxolitinib. [redacted] The exact collection date and time of all samples must be documented on the PK blood collection CRF pages. The date and exact time of dosing, as well as the date and actual time of blood sampling must be recorded on the CRF.

[redacted]

Table 7-3 Pharmacokinetic blood collection log (Group 1)

Week	Day	Profile Day	Scheduled time-point	Dose reference ID		PK Sample No	Sample volume [mL]
Early enrolling subjects							
12	84	1	Pre-morning dose	1	101[a]	1	4
24	168	1	Pre-morning dose	2	201[a]	2	4
24	168	1	Post dose 0.5 h ± 15 min	2	-	3	4
24	168	1	Post dose 2.0 h ± 1h	2	-	4	4
24	168	1	Post dose 4-12 h (suggested 5 h ± 1 h)	2	-	5	4
Unscheduled Sample	---	---				1001+ series	(4)
Total Sample Volume							20 mL

For the PK trough samples the actual date and time of administration of the previous dose of study medication should also be recorded with appropriate Dose reference IDs as indicated in the above table
[a] The first Dose reference ID is for current dose, while the second Dose reference ID is for the last dose the subject received prior to the collection of the PK sample.

Table 7-4 Pharmacokinetic blood collection log (Group 2)

Week	Day	Profile Day	Scheduled time-point	Dose reference ID		PK Sample No	Sample volume [mL]
In all subjects							
12	84	1	Pre-morning dose	1	101[a]	1	4
24	168	1	Pre-morning dose	2	201[a]	2	4
Unscheduled Sample			---	---		1001+ series	(4)
Total Sample Volume							8 mL

For the PK trough samples the actual date and time of administration of the previous dose of study medication should also be recorded with appropriate Dose reference IDs as indicated in the above table.
[a] The first Dose reference ID is for current dose, while the second Dose reference ID is for the last dose the subject received prior to the collection of the PK sample.

7.2.3.1 Analytical method

The plasma samples from patients will be assayed for ruxolitinib concentrations using validated liquid chromatography-tandem mass spectrometry method (LC-MS/MS). Values below the lower limit of quantification (LLOQ) of INC424 at approximately 0.50 ng/mL will be reported at 0.0 ng/mL. Missing values will be labeled accordingly.

[redacted]

[redacted]

7.2.5 Patient reported outcomes

Patients with MF often experience significant symptoms that interfere with their quality of life (QoL) including, fatigue, early satiety, pruritus, weight loss, weakness and night sweats. The effect of ruxolitinib on patient symptoms and QoL will be measured using several assessment tools including the MF-7, the EQ-5D-5L [redacted] All questionnaires are patient-reported outcomes (PROs). The PRO questionnaires

[redacted]

provided electronically (ePRO) are to be completed by the patient. The site will review for completeness.

Instructions for all PROs will be provided as separate documents. Patients must complete the questionnaire(s) before other clinical assessments at any given visit. The PRO questionnaires should be completed in the same order at each visit to ensure that the patient is answering them as consistently as possible. The questionnaires should be given in the following order:

1. MF-7
2. EQ-5D-5L

[redacted]

Patient Reported Outcomes will be collected according to the Visit Schedule outlined in Table 7-1. The patient should be given sufficient space and time to complete the PRO questionnaires. The site personnel should check the questionnaires for completeness and ask the patient to complete any missing responses. The original questionnaire will be kept with the patient's file as the source document.

Completed questionnaire(s) and any unsolicited comments written by the patient should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, study investigators should not encourage the patient to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 8 (e.g. reference "Adverse Events" section) of the study protocol.

MF-7

The Myelofibrosis 7 Item Symptom Scale (MF-7) (Appendix 4) is a disease specific questionnaire comprised of 7 items that measures the severity of seven of the most prevalent associated symptoms including: tiredness, early satiety, abdominal discomfort, night sweats, itching (pruritus), bone pain (diffuse not joint or arthritis) and pain under ribs on left side. Each item is scored on a scale ranging from 0 (absent) to 10 (worst imaginable). The MF-7 score is computed as the sum of the observed scores in the individual items to achieve a 0-to-70 score. There would be one recall period of 24 hours used in this questionnaire.

EQ-5D-5L

EQ-5D-5L (Appendix 4) is a standardized instrument for measuring health outcomes in a wide range of health conditions and treatments. It consists of a descriptive system and a visual analogue scale (EQ VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'worst imaginable health state'. The EQ-5D scores can be summarized into a single index score that provides a simple measure of health for clinical and economic appraisal.

[redacted]

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

For patients who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event CRF.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination,

[redacted]

laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates) (add or Ongoing at End of Study for NOVDD)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown) Delete for NOVDD Trials as outcome is not collected
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Confirmation of progression of disease, based on criteria described in Section 10.4.1 should not be reported as adverse event. However death should be reported as SAE (Section 8.2).

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

[redacted]

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

Refer to Section 8.1 for details on protocol exempt AEs and SAEs.

