NOVARTIS

Clinical Development

INC424/ruxolitinib/Jakavi®

Oncology Clinical Protocol CINC424A2411 / NCT02966353

A multicenter phase II, open label, single arm study to evaluate the efficacy and safety of ruxolitinib in the treatment of anemic myelofibrosis patients.

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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
b.i.d./BID	*bis in diem*/twice a day
BAT	Best available therapy
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
COMFORT	COntrolled MyeloFibrosis Study With ORal JAK Inhibitor Treatment
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CR	Complete response
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYPs	Cytochrome P450 system of metabolizing enzymes, includes isoenzymes designated CYP3A4, CYP2C11, CYP2C13
DAR	Dosage Administration Record
DDI	Drug-Drug Interaction
DIPSS	Dynamic International Prognostic Scoring System
dL	Deciliter (100 mL)
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form; the term eCRF can be applied to either EDC or Paper
EDC	Electronic Data Capture
EOT	End of treatment
ET	Essential thrombocythemia
FAS	Full analysis set
FDA	Food and Drug Administration
FPLV	First patients last visit
GCP	Good clinical practice
HDL	High Density Lipoprotein
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

[redacted]

INC424	Ruxolitinib
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IUD	Intrauterine device
IUS	Intrauterine system
IVRS	Interactive Voice Response System
IWG MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
JAK	Janus kinase
L	Liter
LDH	Lactate dehydrogenase
LDL	Low Density Lipoprotein
LPFV	Last patient first visit
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
MF	Myelofibrosis
MF-7	Myelofibrosis 7 Item Symptom Scale
MFSAF	Myelofibrosis Symptom Assessment Form
mg	Milligram(s)
mL	Mililiter(s)
MM	Multiple Myeloma
MPD	Myeloproliferative disorder
MPN	Myeloproliferative neoplasms
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
o.d.	*omnia die*/once a day
PD	Pharmacodynamic (s)
PE	Physical examination
PET-MF	Post essential thrombocythemia-myelofibrosis
PGIC	Patient Global Impression of Change
PLT	Platelet
PK	Pharmacokinetics
p.o.	*per os*/by mouth/orally
PHI	Protected Health Information
PMF	Primary myelofibrosis
PML	Progressive multifocal leuko-encephalopathy
PPS	Per-Protocol Set
PPV-MF	Post polycythemia vera-myelofibrosis
PRO	Patient Reported Outcomes

[redacted]

PS	Performance status
PV	Polycythemia vera
QD	Once a Day
QoL	Quality of life
RA	Rheumatoid Arthritis
RDC	Remote data capture
REB	Research Ethics Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SOP	Standard Operating Procedure
$T_{1/2}$	Half life
TD	Transfusion Dependent
TI	Transfusion Independence
T_{max}	Time to maximum concentration
ULN	Upper limit of normal
USA	United States of America
VS	Vital signs
WBC	White blood cell count
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
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
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug 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
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

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Protocol summary:

Title	A multicenter phase II, open label, single arm study to evaluate the efficacy and safety of ruxolitinib in the treatment of anemic myelofibrosis patients.
Brief title	Anemia trial in MF patients
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This is a study of treatment with ruxolitinib in patients who present with transfusion dependent or independent anemia at screening defined as an hemoglobin <10 g/dL with 10 mg BID starting dose with subsequent up titrations depending on safety and efficacy. This dosing approach for anemic MF patients will be systematically studied in this prospective multicenter phase II open label single arm trial to determine if the levels of spleen length reduction and symptom improvement are consistent with those reported in previous clinical trials with ruxolitinib in patients with anemia and doses according to platelet counts at the moment of treatment initiation, and whether this lower starting dose and up titration approach may minimize the initial hemoglobin and platelet declines and transfusion requirements.
Primary Objective	To determine the spleen length response rate at week 24.
Secondary Objectives	• To evaluate safety. • To determine the spleen length response rate at week 48. • To evaluate the effect of ruxolitinib on spleen length. • To evaluate the effect of ruxolitinib on symptoms. • To evaluate the effect of ruxolitinib on Patient Global Impression of Change (PGIC). • To evaluate the effect of ruxolitinib on transfusion requirements.
Study design	This is an open-label, single-arm study of treatment with ruxolitinib in patients who presents with transfusion dependent or independent anemia at screening defined as an hemoglobin <10 g/dL. The starting dose is 10 mg BID for all enrolled patients and gradual up titrations will start at week 12 determined by the level of efficacy achieved and the tolerability.
Population	Patients with Primary Myelofibrosis (PMF), Post-Polycythemia Vera-Myelofibrosis (PPV-MF), or Post-Essential Thrombocythemia Myelofibrosis (PET-MF) who have splenomegaly that is equal to or greater than 5 cm below the left costal margin and with anemia defined by Hb less than 10 g/dL.
Inclusion criteria	**Key Inclusion criteria: (See Section 5.2 for details)** • Male or female patients aged ≥ 18 years of age. • Patients must be diagnosed with PMF, according to the 2016 revised International Standard Criteria (Arber et al, 2016), PPV MF or PET-MF (Barosi 2008), irrespective of JAK2 mutation status. • Patients with palpable splenomegaly that is equal to or greater than 5 cm below the left costal margin. • Patients with a hemoglobin less than 10 g/dL • Patients with a history of transfusions must have a documented transfusion record in the previous 12 weeks to baseline. • Patients with a peripheral blood blast percentage count of < 10%.

