NOVARTIS

Clinical Development

INC424/ruxolitinib/Jakavi®

Protocol CINC424B2001X / NCT02292446

An open-label, multi-center, Expanded Treatment Protocol (ETP) of ruxolitinib in patients with Polycythemia Vera who are Hydroxyurea resistant or intolerant and for whom no treatment alternatives are available.

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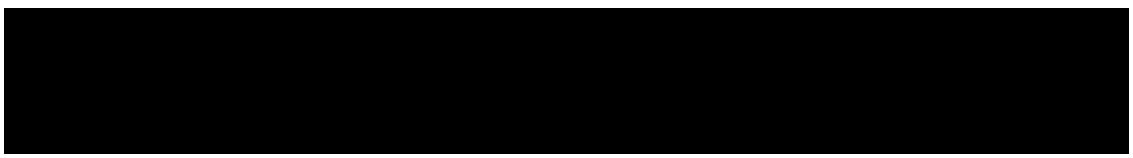

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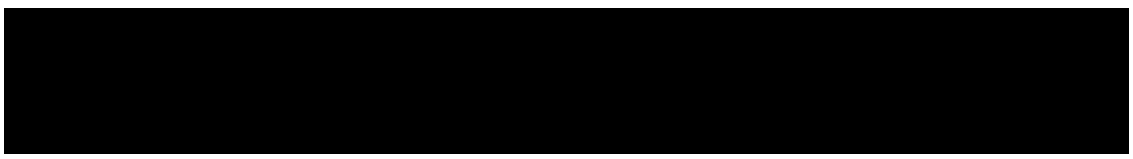
List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Concentration-Time Curve
b.i.d.	*bis in diem*/twice a day
BAT	Best Available Treatment
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
cm	Centimeter
C_{max}	Maximum plasma concentration
C_{min}	Pre-dose (trough) plasma concentration
CRF	Case Report/Record Form; the term CRF may be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
ECLAP	European Collaboration on Low-Dose Aspirin in Polycythemia Vera
ECOG	Eastern Cooperative Oncology Group
ELN	European Leukemia Net
EOT	End of Treatment
ET	Essential Thrombocythemia
GCP	Good Clinical Practice
GI	Gastrointestinal
Hb	Hemoglobin
hCG	Human Chorionic Gonadotropin
Hct	Hematocrit
HDL	High Density Lipoproteins
HIV	Human Immunodeficiency Virus
HU	Hydroxyurea
IB	Investigators Brochure
IC50	Inhibitory Concentration of 50%
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology: includes Interactive Voice Response System and Interactive Web Response System
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
IU	International Unit



IUD	Intrauterine Device
IUS	Intrauterine System
JAK	Janus Kinase
kg	Kilogram
LDL	Low Density Lipoproteins
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDRD-eGFR	Modification of Diet in Renal Disease - estimate glomerular filtration rate
MF	Myelofibrosis
mg	Milligram
mL	milliliter
MPD	Myeloproliferative Diseases
MPN	Myeloproliferative Neoplasm
MPN-SAF TSS	Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score
NYHA	New York Heart Association
PD	Pharmacodynamic(s)
PEG-IFN	Pegylated-Interferon
PK	Pharmacokinetic(s)
PHI	Protected Health Information
PLT	Platelets
PML	Progressive multifocal leukoencephalopathy
PT (INR)	Prothrombin Time (International normalized ratio)
PTT	Partial Thromboplastin Time
PV	Polycythemia Vera
qd	Every Day (Latin: Quaque die)
RAP	Reporting and Analysis Plan
RBC	Red Blood Count
REB	Research Ethics Board
RESPONSE	Randomized, open label, multicenter phase III study of efficacy and safety in polycythemia vera subjects who are resistant to or intolerant of hydroxyurea: JAK inhibitor INC424 tablets versus best available care
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
WBC	White Blood Count
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	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. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
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
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls 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 no further assessments are planned, unless the patient will be followed for progression and/or survival
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
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	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
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
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Protocol summary:

Protocol number	CINC424B2001X Version 01
Title	An open-label, multi-center, Expanded Treatment Protocol (ETP) of ruxolitinib in patients with Polycythemia Vera (PV) who are Hydroxyurea (HU) resistant or intolerant and for whom no treatment alternatives are available
Brief title	Expanded Treatment Protocol of ruxolitinib in Polycythemia Vera patients who are HU resistant or intolerant.
Sponsor and Clinical Phase	Novartis Phase: IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To provide early treatment access and evaluate the safety of ruxolitinib in patients with Polycythemia Vera who are intolerant or resistant to Hydroxyurea.
Primary Objective(s)	To evaluate the safety of ruxolitinib
Secondary Objectives	To evaluate change in hematocrit levels To evaluate change in spleen length To evaluate change in MPN-SAF TSS score
Study design	A global, open-label, single arm, multicenter, expanded treatment protocol with ruxolitinib.
Population	Approximately 500 Polycythemia Vera patients who are hydroxyurea resistant or intolerant and for whom no other standard treatment options are available.
Inclusion criteria	● Male or female patients aged ≥18 years of age. ● Confirmed diagnosis of PV according to the 2008 WHO criteria. ● HU resistant or intolerant ● Peripheral blood blast count of 0% at screening ● ECOG score of 0, 1 or 2 at baseline ● Must have recovered or stabilized sufficiently from adverse drug reactions associated with any prior treatments before beginning ruxolitinib ● Does not have access to a comparable or satisfactory alternative treatment ● Is not eligible for participation in any of the ruxolitinib ongoing clinical trials or has recently completed a clinical trial that has been terminated ● Is not being transferred from an ongoing clinical trial for which they are still eligible.

Exclusion criteria	● Subjects with known hypersensitivity to ruxolitinib or any of its excipients
	● Patients with severely impaired renal function defined by:
	● Serum creatinine > 2 mg/dL (> 176.8µmol/L).
	● 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.
	● Platelet count < 50 ×109/L or an ANC of < 1 × 109/L
	● Being treated concurrently with a potent systemic inhibitor or inducer of CYP3A4 at the time of Screening.
	● Clinically significant bacterial, fungal, parasitic or viral infection which requires therapy
	● History of progressive multifocal leukoencephalopathy (PML)
	● Any concurrent condition that, in the Investigator's opinion would jeopardize the safety of the patient.

Investigational and reference therapy	ruxolitinib 10 mg bid

[redacted]

Efficacy assessments	Hematocrit, spleen length
Safety assessments	Adverse Events, vital signs, hematology
Other assessments	PRO: MPN SAF
Data analysis	Data will be summarized with respect to demographic and baseline characteristics and safety observations and measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.
Key words	Polycythemia Vera, Hydroxyurea resistant or intolerant, ruxolitinib, INC424, myeloproliferative neoplasm, myeloproliferative disorder, blood disorder

[redacted]

Amendment 1

Study Status

The study is ongoing with 65 patients enrolled.

The primary intent of the amendment is to harmonize the standard language for a matter of consistency among all Novartis sponsored clinical studies. In this regards, the overview of ruxolitinib has been updated, including the ruxolitinib approval status for the new indication Polycythemia vera.

The changes to the protocol are summarized in the table below:

Changes to the Protocol are listed below. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike-through red font for deletions, and red and bold for insertions:

Protocol summary:

- This section has been updated with the sample size (number of patients), revised to 500 from 1500 based on a number of countries declining participation due to an earlier approval of the Polycythemia Vera indication.
- This section has been updated as per the new program standard language issued in Sep 2015.

Section 1.2.1 Overview of Ruxolitinib:

- This section has been updated as per the new program standard language issued in Sep 2015.

Section 1.2.1.3.3 Phase III:

- This section has been updated as per the IB update version 14 with latest information from clinical trials.

Section 5.2 Inclusion criteria:

- The Inclusion criterion #3, requiring a treatment history for PV that meets the definition of resistance or intolerance to hydroxyurea has been removed
- Inclusion criterion #2 has been updated to the following requirement: Confirmed diagnosis of PV according to the revised WHO criteria (see Appendix 1), with resistance or intolerance to hydroxyurea.
- The reference of Barosi et al. 2009 has been removed as this is not anymore relevant as PV is now approved.
- The inclusion criterion requiring palpable spleen has been removed. This criterion will allow patients without splenomegaly to enter the trial.

Section 5.3 Exclusion criteria:

- All the exclusion criteria #1 to #18 have been changed according to the new program standard language issued in Sep 2015.

[redacted]

- Updated of the pregnancy language as per the new program standard language issued in Sep 2015 and as per the new guideline on prevention of Pregnancies in Participants in Clinical Trials issued in 2015.

Section 6.3.2 Dose reductions due to hematological changes:

- This section has been updated as per the new program standard language issued in Sep 2015.

Table 6-3 Dose modifications for hematologic toxicity:

- The table including the title has been fully updated to reflect the changes recommended as per the new program standard language issued in Sep 2015.

Section 6.3.4 Ruxolitinib starting dose for patients with platelets less than $100x10^9/L$:

- This section has been updated as per the new program standard language issued in Sep 2015.

Section 6.3.5 Dose modification for renal impairment:

- This section has been added as per the new program standard language issued in Sep 2015.

Section 6.3.6 Dose reduction for non-hematological safety:

- This section has been added as per the new program standard language issued in Sep 2015.

Section 6.3.7 Dose reduction for concomitant CYP inhibitor use:

- Administrative change in this section: change from Section 6.3.5 to Section 6.3.7 for a matter of clarity.

Section 6.3.8 Optional dose tapering strategy in the event of discontinuation:

- Administrative change in this section: change from Section 6.3.6 to Section 6.3.8 for a matter of clarity.