8.2.2 Reporting

For patients who sign the molecular pre-screening ICF, SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (molecular screen failure), SAE collection ends 30 days after the last study related procedure.

For patients who sign the main study ICF, SAE collection starts at time of main study informed consent whether the patient is a screen failure or not.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE

occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential for effective treatment of the patient. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IRT. When the investigator contacts the IRT to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient. The system will automatically inform the Novartis monitor for the site and the Study Lead that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study treatment name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) will

[redacted]

be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable. However, if a mechanism is already in place to ensure that the investigator and/or back-up can always be reached in case of emergency then the procedure above is not required.

If a patient is unblinded due to an emergency, he/she may continue to receive study treatment and followed up as described in the protocol if the investigator believes it is beneficial for the patient and after consultation with Novartis personnel.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator Brochure]. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

This study will institute a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be constituted prior to the randomization of the first patient. Further details on the function and responsibilities of the data monitoring committee will be outlined in the DMC charter.

8.7 Steering Committee

A Steering Committee (SC) will be established for this study. Further details on the functions and responsibilities will be outlined in the Steering Committee charter.

[redacted]

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator’s meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data that will be processed centrally will have results sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the treatment codes will be unblinded and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

The data from all participating centers in this protocol will be combined. The interim analysis will be performed once 45 PFS-1 events have been documented. The primary analysis of study data will be conducted when approximately 90 PFS-1 events have been documented. This data will be summarized in the primary Clinical Study Report (CSR). All available data from all patients up to this cutoff date will be analyzed.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication, where treatment received is defined as the randomized treatment if the patient takes at least one dose of that treatment or the first treatment received if the randomized treatment is never received.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who have at least one post-baseline assessment for PFS and no major protocol deviations.

All major protocol deviations leading to exclusion from the PPS will be detailed in the analysis plan.

10.1.4 Pharmacokinetic analysis set

The pharmacokinetic Analysis Set (PAS) consists of all patients set who have received at least one dose of ruxolitinib and provided evaluable pharmacokinetic (PK) data.

Evaluable PK data must fulfill the following criteria:

1. Post-dose data must not be associated with a vomiting event within 4 hours of ruxolitinib dosing
2. Pre-dose sample must not be associated with vomiting within 4 hours of last dose.
3. Post-dose PK samples must be collected within the time window indicated in the PK collection log.

The PAS will be used for the Population PK analysis.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively by treatment group for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The safety set will be used for the analyses below.

The actual dose and duration of ruxolitinib and placebo treatment as well as the dose intensity (computed as the ratio of total dose received and actual treatment duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity), will be listed and summarized by treatment group. Dose reductions and dose interruptions (including the reasons for these) will be listed and summarized by treatment group.

Concomitant medications including prohibited medications, and significant non-drug therapies prior to and after the start of the study treatment will be summarized for all patients and by treatment group.

Duration of follow up will be summarized descriptively by treatment group.

10.4 Primary objective

The primary objective for this study is to evaluate the effect of ruxolitinib in delaying progression of MF from early disease to more advanced disease stages.

10.4.1 Variable

The primary endpoint is **progression free survival (PFS-1) in Treatment Period 1** . It is defined as the time from date of randomization until earliest time for one of the following events:

- Progressive splenomegaly as assessed by doubling of spleen volume (by MRI/CT); in addition to an absolute spleen volume of greater than 450 cm^3.
- Circulating peripheral blast counts > 10% (requires confirmation after 8 weeks)
- Leukemic transformation defined by an increase in peripheral blood blast percentage to ≥ 20% that is sustained for at least 8 weeks or a bone marrow blast count of ≥ 20%
- Hb < 10g/dl with an absolute decrease of at least 3 g/dl from baseline levels (requires confirmation following 2 week of dose interruption/reductions to ensure this is not drug induced cytopenia. In case of Hb stabilizing following dose modification within the 2 weeks, study drug can be re-escalated based on investigators discretion. See section 6.3 for guidance on dosing modifications
- WBC counts > 25 x 10^3/ μL

[redacted]

- Confirmed MF-7 score of ≥ 30 in addition to an individual symptom score of ≥7 in at least one non-splenomegaly related symptom, i.e., tiredness, night sweats, itching (pruritus), bone pain (diffuse not joint pain or arthritis). (Confirmed on two consecutive weeks)
- Death from any cause

As the proposed study intends to investigate the benefit of ruxolitinib in delaying the emergence of MF associated symptoms, MF-7 is expected to objectively evaluate disease progression based on the worsening of symptoms through symptom scores. A clinically relevant threshold of ≥ 30 was set to capture the time point when the patient begins experiencing more symptomatic disease (disease progression) reflected by a minimum of doubling in the baseline MF-7 scores. Additionally, progression by symptom will also require an individual score of ≥7 in at least one non-splenomegaly related symptom, i.e., tiredness, night sweats, itching (pruritus), bone pain (diffuse not joint pain or arthritis).