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Exclusion criteria	**Key Exclusion Criteria (See Section 5.3 for details)**
	• Patients with prior treatment with any JAK1 or JAK2 inhibitor.
	• Patients with inadequate bone marrow reserve at baseline visit as demonstrated by at least one of the following:
	  • ANC that is ≤ 1,000/μL.
	  • Platelet count that is <50,000/μL without the assistance of growth factors, thrombopoietic factors or platelet transfusions.
	  • Hemoglobin count that is ≤ 6.5 g/dL despite transfusions.
	• Patients with severely impaired renal function
	• Patients with inadequate liver function
	• Patients being treated concurrently with a strong (potent) systemic inhibitor or inducer of CYP3A4 at the time of Screening
	• Acute viral hepatitis or active chronic hepatitis B or C infection.
	• History of progressive multifocal leuko-encephalopathy (PML)

Investigational therapy	Ruxolitinib will be self-administered as BID oral treatment. The starting dose is 10 mg BID for all enrolled patients and gradual up titrations will start at week 12 determined by the level of efficacy achieved and the tolerability.
Efficacy assessments	• Spleen length • Transfusions over time
Safety assessments	• Adverse events • Hematology parameters • Chemistry parameters

Other assessments	• An assessment of Patient reported outcomes using
	  • Myelofibrosis 7 Item Symptom Scale (MF-7)
	  • Separate question on Inactivity to compute Modified MFSAF v2.0.
	  • Patient Global Impression of Change (PGIC)
	[redacted]

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. Approximately 50 patients will be enrolled in this study.
Key words	Ruxolitinib, anemia, Primary Myelofibrosis (PMF), Post-Polycythemia Vera-Myelofibrosis (PPV-MF), Post-Essential Thrombocythemia Myelofibrosis (PET-MF)

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1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

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

PMF is a clonal MPN (Myeloproliferative neoplasm) of the pluripotent hemopoietic stem cell, in which the proliferation of multiple cell lineages is accompanied by progressive bone marrow fibrosis. Marrow fibrosis is thought to be secondary to the release of pro - inflammatory cytokines from abnormal clonal cells (primarily megakaryocytes), which act to stimulate fibroblast proliferation and fibrosis. Mild to moderate anemia is found in most patients at presentation and worsens as myelofi brosis progresses. The anemia is in large p art due to reduced erythropoiesis, but may be compounded by hypersplenism, bleeding and iron or folate deficiency (Campbell 2006).