Section 6.4 Concomitant medications:

- This section has been updated as per the new program standard language issued in Sep 2015.

Section 6.4.2 Permitted concomitant therapy requiring caution and/or action

- Higher Aspirin dose has been left in this section however it has been added in the Section 6.4.3 Prohibited concomitant therapy.
- Update of the Section 6.3.8 instead of Section 6.3.6 for the optional dose tapering strategy in the event of discontinuation.

Section 6.4.3 Prohibited concomitant therapy

- This section has been updated to be aligned with program standard language issued in Sep 2015.

[redacted]

Table 7-1 Visit evaluation schedule

- Pregnancy serum test has been added at the EOT to align with the program standard language issued in Sep 2015.
- Pregnancy urine test has been removed at EOT.

Section 7.2.2.5 Laboratory evaluations

- Hemoglobin parameter has added in the laboratory assessment. This parameter is judged as important to assess safety.
- The serum pregnancy test has been added to align with the program standard language issued in Sep 2015.

Section 7.2.2.5.1 Pregnancy and assessments of fertility

- The serum pregnancy test has been added at the EOT as per the new guidance.

Table 7-2 Local clinical laboratory parameters

- Hemoglobin parameter has added in the laboratory assessment
- Pregnancy serum test has been added at EOT.
- Abbreviations have been clarified.

Section 8.1.1 Safety

- The paragraph "Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event" has been removed.
- This paragraph was removed to align with the trial reporting goals.

Section 8.4 Pregnancies:

- The paragraph "Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother" has been removed as per the new guideline on prevention of Pregnancies in Participants in Clinical Trials issued in 2015.

Section 10.8 Sample size calculation

- The sample size (number of patients) has been revised to 500 from 1500.
- This is due to a number of countries declining participation due to an earlier approval of the Polycythemia Vera indication.

Section 13 References

- The reference of Barosi et al. 2009 has been removed as this is not anymore relevant as PV indication is now approved.

Section 14.1 Appendix 1 Guidelines for hydroxyurea resistance and intolerance

- This appendix has been removed as this is not relevant anymore as the PV indication is now approved, and the references to this appendix have been removed from the protocol.

[redacted]

Section 14.7 Appendix 7 Restricted medications:

- The Table 14-5 has been updated based on the new protocol standard language.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Polycythemia Vera (PV) is classified as a myeloproliferative neoplasm (MPN) along with two other BCR-ABL-negative MPNs, myelofibrosis (MF) and essential thrombocythemia (ET) (Vardiman et al 2009). PV is characterized by clonal stem cell proliferation of the erythroid, myeloid, and megakaryocytic lines, and while its predominant characteristic is an increase in red cell mass, increased white blood cell and platelet counts are common (Spivak 2002). The increase in red blood cell mass results in hyperviscosity of the blood, significant morbidity, and a shortened life expectancy (Passamonti et al 2004).

The association between mutations in the Janus Kinase 2 (JAK2) enzyme and MPNs has added a genetic dimension to the diagnosis (Levine and Werning 2006). Virtually all patients with PV have a mutation in JAK2, and more than 95% carry the V617F allele. This observation is reflected in the 2008 revision to the WHO criteria for diagnosis for PV which includes "presence of JAK2V617F or other functionally similar mutation such as JAK2 exon 12 mutation" as one of the two major criteria for diagnosis (Vardiman et al 2009).

Most symptoms noted in the early stages of PV are the consequence of hyperviscosity of the blood and may include headaches, fatigue, hypertension, visual and hearing symptoms, skin reddening from microvascular disturbances, and severe pruritus which are difficult to treat and impair the quality of life (Mesa 2007, Tefferi 2003, Mesa 2009). With disease progression, symptomatic splenomegaly and severe constitutional symptoms are often observed (Finazzi 2007, Spivak 2002). The natural history of PV has been prospectively studied in the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) trial (Marchioli et al 2005). Over time patients may develop cardiovascular complications (especially venous or arterial thrombo-embolic events), acute myeloid leukemia or myelodysplasia, or MF. Survival curves for PV and MF patients converge after 20 years of follow-up, with an 18% survival rate for PV and 13% for MF, underscoring the poor long-term prognosis in PV patients (Vaidya et al 2009).

The current therapeutic approach in PV focuses on lowering the risk for thrombotic events without exposing patients to increased risk of leukemic transformation (Finazzi and Barbui 2008). While phlebotomy and low dose aspirin are accepted as the standard of care for initial therapy, cytoreductive therapy is recommended to aid in the control of erythrocytosis in the presence of poor tolerance to phlebotomy, symptomatic or progressive splenomegaly, or evidence of high thrombotic risk (Finazzi and Barbui 2007). Despite continued uncertainty about its leukemogenic potential, hydroxyurea (HU) remains the myelosuppressive agent of first choice. HU treatment is associated with cytopenias and often unsatisfactory hematological control over time, aphthous and leg ulcers, multiple other toxicities, and a potential risk of leukemia estimated at up to 10% at the 13th year (Tefferi 2003, Najean 1997). Therapeutic options in the second-line setting, beyond HU, are limited (pipobroman, busulfan, chlorambucil, Peginterferon/interferon alpha, ^{32}P, anagrelide), and as a consequence, it is

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estimated that up to 20 - 60% of patients may continue on HU even though response is less than satisfactory (RESPONSE internal data, Najean and Rain 1997).

This trial will allow Polycythemia Vera (PV) patients who are HU resistant or intolerant and have no other treatment options available to them, nor are they eligible for an ongoing clinical trial in PV, the opportunity to obtain ruxolitinib based on the treating physician's opinion that the patient could benefit from treatment while allowing collection of safety and efficacy data.

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, has been implicated as drivers of BCR-ABL-negative myeloproliferative neoplasms (MPN), namely myelofibrosis (MF), 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, JAK2 and mutated JAK2V617F, leading to inhibition of growth factor-mediated cell signaling and tumor cell proliferation. Given this mechanism of action of ruxolitinib as a JAK inhibitor and the role played by dysregulation of the JAK pathway in the pathogenesis of MPNs, the primary clinical development plan for ruxolitinib focused on studies to support regulatory approval in these disorders.

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 inhibited the splenomegaly and morbidity/mortality in mice resulting from intravenous inoculation of cells expressing the same mutated JAK2 (V617F) implicated in the pathogenesis of the majority of Philadelphia chromosome negative MPNs. INC424 inhibited erythroid colony formation from mononuclear cells derived from PV patients (IC50 of 223 nM compared to 407 nM for normal donors). Growth factor independent colony formation, a unique characteristic of PV and other MPNs, was inhibited more potently with an IC50 of 67 nM for INC424 in cells bearing the JAK2V617F mutation compared to cells bearing the wild-type JAK2.

Effects of INC424 noted in 6 month rat and 12 month dog repeat dose toxicology studies were primarily myelosuppressive in nature and are believed to be associated with the mechanism of

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action of INC424 (inhibitor of JAK-STAT signaling). Genetic toxicology assessments (evaluations of INC424 in the bacterial mutagenicity assay, in vitro chromosome aberration assay, and in vivo micronucleus assay) in rats were negative. In safety pharmacology evaluations, an adverse decrease in minute volume in a respiratory study in female rats only was noted at the highest dose. In a cardiovascular evaluation of INC424 in dogs, electrocardiogram (ECG) parameters and ventricular repolarization were unaffected at all doses; whereas the compound lowered blood pressure and increased heart rate compared to vehicle control at the highest dose evaluated. In embryo-fetal assessments in rat and rabbit, maternal toxicity and minimal embryo-fetal toxicity were noted at the highest doses evaluated.

Ruxolitinib was not teratogenic in either rat or rabbit. No effects were noted on reproductive performance or fertility in male or female rats. Increases in post-implantation loss were noted at the higher doses.

More detailed information on pharmacology of ruxolitinib, single and multiple dose pharmacokinetic (PK) studies conducted in multiple species and nonclinical safety evaluations can be found in the IB.

1.2.1.2 Clinical pharmacokinetics and pharmacodynamics

Ruxolitinib exhibits near complete oral absorption, achieving maximal plasma concentration Cmax at approximately 1-2 h post-dose with linear PK over a dose range of 5-200 mg. Ruxolitinib is mainly eliminated by metabolism via CYP3A4 with minor contributions of CYP2C9 with a terminal elimination half-life of approximately 3 h. Administration with food did not affect ruxolitinib's overall exposure. Ruxolitinib may be administered without regard to meals.

Ruxolitinib is metabolized in the liver by the cytochrome (CYP) P450 metabolizing enzyme system, predominantly by the 3A4 isozyme. The effects of the potent CYP3A4 inhibitor ketoconazole on the pharmacokinetics (PK) and pharmacodynamics (PD) of ruxolitinib administered as single oral doses shows that with concomitant dosing of ketoconazole, the observed AUC increase is approximately 2-fold, with a similar effect on the PD effect (cytokine-induced STAT3 phosphorylation). Thus, a dose reduction of approximately 50% for ruxolitinib is appropriate for subjects who take ketoconazole or other potent CYP3A4 inhibitors as concomitant medication.

Ruxolitinib was given as a single 25 mg dose to subjects with varying degrees of renal function ([INCB 18424-142]), including normal, mild, moderate and severe (ClCr < 30 mL/min) renal impairment as well as end stage renal impairment disease (ESRD). There was no statistically significant effect of mild, moderate or severe impairment of renal function on the PK or PD parameters; ESRD subjects requiring dialysis showed prolonged PD activity. In a hepatic impairment study, the PK of ruxolitinib was assessed following a single ruxolitinib dose of 25 mg [INCB 18424-137]. The mean AUC for ruxolitinib was increased by 87%, 28% and 65%, respectively, in subjects with mild, moderate and severe hepatic impairment compared to subjects with normal hepatic function, indicating no clear relationship to the degree of hepatic impairment based on Child-Pugh scores. The terminal elimination half-life was prolonged in subjects with hepatic impairment compared to healthy controls (4.1-5.1 h versus 3 h). Hepatic impairment, in general, decreased the plasma Cmax, but not the AUC

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values, of ruxolitinib metabolites, and no rank correlation was observed between the change in the PK parameters of the metabolites and the degree of hepatic impairment.