10.4.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be the comparison of PFS-1 between the two treatment groups using a log-rank test at one-sided 2.5% level of significance.

Assuming proportional hazards model for PFS, the following statistical hypotheses will be tested to address the primary efficacy objective:

H_{01}: $\theta_1 \geq 0$ vs. H_{a1}: $\theta_1 < 0$

where θ_1 is the log-hazard ratio (test treatment arm vs. control treatment arm) of PFS.

The primary efficacy endpoint PFS-1 will be analyzed at the interim look and final look of a group sequential design based on the FAS population according to the treatment group patients were randomized. PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% confidence intervals (when applicable) will be presented by treatment group.

A Cox regression model will be used to estimate the hazard ratio of PFS, along with 95% confidence interval.

10.4.3 Handling of missing values/censoring/discontinuations

PFS will be censored if no PFS event is observed before the cut-off date or the date when a new anti-neoplastic therapy or another investigational treatment is started, whichever occurs earlier. The censoring date will be the date of last adequate assessment before either of these two dates. If a PFS event is observed after at least two consecutive missing assessments (corresponding to a minimum of 24 weeks), then PFS will be censored at the last adequate assessment prior to the first missing value. If a PFS event is observed after a single missing assessment, the actual date of event will be used and PFS will not be censored.

Since the definition of progression in this study is multimodal the term assessment corresponds to either spleen palpation, laboratory assessment of hematology parameters (hemoglobin, WBC, peripheral blast count) or MF-7 questionnaire. Adequate assessment requires non-missing assessment for all components of PFS.

[redacted]

For each assessment, the assessment date is calculated as the latest of all measurement dates (e.g. laboratory, MRI) if there is no progression. Otherwise, in case of progression the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

If a patient permanently discontinues study treatment for reason other than disease progression and progression event occurs between permanent discontinuation and start of new anti-neoplastic treatment then the PFS time will be censored at last adequate assessment date prior to discontinuation of study treatment.

10.4.4 Supportive analyses

A summary of first progression (PFS-1) events will be tabulated by treatment group.

A subgroup analysis of PFS will be performed by IPSS risk group, type & number of HMR mutations, presence of palpable splenomegaly and/or active symptoms as determined by MF-7.

The analysis of PFS will be repeated for per protocol set.

10.4.5 Sensitivity analyses

If progression event occurs between two scheduled assessments then a date of next schedule assessment will be used as end date for PFS and the outcome will be an event.

If a progression event occurs after two or more missing assessments then date of next scheduled assessment will be used as end date for PFS and the outcome will be an event.

If a patient permanent discontinues study treatment for reason other than disease progression and progression event occurs between permanent discontinuation and start of new anti-neoplastic treatment then the actual date of event will be used and PFS will not be censored.

An alternative definition of PFS excluding MF-7 from progression will be performed.

10.5 Secondary objectives

Secondary objectives related to efficacy include overall survival, time to progression, change in spleen length and volume from baseline, change in symptoms using MF-7 from baseline and progression free survival (PFS-2) in the Treatment Period 2.

Another secondary objective is to assess the effect of ruxolitinib versus placebo on patient reported outcomes (PRO), including disease related symptoms, functioning, and health-related quality of life.

Additional objectives include evaluation of the safety profile of ruxolitinib versus placebo.

10.5.1 Secondary efficacy objectives

Time to primary progression (TTP)

TTP is defined as time from randomization until disease progression as defined for PFS-1 excluding death as an event.

The TTP will be analyzed using log rank test on the FAS population according to the treatment group patients were randomized. TTP will be estimated using the Kaplan-Meier method. The median TTP along with 95% confidence intervals (when applicable) will be presented by treatment group.

The Cox regression model will be used to estimate the hazard ratio (HR) of TTP, along with 95% confidence interval.

Time to first progressive splenomegaly (TTPS)

TTPS is defined as time from randomization until earliest time to progressive splenomegaly as assessed by doubling of spleen volume (by MRI/CT); in addition to an absolute spleen volume of greater than 450 cm^3. Since this endpoint is a component of PFS the censoring rules are similar to PFS.

TTPS will be analyzed using log rank test on the FAS population according to the treatment group patients were randomized. TTPS will be estimated using the Kaplan-Meier method. The median TTPS along with 95% confidence intervals (when applicable) will be presented by treatment group.

A Cox regression model will be used to estimate the HR of TTPS, along with 95% confidence interval.

Time to first symptomatic progression (TTSP)

TTSP is defined as time from randomization until confirmed MF-7 scores of ≥ 30 with at least one symptom score ≥ 7 in at least one non-splenomegaly related symptom, i.e., tiredness, night sweats, bone pain (diffuse not joint pain or arthritis), itching (pruritus) (confirmed on two consecutive weeks). Since this endpoint is a component of PFS the censoring rules are similar to PFS-1.

TTSP will be analyzed using log rank test on the FAS population according to the treatment group patients were randomized. The time to symptomatic progression will be estimated using the Kaplan-Meier method. The median TTSP along with 95% confidence intervals (when applicable) will be presented by treatment group.

A Cox regression model will be used to estimate the hazard ratio (HR) of TTSP, along with 95% confidence interval.

[redacted]

Quality-adjusted life years (QALY)

EQ-5D-5L health states will be converted into index values (utilities) from which the QALY will be calculated.

QALY will be summarized descriptively by treatment arm.

Change in symptoms using MF-7

See Section 10.5.6.

Change in EQ-5D from baseline

See Section 10.5.6.

Overall survival

OS is defined as the time from date of randomization to date of death due to any cause. If a patient is not known to have died, then OS will be censored at the last date the patient was known to be alive.

The analyses for OS will be based on the FAS population according to the randomized treatment group of the patients. OS will be estimated using the Kaplan-Meier method. The median OS along with 95% confidence intervals (when applicable) will be presented by treatment group. A Cox regression model will be used to estimate the HR of OS, along with 95% confidence interval.

Progression free survival after primary progression (PFS-2)

Patients who experienced a first progression (PFS-1) event in either splenomegaly or symptoms (MF-7 score) will be followed for second progression events, defined below. All patients randomized in the study (FAS) will be included in the PFS-2 analysis. PFS-2 is defined as the time from date of randomization until second disease progression or death from any cause, whichever first. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without second disease progression.

Second disease progression is the earliest time for one of the following events:

- Spleen volume increases ≥ 25% over PFS-1 (new baseline) with an absolute volume > 450 cm^3
- MF-7 score ≥ 25% over PFS-1 (new baseline) with absolute scores ≥ 30, an individual symptom score of ≥7 in at least one non-splenomegaly related symptom, i.e., tiredness, night sweats, itching (pruritus), bone pain (diffuse not joint pain or arthritis) (Confirmed on two consecutive weeks)

The thresholds for evaluation of progression in the ruxolitinib Treatment Period 2 (≥ 25% over PFS-1 for both spleen volume increases and MF-7 score worsening) were defined to account for any lack of treatment effect in the post progression Treatment Period and prevent premature discontinuation from treatment due to any transient and borderline worsening in the

[redacted]

symptoms (MF-7 score) and spleen sizes in the immediate post progression period while the patient is switching therapy.

In addition, the following post primary progression parameters assessed in Treatment Period 2 will be summarized descriptively.

- Change in MF-7: Number of patients with 50% reduction in MF-7 score from PFS-1 will be tabulated.
- Change in spleen volume and change in palpable spleen length below costal margin: Number of patients with 35% reduction from PFS-1 will be tabulated.

10.5.2 Safety objectives

10.5.2.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 31 after last dose of study medication.

10.5.2.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on Common Terminology Criteria for Adverse Events [CTCAE] grades), type of adverse event, relation to study treatment by treatment group.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be tabulated.

10.5.2.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE version 4.03 the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

[redacted]

For some cases (e.g. white blood cell differentials) the lower limits of normal ranges used in CTCAE definition have to be replaced by a clinical meaningful limit expressed in absolute counts.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

A listing of laboratory values will be provided by laboratory test, patient, and study day. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory abnormalities).

The following by-treatment summaries will be generated separately for hematology and biochemistry laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4 (see below for details)
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, [redacted]

10.5.2.4 Other safety data

Analyses will be performed on the safety set.

ECG

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

10.5.3 Pharmacokinetics

Objective of the planned pharmacokinetic analyses is as follows:

1. To compare PK characteristics of HMR positive early MF patients with PK characteristics of patients from previous MF studies, and
2. To explore exposure-response relationship across major AEs/ efficacy measures and ruxolitinib exposure.

In order to assess any potential PK differences in this early MF population compared to the previously studied MF patients (Study 251 and 351), newly observed ruxolitinib plasma concentrations stratified into two strata – male and female - will be superimposed over the 5th, [redacted]

50^{th}, and 95^{th} percentiles of simulated observations using the previous MF model and 10 mg BID. Observed ruxolitinib plasma concentrations blood concentrations (C_t in units ng/mL) will be adjusted to the dose (10 mg BID) by the equation: $C_{t,adj} = 10\ mg \times C_t/(actual\ mg\ dose)$.

If the data suggests that there could be any relevant difference in PK compared to the previously studied MF population, then data from Study CINC424A2353 will be pooled with data from Studies 251 and 351. The population pharmacokinetics of study treatment is likely to be adequately described by one or two compartment structural pharmacokinetic model with first order absorption model.

Plasma concentrations of ruxolitinib will be analyzed using non-linear mixed-effects approach in order to characterize the population pharmacokinetics of ruxolitinib and the associated inter-individual and intra-individual variability. After evaluation of adequacy of the data for the objective, additional analyses may be performed to identify and quantify the effects of covariates on the pharmacokinetic variability of ruxolitinib. The main covariate effects to examine are as follows:

1. effects of body weight on central volume and gender on clearance since these were incorporated in the earlier population PK model developed from Studies 251 and 351
2. effect of Study CINC424A2353 on clearance relative to Studies 251 and 351.