The pharmacodynamics of ruxolitinib was characterized by an ex vivo whole-blood assay that involves quantification of phosphorylated STAT3 following IL-6 stimulation. Following single or multiple oral dose administrations, ruxolitinib demonstrated dose-dependent inhibition of cytokine-induced pSTAT3 with maximal inhibition occurring 1-2 h after administration. The pharmacodynamic-time profile (i.e., cytokine-induced pSTAT3 change over time) coincided with peak ruxolitinib plasma and trough concentrations. Additional details regarding the clinical pharmacology of ruxolitinib can be found in the IB.

1.2.1.3 Clinical experience

INCB 18424-256 is an uncontrolled open label dose-ranging Phase II study to determine the safety and efficacy of ruxolitinib in patients with advanced PV or ET refractory to or intolerant of HU. Following an initial 8-week phase in which three dose regimens (10 mg b.i.d., 25 mg b.i.d., or 50 mg q.d.) were evaluated in each patient population (n=6-8/dose), starting doses of 10 mg b.i.d. in PV patients and 25 mg b.i.d. in ET patients were selected, based on efficacy and tolerability, to explore in an expansion cohort. Dose modifications were allowed with the objective of normalizing hematocrit (Hct), platelet and WBC counts in each individual subject while avoiding hematologic toxicity. Primary endpoints include defined ranges for Hct, platelet and WBC counts for each disease; reduction in palpable spleen length; improvement in disease-related symptoms; reduction in the need for phlebotomy (PV only); and safety/tolerability. Thirty-four PV patients and 39 ET patients have been enrolled with a median time from diagnosis at study start of approximately 115 months for PV and 88 months for ET patients.

The first patient was enrolled in this study on 29-Aug-2008. The data were extracted from the clinical study report, 10-March-2011. The following information relates to the PV patients only.

1.2.1.3.1 Efficacy in INCB 18424-256

In total, 56% of PV subjects achieved an overall confirmed response after 8 weeks of ruxolitinib treatment (protocol-specified responder analyses). Unconfirmed response rates were higher, 62% in PV. These overall response rates were driven almost entirely by protocol-defined partial responses. Over the duration of the study, unconfirmed complete response was achieved with low frequency (18% PV), while partial response rates were achieved with greater frequency (91% PV).

Findings from specific and ad hoc analyses conducted for PV indicate normalization of Hct (<45%) was achieved rapidly with ruxolitinib and was sustained in all responding subjects in the absence of phlebotomy for the duration of their available follow-up. After 36 weeks of treatment, 97% of PV subjects achieved Hct control without the aid of phlebotomy and complete hematologic remission was achieved in 45% of subjects.

Within 12 weeks of treatment, 62% of PV subjects with splenomegaly at baseline achieved absence of palpable splenomegaly. Improvement of palpable splenomegaly, based on ≥ 50% reduction from baseline in palpated spleen size was achieved in 81% of subjects after 36

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weeks and was maintained in all responding subjects for the duration of their available follow-up. Enrolled patients demonstrated rapid, marked and durable reductions in patient-reported symptom scores for pruritus, night sweats and bone pain. These responses paralleled positive changes in the EORTC QLQ-C30 instrument.

1.2.1.3.2 Safety and tolerability in study INCB 18424-256

The overall risk-benefit of ruxolitinib in the PV population is favorable. The most frequently reported treatment emergent adverse events (TEAEs) were, respectively, anemia (73.5%), thrombocytopenia (32.4%), and diarrhea (20.6%). Of these most frequently reported TEAEs, relatively few were Grade 3 in severity: the percentage of subjects with Grade 3 anemia was 3%, Grade 3 thrombocytopenia 5.9% and no subject had Grade 3 diarrhea.

TEAEs in PV subjects were thrombocytopenia and pneumonia, each reported by two subjects (5.9%).

Few PV (2; 5.9%) subjects permanently discontinued study medication due to an AE. Few PV subjects (5; 14.7%) reported SAEs. Pneumonia was reported in two subjects with PV, and all other SAEs were reported only once (Verstovsek et al, 2014).

1.2.1.3.3 Phase III

The [CINC424B2301] study (RESPONSE Trial) is a global, randomized, open label pivotal study comparing ruxolitinib (starting dose of 10 mg b.i.d.) with BAT (Best Available Treatment: HU, pipobroman, immunomodulatory drugs, pegylated interferon or interferon, anagrelide, observation only) in PV patients. The protocol is designed for patients, either resistant or intolerant to HU, with evidence of need for phlebotomy for Hct control and presence of splenomegaly. The primary endpoint is a composite one with hematocrit control (Hct < 45% in the absence of phlebotomy from Week 8 to 32) and reduction in spleen volume by MRI (or CT if MRI is clinically contraindicated) of at least 35% measured at 32 weeks. Two key secondary endpoints include durability of the primary endpoint and complete hematologic remission. There are multiple, non-key secondary endpoints including modified clinico-hematologic response (overall response rate, durability and duration), as defined by the European Leukemia Net (ELN). Enrollment was completed in the study with 222 patients enrolled.

The trial met its primary endpoint.

The primary efficacy objective was based on a composite endpoint consisting of hematocrit control (absence of phlebotomy eligibility) and of at least 35% spleen volume reduction as assessed by central radiologic evaluation.

Significantly more patients randomized to ruxolitinib met the primary endpoint at Week 32 when compared to patients randomized to BAT, 22.7% vs. 0.9%, respectively ($p<0.0001$).

Additionally at Week 32, a higher proportion of patients randomized to ruxolitinib achieved either of the individual components of the primary composite endpoint (95% CI are non-overlapping):

- 60.0% (95% CI: 50.2, 69.2) vs. 19.6% (95% CI: 12.7, 28.2) of the patients achieved hematocrit control (absence of phlebotomy eligibility) in the ruxolitinib arm vs. the BAT

[redacted]

arm, respectively. This difference was also reflected in the high proportion of patients randomized to ruxolitinib who had no phlebotomy from Week 8 to Week 32 (80.2%) when compared to patients randomized to BAT (37.6%)

- 40.0% (95% CI: 30.8, 49.8) vs. 0.9% (95% CI: 0.0, 4.9) of the patients achieved at least a 35% reduction in spleen volume from baseline in the ruxolitinib arm vs. the BAT arm, respectively.

Overall, 77.3% of the patients randomized to ruxolitinib met at least one component of the primary endpoint.

The safety profile of ruxolitinib was generally consistent with previous studies based on initial review of the data. .

2 Rationale

2.1 Study rationale and purpose

When cytoreduction is clinically indicated in PV patients, hydroxyurea (HU) is the preferred cytoreductive agent in the first line setting (Finazzi and Barbui 2007). However, HU treatment is associated with cytopenias and often unsatisfactory hematological control over time, aphthous and leg ulcers, multiple other toxicities, and a potential risk of leukemia estimated at up to 10% at the 13th year (Tefferi 2003, Najean 1997 For patients who do not tolerate or are resistant to HU, therapeutic options remain limited. The different available cytoreductive agents have been rarely compared in a randomized fashion and their use is supported by little prospective evidence. The most commonly used second-line therapies include pipobroman, anagrelide, Peginterferon/interferon alpha, ^{32}P and alkylating agents (Marchioli 2005). Imids have shown clinical activity in the MPDs, most specifically in Primary Myelofibrosis and post-ET/PV myelofibrosis (Barosi 2001).

Ruxolitinib is an inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs) that is currently under development for treatment of myeloproliferative neoplasms (MPNs) and advanced hematologic malignancies. A causal role for JAK2 has recently been proposed for PV patients possess the JAK2 V617F mutation. As described in Section 1.2, data from the Phase II Study (INCB 18424-256) in PV patients refractory or intolerant to HU have demonstrated that treatment with ruxolitinib is effective and well tolerated, and can result in normalization of Hct, white blood cell count, and platelet count while eliminating the need for phlebotomy. When present, splenomegaly is markedly improved by ruxolitinib treatment as evidenced by the rapid and durable decreases in palpable spleen length with therapy. The symptomatic burden of enrolled patients, namely pruritus, bone pain, fever and night sweats, are improved by ruxolitinib as reported by patient-reported symptom assessments.

In addition, a global phase III CINC424B2301 study (RESPONSE Trial), randomized, open label comparing ruxolitinib (starting dose of 10 mg b.i.d.) with BAT in PV patients either resistant or intolerant to HU, with evidence of need for phlebotomy for Hct control and presence of splenomegaly has met its primary endpoint. The safety profile of ruxolitinib was generally consistent with previous studies based on initial review of the data. The results of this trial have been submitted to the upcoming ASCO and EHA 2014 meetings.Taken together,

[redacted]

the emerging efficacy and safety profile for ruxolitinib supports further access in PV patients who demonstrate resistance or intolerance to HU therapy.

2.2 Rationale for the study design

2.3 Rationale for dose and regimen selection

The purpose of this open-label, single arm, multi-center Expanded Treatment Protocol (ETP) is to provide early access to ruxolitinib and evaluate safety information in patients with PV, who are HU resistant or intolerant and who have no other standard treatment option, nor do they qualify for another clinical study for PV.