The addition of other covariates to the model, e.g., concomitant medications, will be guided by sample size of subpopulations, by exploratory plots of random effects representing inter-individual variability versus covariates, and by the NONMEM objective function value. Covariates may be dropped from the model based on p-value (e.g., $p>0.01$), relative standard error (e.g., >30%), or reduction in inter-individual variability (e.g., no decrease in the coefficient of variation).

Average steady-state exposures will be computed by the POP PK model accounting for dose modifications or dose interruptions up to the day prior to the day of assessment (assessments include progressions, AE endpoints of interest such as Hg levels, platelet counts, laboratory values as needed). Graphical presentation of exposures presented as quartiles may be related to each response/safety end-point as permitted, Time to progression will be assessed by Kaplan-Meire plots by quartiles of average daily exposure. Incidence rates of Grade 3 or 4 hematological or lab abnormalities will be plotted by average daily exposure quartiles.

During modeling of the pharmacokinetics of study treatment, the broad principles outlined in the FDA guidance will be followed (Guidance for Industry: Population Pharmacokinetics; http://.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072137.pdf).

[redacted]

[redacted]

10.5.5 Resource utilization

Not applicable.

10.5.6 Patient-reported outcomes

The Myeloproliferative Neoplasm-Symptom Assessment Form Total Symptom Score (MF-7)and the EuroQol-5D-5L (EQ-5D) will be used to collect data on the impact of ruxolitinib treatment on the patient's disease-related symptoms, functioning and overall quality of life. The MF-7 and the EQ-5D are identified as the key PRO variables of interest. [redacted]

The FAS will be used for analyzing PRO data. No formal statistical test will be performed. Analysis of time to symptomatic progression and QALY are described in Section 10.5.1. Percent change from Baseline in MF-7 total symptom score and 10 individual symptoms at [redacted]

each visit will be summarized with descriptive statistics. A mixed effect repeated measures analysis model may be used to evaluate the treatment effect over time.

Descriptive statistics will be used to summarize the scored scales at each scheduled assessment time point for the [redacted] and the EQ-5D. Additionally, change from baseline in the domain scores and individual items at the time of each assessment will be summarized for the EQ-5D. Patients with baseline score and at least one non-missing post-baseline score during the treatment period will be included in the change from baseline analyses. [redacted]

Missing items data in a PRO scale will be handled based on each instrument manual. All PRO analyses will include data as imputed according to the scoring manual. No imputation will be applied if the total or subscale scores are missing at a visit.

[redacted]

10.7 Interim analysis

One interim analysis is planned at approximately 45 of the 90 targeted PFS-1 events (50% information fraction). The intent of the interim analysis is to stop early for lack of efficacy (futility). It is expected that 309 patients will be randomized when approximately 45 PFS-1 events have occurred if H_0 is true (HR=1).

The design accounts for one interim look under a 2-look group sequential design. A user-defined gamma spending function (gamma= -2 , as implemented in EAST 5.4) is used as beta-spending function to determine the non-binding futility boundary. The interim analysis is planned when 45 (50%) of the 90 PFS-1 events have been recorded. To conclude futility the observed hazard ratio has to be over 0.89 (or the z-statistic is less than 0.388, or nominal p-value $\geq$ 0.3489) if the interim analysis is based on exactly 45 events. EAST 5.4 was used for the calculations.

Since the observed number of events at the interim analysis may not be exactly equal to the planned 45 PFS-1 events, the futility boundary will need to be re-calculated using the pre-specified β-spending function and based on the actual number of observed events at interim and the total number of targeted events to calculate the exact information fraction. The observed hazard ratio (or p-value, or Z-test statistic) at the interim analysis will then be compared against the re-calculated futility boundary.

If the study continues to the final PFS analysis, the final PFS-1 analysis will be performed when approximately 90 PFS-1 events have been documented. If exactly 45 events are observed at the interim analysis, the study continued and exactly 90 events are obtained at the final analysis, the observed p-value will have to be no more than 0.025.

Based on the stopping boundaries defined above and the timing of interim analysis at 50% information fraction the design has the following operational characteristics based on simulations in East 5.4.

Table 10-1 Simulated probabilities to stop for futility at the interim or final PFS-1 analysis

Scenario	Look	# PFS-1 events	Simulated incremental probabilities (%)
			Stop for futility
Under H0 (HR=1)	Interim	45	66%
	Final	90	-
Under Ha (HR=0.50)	Interim	45	3%
	Final	90	-
Under other Ha (HR=0.70)	Interim	45	21%

Note: Simulation is performed in East 5.4 with number of simulations = 10,000 and random seed =1234.

The interim analyses will be performed by an independent statistician (not involved with the conduct of the study). Further details will be described in the DMC charter. The results of the interim analyses will be provided to the DMC by the independent statistician.

[redacted]

10.8 Sample size calculation

There are very limited published data available regarding the population under investigation in the study, MF patients harboring HMR mutations, with asymptomatic or minimally symptomatic disease. Additionally, there is no data that specifically describes the time to progression of disease from asymptomatic or minimally symptomatic disease to more symptomatic disease in myelofibrosis patients and this, likewise, applies to the subgroup of myelofibrosis patients harboring HMR mutations as well. The estimates for the time to progression of disease from early stage MF disease to more advanced stages were therefore extrapolated from survival data that is available by IPSS categories (Cervantes et al, Blood). As the acquisition of a new hematological abnormality or clinical symptom represents a shift in categorization from one risk group to the next higher one in the IPSS risk categorization tool, it was assessed that the difference in median survival between two consecutive IPSS risk groups, would represent the time taken to progress from one risk category to the next higher category. For instance if the median survival for patients in the low risk IPSS is '(X) years' and the median survival for Int-1 risk IPSS is '(Y) years', the time to progression from a low risk IPSS to Int-1 risk IPSS was estimated to be '(X – Y) years'. Since the markers of progressive disease in the study are largely based on the same components of prognosis that the IPSS uses, the above approach was expected to allow a reasonable estimate of time to progression of disease and thus PFS in MF patients. The PFS estimates in the lower IPSS risk groups (low risk and int-1 risk who have either none or one prognostic factor) were assessed as appropriate for the population under study. Table 10-1 depicts the estimation of the time to progression from one IPSS risk category to the next higher one.

The estimated PFS for MF patients in the various categories thus ranges between 21 and 47 months. To enable a conservative estimate of PFS, the best case estimate of 47 months median PFS was considered. These observations are consistent with the survival estimates for HMR patients categorized by different risk groups conducted by Guglielmelli et al, Leukemia, 2014, although this study categorizes patients into two broader risk groups rather than the four used by IPSS, i.e., lower risk group (IPSS low + Int-1) and higher risk groups (IPSS Int-2 + High). For statistical assumptions in the proposed study, a median PFS of approximately 50 months was thus used.

Assuming exponential distribution for PFS, it was estimated that with the median PFS of 50 months, around 60% of the patients in the control arm would remain progression free following 36 months of treatment. For the investigational arm, it was assumed that an additional 20% patients remaining progression free, i.e., 80% patients remaining progression free after 36 months of treatment would correspond to a median PFS of 100 months. In consultation with clinical experts involved in the care of MF patients, this improvement of treatment effect from the estimated median of 50 months (control) to a median of 100 months, corresponding to a HR of 0.5 was assessed as clinically relevant in this patient population with a clinically indolent but intrinsically aggressive MF disease.

The final analysis of PFS-1 will require 90 PFS-1 events, which is the number of PFS-1 events needed for a one-sided log-rank test at 2.5% significance level to have at least 90% power to show a statistically significant difference when the true hazard ratio is 0.50 (corresponding to a median PFS-1 for ruxolitinib of 100 months and a median PFS-1 in placebo of 50 months). It is estimated that approximately 320 patients will have to be

[redacted]

randomized (1:1 ratio) into 2 treatment arms (160 patients in the ruxolitinib treatment arm and 160 patients in placebo control arm) to observe 90 PFS events by approximately 48 months from the randomization date of the first patient in this trial if the accrual rate is constant at 13 patients per month over the accrual period (24 months), assuming 15% cumulative dropout rate at month 48.

Table 10-2 Time to progression based on IPSS risk group

Risk group	Prognostic factors	Median survival (months)	Estimated PFS to next risk group (months)
Low	0	135	135-95 = 40
Int-1	1	95	95 - 48 = 47
Int-2	2	48	48 - 27 = 21
High	>2	27	N/A

10.9 Power for analysis of key secondary variables

Not applicable

10.10 Design adaptation

Considering the disease setting and limited data on the PFS endpoint from other studies, a blinded review of the confirmed PD events will be performed at about 25% information fraction or 24 months after first patient enrolled whichever comes first. This will allow assessing event accrual as per assumption and future prediction of anticipated timing for the IA/FA (Interim analysis/Final analysis). The potential outcome of this review could be either:

- to increase the sample size and extend the accrual duration if
  1. event rate is lower than per assumption;
  2. accrual is within assumption;
  3. dropout rate is within assumption of 15% by month 48.
- to recommend the futility interim analysis proceed at month 48, based on calendar time rather than number of events if
  1. event rate is low;
  2. accrual is low;
  3. dropout rate is high, i.e. posterior predictive probability of observing 50% information fraction by month 48 is less than 40%.