The available data from Study INCB 18424-256 established 10 mg bid starting dose of ruxolitinib as an active, safe and well tolerated dose in patients with PV. Primary endpoints include defined ranges for Hct, platelet and WBC counts; reduction in palpable spleen length; improvement in disease-related symptoms; reduction in the need for phlebotomy; and safety/tolerability. Thirty-four PV patients were enrolled. Section 1.2.1.3 provides more information on the safety and efficacy results from this study that support the use of a 10 mg bid starting dose in the PV patient population.

In this study, all patients will be initiated at a dose of 10 mg bid (see Section 6.3.4 and Section 6.3.7 for exceptions). Dose levels of ruxolitinib will be adjusted based on safety and efficacy so that each patient is titrated to their optimal dose, and the starting ruxolitinib dose will likely not be the final dose for many patients. In addition, the global phase III ([CINC424B2301] or the RESPONSE Trial) confirmed that a starting dose of 10 mg b.i.d, is an active and well tolerated dose.

The highest ruxolitinib dose allowed in study INCB 18424-256 and CINC424B2301 was 25 mg bid. This dose has been established as the maximally tolerated dose in healthy volunteers, and has been safe and well tolerated in MF and PV when the dose level has been implemented as part of individualized dose titration.

See the IB for more information on ruxolitinib PV clinical study findings.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

Not applicable.

[redacted]

3 Objectives and endpoints

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To evaluate the safety of ruxolitinib	AEs, Grade 3&4 AEs & SAEs, events of special interest, AEs leading to discontinuation, and deaths. Evaluate changes in hematology."	
Secondary		
Efficacy		Refer to Section 10.5.2
To evaluate change in hematocrit levels	Change in Hct levels from Baseline to each visit where measured	
To evaluate change in spleen length	Change in spleen length from Baseline to each visit where measured.	
Patient Reported Outcome		Refer to Section 10.5.6
To evaluate change in MPN-SAF TSS score	Change in MPN-SAF TSS score from baseline to each visit where measured.	

4 Study design

4.1 Description of study design

This is a global, single arm, open-label, multi-center protocol designed to provide early access and evaluate the safety of ruxolitinib in patients with polycythemia vera who are HU resistant or intolerant and who have no other standard treatment options. Efficacy and patient reported outcomes will also be assessed.

There are limited therapeutic options in this disease setting. Ruxolitinib will be provided until it becomes commercially available for this indication in each participating country or until 31 December 2017, whichever date occurs first.

Screening/baseline phase

- Screening/baseline assessments will be performed within 35 days prior to the first dose of ruxolitinib treatment (e.g., labs including hematology, blood chemistry, urine, and pregnancy tests, physical examination including spleen palpation, vital signs, and ECOG Performance Status).
- If all screening lab assessments are received, reviewed, and within protocol parameters and patient meets all inclusion and none of the exclusion criteria, the screening labs may be used as baseline and patient may continue to Day 1 within 14 days of the screen after the eligibility checklist has been completed in the IRT system.

Treatment phase/duration of treatment

- Patients who are eligible will receive ruxolitinib at a starting dose of 10 mg bid (see Sections 6.3.4 and Section 6.3.7 for exceptions). The first dose of ruxolitinib treatment is

[redacted]

administered on Day 1. Patients will have clinic visits every 4 weeks until Week 24 and every 12 weeks thereafter. The dose of drug may be adjusted during the study based on efficacy and safety to a maximum of 25mg bid (see Sections 6.3 for guidance). Clinical suspicion of disease progression to MF, MDS, or AML (see Appendix 4and Appendix 5 for definitions) or the occurrence of a Grade 3 or 4 events at any time requires a physical examination to assess disease status. This examination is to be performed promptly rather than waiting for the next scheduled visit.

- Patients may continue to receive ruxolitinib treatment until disease progression, (see Appendix 4and Appendix 5), as determined by the local investigator, unacceptable toxicity, death, withdrawal of consent for protocol specified procedures, or discontinuation from the treatment for any other reason until the drug becomes commercially available in each participating country or until 31 December 2017, whichever occurs first.

4.2 Timing of interim analyses and design adaptations

Not applicable.

4.3 Definition of end of the study

The study will end for each country 3 months after the drug is commercially available in the country or by 31 December 2017, whichever occurs first. The entire study will end when all countries have completed participation.

Should ruxolitinib not be available to patients after the drug is commercially available in the country, Novartis Country Pharma Organization will have a transition plan in place to ensure that patients have access without delays in treatment.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible (for a prematurely 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 IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The patient population will consist of male or female individuals, aged 18 years or older who have been diagnosed with Polycythemia Vera (PV, see Appendix 1), and who are hydroxyurea (HU) resistant or intolerant and have no other treatment options or are not eligible for a clinical study with an investigational medicinal product for PV.

Patients in the study may not participate in any other interventional clinical studies of other investigational agents or devices. Patients who have discontinued the study may not be re-enrolled for a second course of treatment.

[redacted]

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

5.2 Inclusion criteria

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

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

1. Male or female aged 18 or over,
2. Confirmed diagnosis of PV according to the revised World Health Organization (WHO) criteria (see Appendix 1), with resistance or intolerance to hydroxyurea.
3. ECOG performance status of 0, 1, or 2 at Baseline,
4. Peripheral blood blast count of 0% at screening,
5. Must have recovered or stabilized sufficiently from adverse drug reactions associated with any prior treatments before beginning treatment with ruxolitinib,
6. Does not have access to a comparable or satisfactory alternative treatment (i.e., comparable or satisfactory treatment is not available or does not exist),
7. Is not eligible for participation in any of the ruxolitinib ongoing clinical trials or has recently completed a clinical trial that has been terminated and, after considering other options (e.g., trial extensions, amendments, etc.), the clinical team has determined that treatment is necessary and there are no other feasible alternatives for the patient),
8. Is not being transferred from an ongoing clinical trial for which he/she is still eligible.

5.3 Exclusion criteria

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

Lab and Clinical Abnormalities

1. Subjects with known hypersensitivity to ruxolitinib or any of its excipients
2. Patients with severely impaired renal function defined by:
   Serum creatinine > 2 mg/dL (> 176.8µmol/L)
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. Platelet counts < 50 $\times 10^9$/L or an Absolute Neutrophil Count (ANC) < 1 $\times$ 10^9/L at screening.

Concurrent Diseases / Medication History

5. Patients being treated concurrently with a strong (potent) systemic inhibitor or inducer of CYP3A4 (refer to Appendix 7) at the time of Screening.
6. Presence of active bacterial, fungal, parasitic, or viral infection which requires therapy.

[redacted]

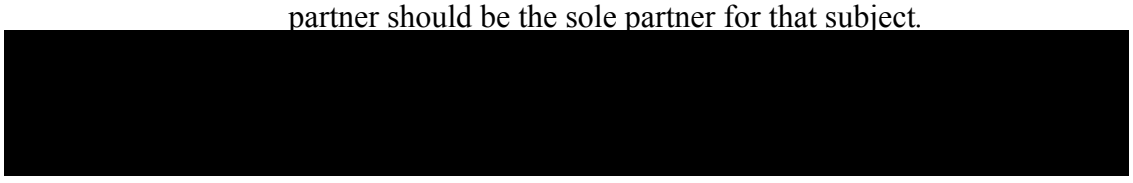
7. Known history of human immunodeficiency virus (HIV) infection or other immunodeficiency syndromes such as X-linked agammaglobulinemia and common variable immune deficiency
8. Acute viral hepatitis or active chronic hepatitis B or C infection.
9. History of progressive multifocal leuko-encephalopathy (PML).
10. 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).
11. 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)
12. Significant concurrent, uncontrolled medical condition which, in the investigator's opinion, would jeopardize the safety of the patient or compliance with the protocol.
13. Subjects undergoing 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 drug.
14. Patients with a history of malignancy in the past 3 years except for treated, early-stage squamous or basal cell carcinoma.
15. Receiving PEG-IFN-alpha-2a within 5 weeks of first dose.

Ability to comply with Protocol

16. Patients who are unable to comprehend or unwilling to sign an informed consent form (ICF).

Pregnancy and Birth Control

17. Pregnant or nursing (lactating) women
18. 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 taking study treatment. 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 oral contraception you should have been using the same pill on a stable dose 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) 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.

6 Treatment

6.1 Study treatment

INC424/ruxolitinib tablets will be the only investigational drug in this study.

6.1.1 Dosing regimen

The starting dose of ruxolitinib will be 10 mg bid (see Section 6.3.4 and Section 6.3.7 for exceptions). A standardized dosing paradigm will be used to determine dose adjustments for safety and efficacy so that each patient is titrated to their most appropriate dose (see Section 6.3.1 of the protocol). The ruxolitinib dose should not exceed 25 mg bid and should not be less than 5 mg once a day unless there is an adverse event that warrants interruption.

Patients may self-administer daily ruxolitinib tablets qd or bid (see Section 6.3.4 and Section 6.3.7 for exceptions) orally, without regard to food, in an outpatient setting in accordance with the specified dosing schedule provided by the investigator.

Patients who miss a dose should be counseled to take the next dose as scheduled and not to take double the dose.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
INC424/ ruxolitinib	Tablet for oral use	Starting dose 10 mg bid (approximately 12 hours apart: morning and night), to be increased or decreased (5 mg steps) per standardized dosing paradigm and not to exceed 25 mg bid (see Section 6.1.1)	Daily, unless instructed to temporarily withhold dosing for safety

The investigator will instruct the patient to take the study drug as per protocol. All dosages prescribed and dispensed to the patient and all dose changes during the study should be recorded on the Dosage Administration Record eCRF.

[redacted]

6.1.2 Ancillary treatments

All patients should receive low dose aspirin (75-150 mg/day), as standard of care for PV patients, unless medically contraindicated. In this case, other prophylactic antithrombotic agents may be used. Higher doses of aspirin (> 150 mg/day) should not be used except when medically indicated per the treating physician.

Aspirin and other antithrombotic use will be documented in the eCRF.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

Not applicable.

6.1.5 Treatment duration

Patients may continue ruxolitinib treatment until they experience any of the following:

- Disease progression determined by the local investigator (see Appendix 4 and Appendix 5),
- Unacceptable toxicity that precludes further treatment,
- Start of a new anti-cancer therapy,
- Pregnancy,
- Treatment is discontinued at the discretion of the investigator or patient,
- Lost to follow-up or withdrawn consent,
- Death,
- Study terminated by the sponsor,
- Study is completed (see definition below).

Treatment duration is considered "completed" three months after ruxolitinib becomes commercially available in the patients participating country or by 31 December 2017, whichever comes first, and the patient should be transitioned to commercial product. Study sites should stop all patients' study participation on the ETP at this time.

6.2 Dose escalation guidelines

Not applicable to the study.

6.3 Dose modifications

6.3.1 Dose escalations due to inadequate efficacy

The initial dose of ruxolitinib will be 10 mg bid up to Week 4 (see Section 6.3.4 and Section 6.3.7 for exceptions). Based upon hematology and spleen palpation results, the dose of ruxolitinib **may** be increased by 5 mg bid from the previous 4 weeks in patients who meet the following conditions:

1. Inadequate efficacy as demonstrated by one or more of the following:

[redacted]

a. Hct > 45%,
b. WBC > upper limit of normal range,
c. A clinically relevant increase in palpable spleen as determined by the investigator.

AND

2. The patient should have demonstrated adequate safety to increase the dose with all of the following:
   a. Platelet count $\geq 140 \times 10^9$/L,
   b. Hemoglobin $\geq$ 12 g/dL
   c. ANC $\geq 1.5 \times 10^9$/L.
   d. No treatment-related toxicity must have occurred with the current dose level, resulting in treatment reduction or interruption in the previous 28 days.

The total dose should never exceed 25 mg bid.

Table 6-2 Ruxolitinib allowed dose escalation due to inadequate efficacy

Week of Study	Maximum Dose	Based on (no potent CYP3A4 inhibitor use)
1 to 4	10 mg bid	Eligibility for study
5 to 8	15 mg bid	Hematology, spleen palpation, AEs
9 to 12	20 mg bid	Hematology, spleen palpation, AEs
13 to EoT	25 mg bid	Hematology, spleen palpation, AEs

6.3.2 Dose reductions due to hematological changes

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Dose reductions or interruptions for hematological changes are described in Table 6-3.

The objective of the ruxolitinib dose adjustment rules is to optimize response for each individual patient (namely achieve and maintain Hct < 45% and normalize WBC and PLT counts) while avoiding specific Grade 2 or higher cytopenias.

Doses may be titrated based on safety. Treatment should be interrupted for platelet counts less than 50×10^9/L or absolute neutrophil counts less than 0.5×10^9/L.

The treatment should also be interrupted when hemoglobin is below 8 g/dL (80 g/L).

Dose reductions should be considered if the platelet counts decrease below 100×10^9/ L with the goal of avoiding dose interruptions for thrombocytopenia. The dose reduction should also be considered if hemoglobin decreases below 12 g/dL (120 g/L) and is recommended if hemoglobin decreases below 10 g/dL (100 g/L).

After dose interruption, when blood counts recover, dosing may be restarted at 5 mg twice daily and gradually increased based on careful monitoring of blood cell counts.

All dose changes should be recorded on the Dosage Administration Record eCRF.

The following guidelines should be applied:

[redacted]

Table 6-3 Dose modifications for hematologic toxicity

Hematology Parameters	Reduction or Interruption
Platelet count < 100 x 10^9/L	Dose reduction should be considered.
Platelet count < 50 x 10^9/L	Treatment should be interrupted.
Absolute neutrophil count < 0.5 x 10^9/L	Treatment should be interrupted.
Hemoglobin < 12 g/dL (120 g/L)	Dose reduction should be considered
Hemoglobin < 10 g/dL (100 g/L)	Dose reduction is recommended
Hemoglobin < 8 g/dL (80 g/L)	Treatment should be interrupted.

6.3.3 Restarting or increasing dose after hematological decline

Dosing may be restarted or increased following recovery of the hematologic parameter(s) to acceptable levels. Table 6-4 illustrates the maximum allowable dose that may be used after restarting or increasing doses following a previous interruption or dose decrease.

Table 6-4 Ruxolitinib maximum allowable dose levels after dose interruption or reduction due to hematological decline

Current Hb (g/dL)	**Maximum allowable dose**
< 8	Continue hold
8 to < 10	5 mg bid for at least 2 weeks, if stable may increase to 10 mg bid
10 to < 12	10 mg bid for at least 2 weeks, if stable may increase to 15 mg bid
≥ 12	15 mg bid for at least 2 weeks, if stable may increase to 20 mg bid
Current PLT (x 10^9/L)	**Maximum allowable dose**
< 50	Continue hold
50 to < 75	5 mg bid for at least 2 weeks, if stable may increase to 10 mg bid
75 to < 100	10 mg bid for at least 2 weeks, if stable may increase to 15 mg bid
≥ 100	15 mg bid for at least 2 weeks, if stable may increase to 20 mg bid
Current ANC (x 10^9/L)	**Maximum allowable dose**
< 1.0	Continue hold
1.0 to < 1.5	5 mg bid for at least 2 weeks, if stable may increase to 10 mg bid
1.5 to < 2.0	10 mg bid for at least 2 weeks, if stable may increase to 15 mg bid
≥ 2.0	15 mg bid for at least 2 weeks, if stable may increase to 20 mg bid

Dose increases should be in increments of 5 mg bid and should not occur more often than every 2 weeks.

When restarting ruxolitinib after dose interruption, the Hb, PLT, and ANC levels must be considered to determine the restart dose, regardless of which level caused the dose interruption. The lowest calculated dose per Table 6-4 should be used. The restart dose should be at least 5 mg LESS that the dose that resulted in the interruption.

Patients who required dose interruption while receiving a dose of 5 mg bid may resume at a dose of 5 mg bid or 5 mg qd, but never higher, once:

- Hb is ≥ 10 g/dL
- PLT is ≥ 75 x 10^9/L,
- and ANC is ≥ 1.5 x10^9/L

[redacted]

6.3.4 Ruxolitinib starting dose for patients with platelets less than 100x10^9/L

Patients who enter the study with a platelet value between 50 x 10^9/L and <100x10^9/L should start ruxolitinib with a starting dose of 5mg bid. It is recommended that these patients' platelet values are monitored more frequently per Table 6-3.

6.3.5 Dose modification for renal impairment

No specific dose adjustment is needed in patients with mild or moderate renal impairment while receiving ruxolitinib.

Patients diagnosed with severe renal impairment while receiving ruxolitinib should be carefully monitored and need to have their doses reduced to avoid adverse drug reactions (ADRs).

6.3.6 Dose reduction for non-hematological safety

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 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.

6.3.7 Dose reduction for concomitant CYP inhibitor use

Ruxolitinib is metabolized in the liver by the cytochrome (CYP) P450 metabolizing enzyme system, predominantly by the CYP 3A4 isozyme. With concomitant dosing of potent CYP3A4 inhibitors such as systemic ketoconazole, plasma exposure of ruxolitinib increases by approximately 2-fold. Thus, a dose reduction of ~ 50% for ruxolitinib is appropriate for patients who take systemic ketoconazole or other potent CYP3A4 inhibitors systemically as concomitant medication (see Appendix 7).

Potent inhibitors of CYP3A4 include systemic ketoconazole, clarithromycin, itraconazole, nefazodone and telithromycin. The use of these agents on Study Day 1 will require that patients initiate ruxolitinib therapy at 10 mg qd.

NOTE: once the course of therapy using a potent CYP3A4 inhibitor has been completed, the patient may resume his/her prior bid dose regimen of ruxolitinib beginning the next day.

6.3.8 Optional dose tapering strategy in the event of discontinuation

When a decision is made to permanently discontinue ruxolitinib therapy for reasons other than for hematologic safety, a dose tapering strategy may be considered, based on evaluation of the condition of the patient, the current dosing regimen and the clinical judgment of the investigator. If considered to be medically necessary, the investigator may use any treatment to manage withdrawal from ruxolitinib including a gradual tapering of the study drug dosage or use of other medications to manage events occurring after discontinuation.

Short-term courses of corticosteroids have been used in patients with MF and may be considered as part of a tapering strategy. Corticosteroids may be started prior to, or concurrent with, ruxolitinib tapering. When a decision has been made to discontinue the patient utilizing

[redacted]

a tapering strategy, routine study visits and study assessments should continue to be completed per the protocol schedule (see Table 7-1) until the patient completes the ruxolitinib tapering, regardless of any concomitant medications. The follow-up phone call (30 days post last dose) should also occur as scheduled.

6.4 Concomitant medications

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, and herbal/natural medications) administered during the study must be listed on the Concomitant Medications/Significant Non-Drug Therapies of the eCRF. All prior medications used to treat Polycythemia vera will 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

6.4.1.1 Hormonal contraception

Females of childbearing potential will be allowed to use oral, injectable or implanted contraceptives that have been determined to be at least 99% effective as indicated in Exclusion Criterion (see Section 5.3).