Blinded sample size review

The blinded sample size review will be performed prior to the unblinded futility interim analysis. It will be conducted by blinded Novartis personnel using data pooled across treatment arms. No one with access to unblinded data, e.g. during the preparation of the futility interim analysis or unblinded safety DMC reports, will be involved in the sample size review. Prior to the completion of enrolment, a review of blinded progression data will be performed to re-assess the assumptions of the sample size calculation. With time-to-event data the information of a trial depends on the number of events and not on the number of patients enrolled. The study will be completed once a total of 90 patients with primary disease

[redacted]

progression are observed (90 PFS-1 events). The sole purpose of the blinded sample size review is to control the length of the trial with the aim to keep it as close as possible to the projected 48 months. The preplanned number of events will be kept at 90 and will not be changed in the sample size review.

Once 25% of events are accumulated or 24 months after first patient enrolled whichever comes first and while the enrollment is still ongoing, a review of blinded data will be performed to re-assess the assumptions regarding the nuisance parameters in the sample size calculation for the disease progression endpoint, i.e. the overall progression free survival time and time-to-dropout pooled across the treatment arms. The overall time-to-event processes will be modeled (e.g. using exponential, piecewise exponential, or Weibull distributions). The assumption regarding the treatment effect will remain unchanged, i.e. proportional hazards with a hazard ratio of 0.50. Under this assumption the overall time-to-event processes can be split into two treatment groups to obtain treatment specific estimates under the assumed hazard ratio. For instance, assuming exponential distributions, the pooled hazard rate will be estimated by the total number of events divided by the time under risk aggregated over all patients. The overall rate across treatment arms is a weighted average of the treatment specific rates and therefore treatment specific rates can be calculated assuming a certain rate ratio. Based on the updated hazard rate and drop-out rate assumptions, the observed recruitment so far and the expected recruitment in the coming months, the sample size necessary to achieve a total of 90 progressions within 48 months is computed. If this calculation indicates that a sample size larger than the preplanned total of 320 patients is required, then the enrollment period (which will be still ongoing at the time of the sample size review) will be extended and the total sample size increased, so that, if feasible, the expected duration of the study will be about 48 months. The maximum sample size is set to 420 patients and if the recalculated sample size exceeds this maximum, an extension of the trial beyond 68 months will be considered or a decrease in power will be accepted. The final decision on a sample size increase will be made by the sponsor.

During the sample size review no unblinded data will be used and no adjustment of the significance level is necessary.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study

in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed molecular informed consent form and a main informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical

records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

13 References (available upon request)

Abdel-Wahab, Levine (2009) Primary myelofibrosis: update on definition, pathogenesis, and treatment. Annu Rev Med;60:233-245.

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Cervantes et al (2009) New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood;113:2895-2901.

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Vannucchi et al (2015) A pooled analysis of overall survival in COMFORT-I and COMFORT-II, 2 randomized phase 3 trials of ruxolitinib for the treatment of myelofibrosis. Haematologica June 11, 2015.

[redacted]

14 Appendices

Appendix 1

Table 14-1 List of CYP3A4 inhibitors and inducers

Category	Drug Names
Strong inhibitors[a] of CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice[1], idelalisib, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, LCL161, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, troleandomycin,
Moderate inhibitors[b] of CYP3A	amprenavir, aprepitant, atazanavir, atazanavir/ritonavir,, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporin, duranavir, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, faldaprevilr, fluconazole[2], fosamprenavir, grapefruit juice[1], imatinib, lomitapide, netupitant,nilotinib, schisandra sphenanthera[3], tofisopam, verapamil
Strong inducers[c] of CYP3A	avasimibe, carbamazepine, enzalutamide, mitotane,phenytoin, rifampin, St. John's wort[3], rifabutin, phenobarbital,
Moderate inducers[d] of CYP3A	bosentan, efavirenz, etravirine, genistein[3], lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat[4], talviraline[4], thioridazine, tipranavir,
The list of CYP inhibitors and inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database. Note that this may not be an exhaustive list. Please refer to footnotes. [1] Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol. [2] Fluconazole is a dual CYP3A4 and CYP2C9 inhibitor. Fluconazole is a strong CYP2C9 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor. [3] Herbal product. [4] Drugs not available in the US Market. [a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by equal or more than 5-fold. [b] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold [c] A strong inducer for a specific CYP is defined as an inducer that decreases the AUC of a sensitive substrate for that CYP by equal or more than 80%. [d] A moderate inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 50-80%.	

Dual CYP2C9/CYP3A4 inhibitor:

Fluconazole: Avoid the concomitant use of ruxolitinib with fluconazole doses ≥ 200 mg daily; If clinically necessary to use doses ≥ 200 mg daily consultation with Sponsor is required. Please refer to Section 6.4.2 (Permitted concomitant therapy requiring caution and/or action).

[redacted]

Appendix 2

Table 14-2 European Consensus on the grading of myelofibrosis (adapted from literature)

Grading	Description*
MF - 0	Scattered linear reticulin with no intersections (cross-overs) corresponding to normal bone marrow
MF - 1	Loose network of reticulin with many intersections, especially in perivascular areas
MF - 2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
MF - 3	Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

*Fiber density should be assessed in hematopoietic (cellular) areas.