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 ruxolitinib is administered during the study:

- Systemic corticosteroid doses greater than the equivalent of 10 mg prednisolone per day is not permitted, unless used as part of a ruxolitinib-dose tapering strategy (see Section 6.3.8 Optional dose tapering strategy in the event of discontinuation)
- Low dose aspirin (75-150 mg/day) and non-steroidal anti-inflammatory agents (acetaminophen, ibuprofen) may be used. Higher doses of aspirin (> 150 mg/day) should not be used except when medically indicated and recommended by the treating physician.
- When concomitant administration of an anticoagulant/antiplatelet medication is required for patient management, the platelet count history, and any observations of thrombocytopenia during the study while on study drug should be considered.
- Granulocyte growth factors are not allowed while study medication is being administered but may be used for severe neutropenia at the Investigator's discretion while study medication is being withheld.
- Inducers or inhibitors of the metabolizing enzyme CYP3A4 (Refer to Appendix 7):
- When concomitant administration of a strong (potent) systemic inhibitor of CYP3A4 metabolizing enzymes or dual CYP2C9/CYP3A4 inhibitors (see Appendix 7) 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.

[redacted]

- Note: No dose adjustment of ruxolitinib 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 systemic CYP3A4 inducers (See Appendix 7) are co-administered with study treatment.

6.4.3 Prohibited concomitant therapy

The following medications are prohibited during the study until treatment discontinuation:

a. Any investigational medication (other than ruxolitinib) 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 drug and during the study through the Safety Follow-up Visit is prohibited.
b. Use of PEG-IFN-alpha-2a within the 5 weeks prior to Study Day -1 is prohibited.
c. Use of any medication to treat PV disease (except for low-dose aspirin) is prohibited once dosing with ruxolitinib begins on or after Study Day 1.
d. Use of ^{32}P prior to or during the study until treatment discontinuation at any time is prohibited.
e. Use of busulfan or chlorambucil during the study until treatment discontinuation at any time is prohibited.

Aspirin in doses exceeding 150 mg per day is prohibited unless medically indicated.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Patient Number that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. 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 patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No.

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 Patient Number must not be reused for any other patient and the Patient Number for that individual must not be changed, even if the patient is re-screened. If the patient fails to be dosed, the reason will be entered into the Screening Log page.

6.5.2 Treatment assignment

Prior to dosing, all patients who fulfill all entry criteria will be assigned to treatment via IRT. The investigator or his/her delegate will contact the IRT and confirm that the patient fulfills the protocol's entry criteria.

[redacted]

6.5.3 Treatment blinding

Not applicable.

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

Table 6-5 Preparation and dispensing

Study treatment	Dispensing	Preparation
INC424/ruxolitinib	Tablets including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study drug for self-administration at home until their next scheduled study visit.	Not applicable

6.6.1 Study drug packaging and labeling

INC424/ruxolitinib can be provided as global supply or as local commercial material where appropriate and per local regulation. If INC424/ruxolitinib is sourced and labeled in-country, the locally approved form and packaging will be used.

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

6.6.2 Drug supply and storage

INC424/ruxolitinib 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.

Sites should counsel patients if patient compliance falls below 80% of the prescribed dose.

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

[redacted]

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 7-1lists 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.

All visits are to be scheduled according to the appropriate number of calendar days from Day 1 of ruxolitinib drug administration. There is a visit window of +/- 7 for visits up to Week 24 and +/- 14 days for visits after.

Note: If treatment with ruxolitinib is withheld at any time, all study visits, and safety assessments should continue according to the appropriate number of calendar days from Day 1 as per the schedule of assessments.

All data obtained from these assessments must be supported in the patient's source documentation. No eCRF will be used as a source document except for the MPN-SAF TSS. The table indicates which assessments produce data to be entered into the database (D) or remain in the source documents (S).

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening	Baseline	+/- 7 day window							Every 12 Weeks (+/- 14 days)	End of study treatment (EoT)	End of Study (EoS)
Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10, 11, 12, etc.,**	**(777)**	**30 day phone call (778)**
Week			**--5 to -1**	**-1**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**36, 48, 60, ...**		
Day			**-35 to -1**	**-14 to -1**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**252, 336, 420...**	**Last**	
Obtain Informed Consent	D	7.1.1.	X											
Patient History														
Demography	D	7.1.1.3	X											
Inclusion/exclusion criteria	D	7.1.1.1	X											
Eligibility Screening Checklist in IRT	D	7.1.1.1	X											
PV Disease History including phlebotomy history	D	7.1.1.3	X											
Prior antineoplastic therapy (Hydroxyurea)	D	7.1.1.3	X											
Prior antineoplastic therapy (Hematologic disease)	D	7.1.1.3	X											
Smoking history	D	7.1.1.3	X											
Prior/concomitant medications	D	7.1.1.3	X	X	continuous									X
Relevant medical history/current medical conditions	D	7.1.1.3	X											
Phlebotomy procedures	D	7.1.1.3		X		X	X	X	X	X	X	X	X	X
Physical examination	S	7.2.2.1	X	X				X			X	X	X	
ECOG Performance status	D	7.2.2.4	X	X				X			X	X	X	
Height	D	7.2.2.3	X											

[redacted]

	Category	Protocol Section	Screening	Baseline	+/- 7 day window							Every 12 Weeks (+/- 14 days)	End of study treatment (EoT)	End of Study (EoS)
Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10, 11, 12, etc.,**	**(777)**	**30 day phone call (778)**
Week			**--5 to -1**	**-1**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**36, 48, 60, ...**		
Day			**-35 to -1**	**-14 to -1**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**252, 336, 420...**	**Last**	
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 palpation	D	7.2.2.1	X	X				X			X	X	X	
Patient Reported Outcome														
MPN-SAF	D	7.2.5		X				X			X	X	X	
Laboratory Assessments														
Hematology	S/D	7.2.2.5	X	X		X	X	X	X	X	X	X	X	
Chemistry	S	7.2.2.5	X	X		X	X	X	X	X	X	X	X	
Coagulation	S	7.2.2.5	X					X			X	X	X	
Urinalysis (macroscopic)	S	7.2.2.5	X										X	
Pregnancy Test, Serum	D	7.2.2.5.1	X										X	
Pregnancy test, Urine	D	7.2.2.5.1		X		X	X	X	X	X	X	X		
Safety Assessments														
Adverse Events	D	8.1	X	X	continuous									X
Study Drug administration	D	7.1.2			X	X	X	X	X	X	X	X		
End of Treatment Disposition	D	7.1.3.1											X	
Disease Progression Status including diagnostic criteria	D	7.1.3.1											X	
End of Study Disposition	D	7.1.3												X

[redacted]

7.1.1 Screening

Written informed consent must be obtained before any study specific procedure is performed. Screening assessments to confirm eligibility should be performed as per the schedule of assessments in Table 7-1.

All assessments should be completed within the 35 day screening period.

Re-screening of patients will be allowed, if all entry criteria are not met during the screening period (-35 days to -1 day).

7.1.1.1 Eligibility screening

Patients must meet all inclusion (Section 5.2) and none of the exclusion (Section 5.3) criteria during the Screening phase in order to be eligible to proceed to the Treatment Phase of the study. Patient eligibility will be confirmed by using the following processes:

- Investigative staff will capture patient eligibility within the source documents maintained at the site,
- All screening assessment results must be received and reviewed by the investigator/designee to be within protocol required parameters before the patient starts study treatment,
- Patient eligibility will be confirmed by the site within the IRT system. Following registering in IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. An end of screening phase disposition will be completed. Please refer and comply with detailed guidelines in the IRT manual. Only when eligibility has been confirmed will the IRT system indicate patient can proceed with study treatment.

Additionally, sites will enter patient information into the eCRF, and automated queries will be generated for immediate resolution should patient eligibility be in question based on the patient information entered.

7.1.1.2 Information to be collected on screening failures

A patient who signs an informed consent but fails to satisfy all eligibility criteria for any reason will be considered a screen failure. The reason for not starting dosing 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 patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details).

Patients who signed ICF but are considered ineligible after signing the study consent will be considered as screening failures, and data will be handled in the same manner.

The following eCRFs must be completed for screening failure patients:

- Screening Phase Disposition page (including reason for not satisfying eligibility criteria and being started on treatment)

[redacted]

- Informed consent
- Demography
- Adverse Events (only if an SAE occurs)
- Inclusion/Exclusion Criteria

In order to be officially considered a screen failure, the IRT system should be notified, preferably within 2 days of the decision to screen fail the patient.

7.1.1.3 Patient demographics and other baseline characteristics

Data to be collected on patient characteristics at screening include:

- Demography (including: date of birth, age, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)
- Relevant medical history including: smoking history, previous cardiovascular and thromboembolic events. Any history of previous pre malignant or malignant cutaneous lesions should be collected.
- PV diagnosis and extent of disease, including:
  - Date of diagnosis
  - Estimated number of phlebotomies in the past 52 weeks
  - Prior antineoplastic therapies including use of hydroxyurea
- Prior and Concomitant Medications, surgical and medical procedures

All medications taken from screening must be recorded on the Prior and Concomitant medication eCRF page and updated on a continual basis if there is a new change to the medication.

7.1.2 Treatment period

Following completion of screening procedures and verifying patient eligibility, the patient will be approved for treatment via the IRT.

The study treatment phase begins on Day 1 with the first administration of ruxolitinib and will continue until disease progression (see Appendix 4 and Appendix 5), unacceptable toxicity, death, withdrawal of consent for protocol specified procedures, or discontinuation from the study for any other reason until the drug becomes commercially available in each participating country.

Patients will be assessed as per visit schedule in Table 7-1.

Visit windows of ± 7 days from scheduled study assessments will apply up to Week 24 and ± 14 days for visits after Week 24.

7.1.3 End of treatment visit including study completion and premature withdrawal

At the time patients discontinue study treatments, a visit should be scheduled as soon as possible, at which time all of the assessments listed for the End of Treatment (EOT) visit will

[redacted]

be performed and an End of treatment CRF page will be completed giving the date and reason for stopping treatment.

At a minimum, all patients who discontinue treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations 30 days following the last dose of treatment by phone.

Patients who discontinue treatment should be considered withdrawn after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

If a withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the study Evaluation Completion CRF page.

7.1.3.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the ETP at any time.

Patient death will be considered as a withdrawal from the study. Patients may also be withdrawn (the physician may decide to remove the patient from any further study activity) if any of the following occur:

- Adverse event(s) (see Section 8.1)
- Major protocol deviation
- Technical problems
- Physician decision
- Non-compliance with study treatment

Patients must be withdrawn if any of the following occur:

- Lost to follow-up
- Patient/guardian decision
- Study terminated by sponsor
- Pregnancy (Pregnancy will be followed for outcome)
- Disease progression – sites should indicate type of progression and include information on the diagnostic bone marrow biopsy result if obtained as per diagnostic criteria (see Appendix 4 and Appendix 5).
- Withdrawal of consent

Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Treatment duration is considered "completed" three months after the expanded treatment plan's drug becomes commercially available for the PV indication in the patients participating country or by 31 Dec 2017, whichever comes first, and the patient should be transitioned to commercial product. Study sites should stop all patients' study participation on the study at this time.

[redacted]

7.1.3.2 Replacement policy

Patients will not be replaced on study

7.1.4 Follow up period

All patients must have a follow up safety phone evaluation 30 days after the last dose of treatment (Study Evaluation Completion or EoS).

Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.2 Assessment types

7.2.1 Efficacy assessments

Assessments for efficacy will consist of Hct measured locally, spleen by palpation, and MPN-SAF TSS.

- Samples for hematology assessments will be prepared and analyzed locally as indicated in Table 7-1. Data for specific Hematology tests will be recorded in the eCRF as indicated in Table 7-2.

7.2.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit. For details on AE collection and reporting, refer to. Significant findings that were present prior to the signing of informed consent must be included in the relevant medical history/current medical conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

7.2.2.1 Physical examination

Physical examinations will include an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and a basic nervous system evaluation. Information about the physical examination must be present in the source documentation at the center. For the assessment schedule refer to Table 7-1.

Spleen will be assessed by palpation at visits indicated in Table 7-1. If palpable, a soft ruler should be used to document the spleen size, rounded to the nearest centimeter, from the left costal margin to the point of greatest splenic protrusion Spleen size will be used to determine if dose increases for lack of efficacy should be considered at or subsequent to Week 4 and for routine patient management. Spleen length information will be documented in the eCRF.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that

[redacted]

begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF except for spleen length which will be documented in a separate eCRF page.

7.2.2.2 Vital signs

Vital signs include body temperature and blood pressure. Blood pressure (systolic and diastolic) should be measured after the patient has been sitting for five minutes.

For the assessment schedule refer to Table 7-1

7.2.2.3 Height and weight

Height in centimeters (cm) will only be collected at screening. Body weight (to the nearest 0.1 kilogram (kg) with indoor clothing on, but without shoes) will be measured at every study visit.

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 (see Appendix 2).

7.2.2.5 Laboratory evaluations

Local site laboratories will be used for the analysis of scheduled hematology, biochemistry, urine, and other blood specimens collected as part of safety monitoring. All unscheduled blood testing will be performed locally. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 7.1)

Laboratory abnormalities that are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in ruxolitinib treatment (see Section 8.1) constitute an adverse event (AE) and must be reported as an AE on the AE CRF page.

Laboratory values obtained at the screening visit will be used to assess eligibility to meet inclusion criteria. If patient meets all inclusion and no exclusion criteria, the screening labs can be used for baseline if patient is dosed within 14 days of the screening visit. If patient cannot be dosed within 14 days of screen, then the labs should be repeated the day before patient starts dosing (see baseline visit in Table 7-1).

Only Hematocrit (Hct), Hemoglobin (Hb), Platelet (Plt), White Blood Count (WBC), absolute or % neutrophils and pregnancy values will be collected on the eCRF.

Table 7-2 Local clinical laboratory parameters

Test Category	Documentation	Test Name
Hematology	eCRF	Hematocrit, Hemoglobin, Platelets, WBC, Absolute or % Neutrophils
Hematology	Source documents	Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin (MCH) , Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), Platelets, Red blood cells, White blood cells, %Blasts, Red Blood Count (RBC), White Blood Cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

[redacted]

Test Category	Documentation	Test Name
Chemistry	Source Documents	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Chloride, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid
Urinalysis	Source Documents	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation	Source Documents	Prothrombin time (PT) or International normalized ratio [INR]), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)
Pregnancy	eCRF	Serum at screening and End of Treatment (EOT); Urine - all other time points

7.2.2.5.1 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum hCG test at screening. Thereafter, the patients will have a urine pregnancy test. At the End of Treatment visit a serum hCG test will be done. 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. All the urine pregnancy tests will be performed locally. See Section 5.3 for further information on required birth control methods.

The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit. Refer to Table 7-1. If local requirements dictate otherwise, local regulations should be followed.

If a positive pregnancy test is performed in between visits, the patients must immediately notify the investigator.

7.2.2.6 Cardiac assessments

Not applicable.

7.2.3 Biomarkers

Not applicable.

7.2.4 Resource utilization

Not applicable.

7.2.5 Patient reported outcomes

Patient reported Outcomes will be collected through the MPN-SAF according to the Visit Schedule outlined in Table 7-1.

The patient should be given sufficient space and time to complete the questionnaire. The site personnel should check the questionnaire 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.

[redacted]

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.

MPN-SAF

The MPN-SAF (Appendix 6) is a disease specific questionnaire comprised of 10 items that measures fatigue related to MPN disease and the severity of nine of the most prevalent associated symptoms including: early satiety, abdominal discomfort, inactivity, concentration, night sweats, itching, bone pain, fever and weight loss. There are three recall periods used in this questionnaire, they are 24 hours for fatigue, the past week for symptoms of early satiety, abdominal discomfort, inactivity, concentration, night sweats, itching, bone pain and fever, and the past 6 months for weight loss, Each item is scored on a scale ranging from 0 (no fatigue/absent) to 10 (As bad as you can imagine/worst imaginable). The MPN-SAF TSS is computed as the average of the observed items multiplied by 10 to achieve a 0-to-100 scale. The MPN-SAF TSS thus has a possible score range of 0 to 100.

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.

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 (or 5 half-lives, whichever is longer) 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.

[redacted]

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, 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)
3. Reasonable possibility that AE is related to ruxolitinib (no, yes)
4. Action taken with respect to ruxolitinib (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. 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.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

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.

[redacted]

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.

8.2 Serious adverse events

8.2.1 Definitions

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

1. Is fatal or life-threatening
2. Results in persistent or significant disability/incapacity
3. Constitutes a congenital anomaly/birth defect
4. 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
5. Requires inpatient hospitalization or prolongation of existing hospitalization,
6. 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

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided 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

[redacted]

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

Not applicable.

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 ruxolitinib of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

The procedures that will be followed based on whether a pregnancy is confirmed by a positive serum or urine test result during the study or within 30 days of stopping study drug, are listed below:

- Investigator and patient must notify each other immediately.

[redacted]

- Investigator must notify the Sponsor/designee immediately (see Section 9.2).
- Discontinue study drug immediately.
- Perform the required End-of-treatment visit study evaluations.
- Investigator must complete and submit the Pregnancy Initial and Follow-up report forms to the Sponsor.
- A serum pregnancy test must be performed to confirm the urine test result. (The serum test should be performed at the investigative site to ensure the test will be performed promptly and the result available immediately for review.)
- Withdraw the patient from the study.
- If a negative serum test does not confirm the urine test result, then: the investigator will use his/her expert judgment, based on an assessment of the potential benefit/risk to the patient, to determine if it is in the patients best interest to resume study drug and continue participation in the study.

The outcome of all such pregnancies (i.e., spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be documented and followed-up on a form that will be provided by the Sponsor. The pregnancy will be followed to term and the outcome, including any premature termination, must be reported to the Sponsor. All live births must be followed for a minimum of 30 days or to the first well-baby visit. All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as an SAE for this study. Elective abortion procedures, without complications, should not be considered as AEs.

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

Not applicable.

8.7 Steering Committee

Not applicable.

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

[redacted]

- 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.

An inclusion/exclusion checklist 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).

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 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

Novartis and/or a designated CRO will perform all analyses. Any data analysis carried out independently by the investigator should not be presented or published before the final analysis is completed. The data from all centers that participate will be combined in the analyses.

Final analyses will be performed when all patients have been followed for 30 days after they have either prematurely discontinued or been discontinued from the study after completing treatment as per protocol (i.e., until the drug is commercially available for this indication in each participating country).

[redacted]

The data will be summarized with respect to demographic and baseline characteristics, and safety observations and measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

10.1 Analysis sets

The following analysis sets will be used for statistical analysis and data reporting.

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study treatment.

10.1.3 Per-Protocol Set

Not applicable.

10.1.4 Dose-determining analysis set

Not applicable.

10.1.5 Pharmacokinetic analysis set

Not applicable.

10.1.6 Other analysis sets

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic, disease characteristics and other baseline data will be summarized descriptively for the FAS.

10.3 Treatments (study treatment, concomitant therapies, compliance)

All analyses from this section will be performed on all patients from the safety set.