Adapted from: Thiele J et al. 2005; Haematologica ; 90:1128-1132 (European consensus on grading bone marrow fibrosis and assessment of cellularity).

[redacted]

Appendix 3

Table 14-3 Eastern Cooperative Oncology Group performance status

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

[redacted]

Appendix 4

Patient reported outcomes – Questionnaires

MF-7 Myelofibrosis 7 Item Symptom Scale

Myelofibrosis 7 Item Symptom Scale (MF-7)	
Symptom	**0 to 10 Ranking**
Select the one number that describes the worst severity you have experienced with each of the following in the past 24 hours	
Tiredness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Filling up quickly when you eat	(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)
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)
Pain under ribs on left side	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

[redacted]

EQ-5D-5L Health Questionnaire

EQ-5D-5L Health Questionnaire

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

MOBILITY

- I have no problems walking ☐
- I have slight problems walking ☐
- I have moderate problems walking ☐
- I have severe problems walking ☐
- I am unable to walk ☐

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 ☐

[redacted]

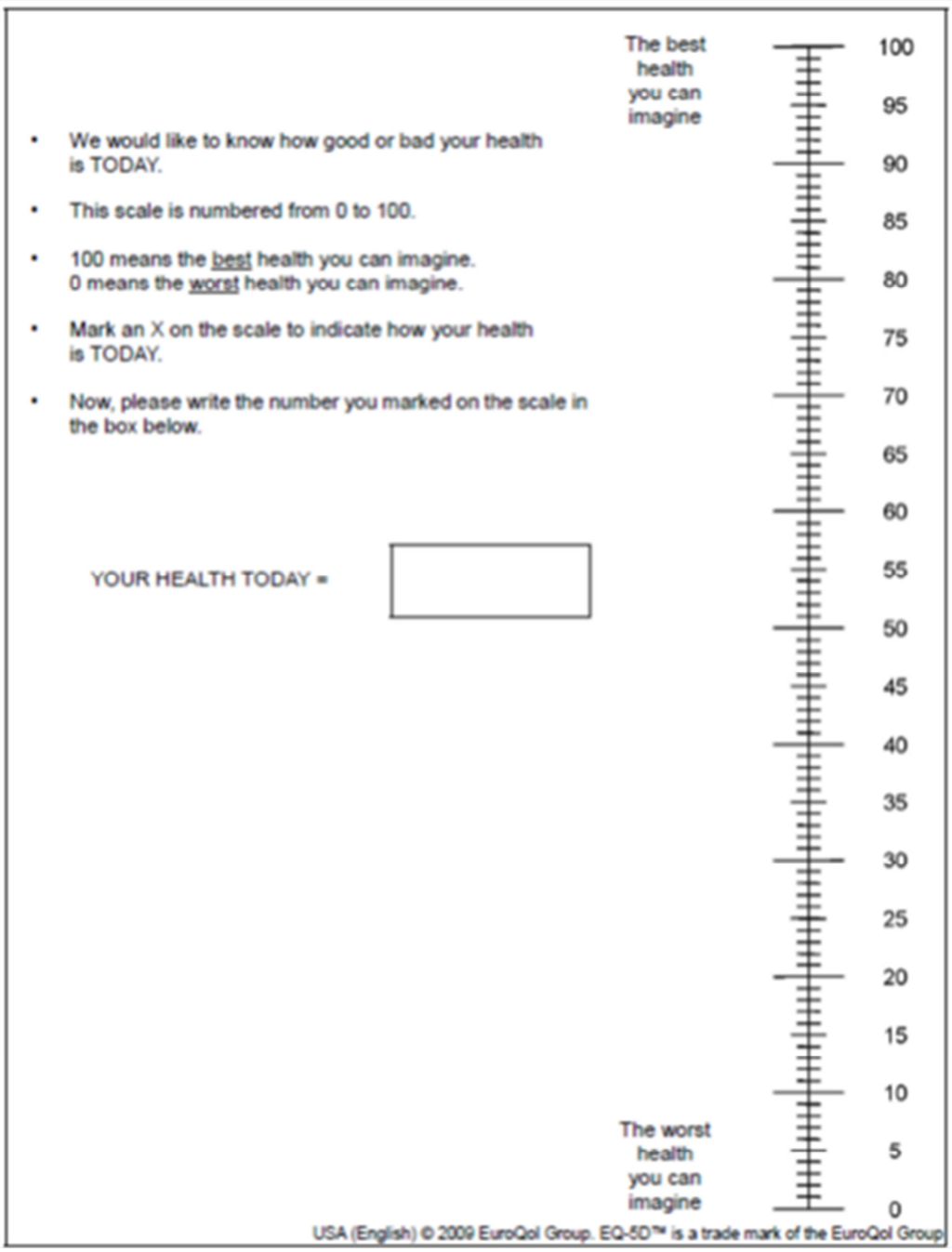
PAIN / DISCOMFORT

- 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 ☐

[redacted]


The best health you can imagine
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
The worst health you can imagine
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 =
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