Duration of ruxolitinib treatment exposure and cumulative dose and dose intensity will be summarized. The number of patients with dose changes/interruptions will be presented, along with reasons for the dose change/interruption.

Concomitant medications and significant non-drug therapies prior to and after the start of the treatment will be summarized by ATC code.

10.4 Primary objective

The primary objective is to evaluate safety data in patients with PV who are hydroxyurea resistant or intolerant. The safety set will be used for the analysis of clinical safety data.

10.4.1 Variable

The analysis of the primary objective is described in Section 10.5.3.

10.4.2 Statistical hypothesis, model, and method of analysis

No statistical hypotheses will be tested.

10.4.3 Handling of missing values/censoring/discontinuations

No imputation will be applied for any missing data.

10.4.4 Supportive analyses

Not applicable.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

Not applicable.

10.5.2 Other secondary efficacy objectives

Secondary objectives are described in Section 3 and corresponding efficacy endpoints are outlined in detail in Table 3-1.

Only descriptive statistics will be presented for all secondary efficacy endpoints.

Change from Baseline in Hct and spleen length, to different scheduled visits will be summarized with descriptive statistics.

If multiple assessments are taken within the window of the visit, the assessment used to evaluate a visit will be the one closest to that visit that occurs within the window allowable for the assessment and that is evaluable.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used.

The overall observation period will be divided into 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. If applicable, post-treatment period: starting at day 31 after last dose of study medication.

[redacted]

10.5.3.2 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 CTCAE grades), and type of adverse event.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, the study's biostatistical and reporting team will grade laboratory data accordingly.

In cases of the white cell differentials the lower limits of normal ranges used in CTCAE definition have to be replaced by a clinically 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.

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- 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, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the MAP and/or RAP.

10.5.3.4 Other safety data

Other safety data (including vital signs and weight) will be summarized and listed, notable values will be flagged, and any other information collected will be listed as appropriate.

[redacted]

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

Tolerability will be studied in terms of dose reductions or dose interruption due to an AE.

Number and percentage of patients who have a dose modification due to a treatment related Adverse Event will be summarized by type of dose modification (interruption, dose reduction, and permanent discontinuation).

10.5.4 Pharmacokinetics

Not applicable.

10.5.5 Resource utilization

Not applicable.

10.5.6 Patient-reported outcomes

The MPN-SAF will be used to collect data on the patient's disease-related symptoms. No formal statistical test will be performed.

Missing items data in a scale will be handled based on each instrument manual. No imputation will be applied if the total or subscale scores are missing at a visit.

Descriptive statistics (e.g., mean, median) will be used to summarize the scored scales at each scheduled assessment time point for the MPN-SAF TSS. Additionally, change from baseline in the domain scores at the time of each assessment will be summarized. Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

10.6 Exploratory objectives

Not applicable.

10.7 Interim analysis

No interim analysis is planned. Analyses may be performed if needed to fulfill regulatory requests or for publication purposes.

10.8 Sample size calculation

The planned sample size of approximately 500 patients was chosen based on the expected accrual rates and the planned duration of the trial. It was not based on any statistical consideration. The actual sample size may differ from this planned number.

10.9 Power for analysis of key secondary variables

Not applicable.

[redacted]

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

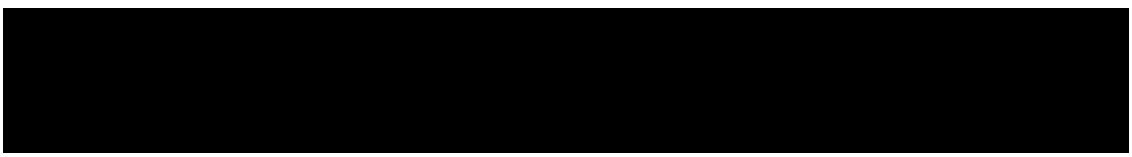
Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will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

Novartis will provide to investigators, in a separate document, a proposed 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.

[redacted]

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.

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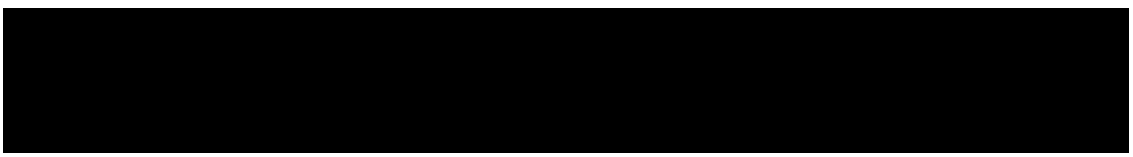

14 Appendices

14.1 Appendix 1: The 2008 World Health Organization diagnostic criteria for polycythemia vera

Diagnosis requires meeting both major criteria and one minor criterion or the first major criterion and two minor criteria.

Major criteria

1. Hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume.*
2. Presence of JAK2V617F or other functionally similar mutation such as JAK2 exon 12 mutation.

Minor criteria

1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation.
2. Serum erythropoietin level below the reference range for normal.
3. Endogenous erythroid colony formation in vitro.

*Hemoglobin or Hct > 99th percentile of method-specific reference range for age, sex, and altitude of residence; or hemoglobin > 17 g/dL in men, 15 g/dL in women if associated with a documented and sustained increase of at least 2 g/dL from an individual's baseline value that cannot be attributed to correction of iron deficiency; or elevated red cell mass > 25% above mean normal predicted value.

(Thiele and Kvasnicka 2009 as adapted from Tefferi et al 2007, Tefferi and Vardiman 2008)

[redacted]

14.2 Appendix 2: Eastern Cooperative Oncology Group Performance Status

Table 14-1 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, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

(Oken et al 1982)

[redacted]

14.3 Appendix 3: New York Heart Association (NYHA) Functional Classification

Table 14-2 New York Heart Association (NYHA) Functional Classification

Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

(The Criteria Committee of the New York Heart Association 1994)

[redacted]

14.4 Appendix 4: 2008 WHO classification for Myelodysplastic Syndromes (MDS)

Table 14-3 2008 WHO classification for Myelodysplastic Syndromes (MDS)

	Auer Rods	**Peripheral Blood Blasts ≥ 1%**	**Bone Marrow Blasts ≥ 5%**	**Isolated del(5q)**
RAEB-2	Yes	No	No	No
RAEB-2	No	Yes (5-19%)	No	No
RAEB-2	No	No	Yes (10-19%)	No
RAEB-1	No	Yes (2-4%)	No	No
RAEB-1	No	No	Yes (5-9%)	No
MDS-del(5q)	No	No	No	Yes
No Auer Rods, Blood Blasts, Bone Marrow Blasts, Isolated del(5q)				
	Multilineage dysplasia	**Unilineage dysplasia**	**≥ 15% Ring sideroblasts**	**Not fitting elsewhere**
RCMD	Yes	No	No	No
RCUD	No	Yes	No	No
RARS	No	Yes	Yes	No
MDS-U	No	No	No	Yes
Minimal criteria for MDS = Presence of ≥ 10% dysplastic cells in bone marrow with a specific myeloid lineage Exclude: AML (≥ 20% peripheral blood or bone marrow blasts) CMML (monocyte count >1x10^9/L)				

- AML - acute myeloid leukemia
- CMML- chronic myelomonocytic leukemia
- RAEB-1 - Refractory anemia with excess blasts-1
- RAEB-2 - Refractory anemia with excess blasts-2
- MDS del(5q) - MDS associated with isolated del(5q)
- RCMD - Refractory cytopenia with multilineage dysplasia
- RCUD - Refractory cytopenia with unilineage dysplasia
- RARS - Refractory anemia with ringed sideroblasts
- MDS-U - Myelodysplastic syndrome, unclassified

Tefferi A, Vardiman, J (2009)

[redacted]

14.5 Appendix 5: IWG-MRT recommended criteria for post-PV MF

Table 14-4 IWG-MRT recommended criteria for post-PV MF

	Required criteria:
1	Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria[1]
2	Bone marrow fibrosis grade 2–3 (on 0–3 scale)[3] or grade 3–4 (on 0–4 scale)[4,a]
	Additional criteria (two are required):
1	Anemia[b] or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis
2	A leukoerythroblastic peripheral blood picture
3	Increasing splenomegaly defined as either an increase in palpable splenomegaly of 5 cm or more (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4	Development of 1 or more of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

(Barosi et al 2008)

[redacted]

14.6 Appendix 6: Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

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

Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours 0 1 2 3 4 5 6 7 8 9 10 (No Fatigue) (As Bad As You Can Imagine)	
Circle the one number that describes during the past week how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early satiety)	0 1 2 3 4 5 6 7 8 9 10 (Absent) (Worst Imaginable)
Abdominal discomfort	0 1 2 3 4 5 6 7 8 9 10 (Absent) (Worst Imaginable)
Inactivity	0 1 2 3 4 5 6 7 8 9 10 (Absent) (Worst Imaginable)
Problems with concentration - compared to before my diagnosis	0 1 2 3 4 5 6 7 8 9 10 (Absent) (Worst Imaginable)
Night sweats	0 1 2 3 4 5 6 7 8 9 10 (Absent) (Worst Imaginable)
Itching (pruritus)	0 1 2 3 4 5 6 7 8 9 10 (Absent) (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	0 1 2 3 4 5 6 7 8 9 10 (Absent) (Worst Imaginable)
Fever (>37.8° C or 100° F)	0 1 2 3 4 5 6 7 8 9 10 (Absent) (Worst Imaginable)
Unintentional weight loss last 6 months 0 1 2 3 4 5 6 7 8 9 10 (Absent) (Worst Imaginable)	

[redacted]

14.7 Appendix 7: Restricted medications

Table 14-5 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 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 and CYP3A4 inhibitors:

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]