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

All currently available pharmacologic treatments are either directed towards the management of MF-originated anemia or the treatment of MF-symptoms including splenomegaly. As these treatments do not cure or modify the disease progression of MF, they are mostly used to treat patients in the higher risk categories. MF patients in the lower risk categories (IPSS Low and Int-1), by virtue of a relatively asymptomatic disease and an indolent disease course, are managed through active surveillance or a ‘watch and wait’ approach until appearance of bothersome symptoms or the definitive progression to the higher risk groups. Allogeneic stem cell transplantation is the only curative option, but it is ofte n associated with a high rate of

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mortality and morbidity (Kroger 2008). Other available treatments include splenectomy, involved field radiotherapy, erythropoiesis stimulating agents, androgen preparatio ns, thalidomide and its analogs, hydroxyurea. More recent advancements in MF treatment include the discovery of ruxolitinib, a Janus Kinase (JAK)1 and JAK2 inhibitor. Ruxolitinib is one of the first treatments in MF that has demonstrated rapid and durable reductions in MF- related splenomegaly, improvement in disease-related symptoms and offers a distinct survival benefit (Vannucchi et al. 2015). Final 5 years analysis of both COMFORT I & II have demonstr ated that long-term ruxolitinib treatment in patients with MF is associated with durable reductions in splenomegaly and significantly longer OS compared with placebo and BAT respectively; supporting ruxolitinib as an effective long-term treatment for patients with intermediate-2 and high-risk MF. (Harrison 2016; Gupta 2016)

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

These mutations are defined as the 'high molecular risk' category (HMR) in PMF based on the presence of at least one of the five prognostically detrimental mutated genes (ASXL1, EZH2, SRSF2, IDH1 and IDH2). Association between some HMR genes (ASXL1 and SRSF2) and anemia has been described (Vannucchi et al 2013).

1.1.1 Inhibition of Janus Kinases (JAK) in MPN

A key feature of MPNs is the dysregulation of JAK/STAT signaling. The JAK/STAT pathway is involved in normal hematopoiesis, inflammation, and immune function (Ghoreschi et al. 2009). The 4 members of the JAK family - JAK1, JAK2, JAK3, and TYK2 - are non-receptor tyrosine kinases that play a central role in signal transduction initiated by cytokines (e.g., interleukin and interferon signaling), growth factors, and hormones (Ghoreschi et al. 2009). Specifically:

- JAK1 - role in lymphopoiesis and cytokine response; ubiquitously expressed
- JAK2 - role in erythropoiesis; ubiquitously expressed
- JAK3 - role in lymphocyte development and proliferation and immune response; expressed primarily in hematopoietic cells
- TYK2 - role in mediation of cytokine signals; ubiquitously expressed

Upon ligand binding, the receptor undergoes conformational changes that allow JAK activation and result in receptor homodimerization (i.e., JAK2/JAK2) or heterodimerization (ie, JAK1/JAK2) (Vainchenker 2008). The activated JAKs create docking sites on the receptor for STAT (signal transducers and activators of transcription) proteins. STAT proteins, once activated, dissociate from the receptor, dimerize, and translocate into the nucleus to initiate transcription of target genes (Ghoreschi et al. 2009). Given the importance of this interaction, this pathway is also known as the JAK/STAT pathway.

[redacted]

Dysregulation of the JAK pathway can occur in a number of ways. Ligand -independent activation of the pathway can occur due to mutations in the JAK recept or. In addition, mutations in or activation of other modulators of the signaling pathway can result in pathway overactivation. Regardless of a particular mutation's presence or absence, dysregulation of the JAK pathway is a hallmark of MPNs. The majority of patients with Myelofibrosis, Polycythemia Vera, and Essential thrombocythemia bear a somatic activating mutation in *JAK2* whereby a G>T nucleotide exchange in exon 14 at position 1849 results in a substitution of valine by phenylalanine at amino acid 617 (JAK2 V617F) (Tefferi et al. 2009a).

Genome-wide association studies suggest that individuals can have a genetic predisposition to the development of JAK2 V617F-positive MPNs. Specific haplotypes have been identified that preferentially acquire the JAK2 V617F mutation and confer susceptibility to MPNs, which may partially explain the phenotypic diversity observed in carriers of the mutation (Tefferi et al. 2009a), (Olcaydu et al. 2009).

With frequencies of greater than 95% in PV and approximately 50% in MF and ET (Tefferi et al. 2009a), the presence of this mutation is a major criterion in the diagnosis of these diseases. Although the JAK2 V617F-activating mutation is the most commonly observed mutation in MPNs, it is not the only JAK pathway-activating mutation noted in MPN patients. Mutations in exon 12 have also been noted, mostly in PV patients (Scott et al. 2007). Indeed, virtually all JAK2 V617F-negative PV patients bear JAK2 exon 12 mutations (Schnittger et al. 2009). Of note, these mutations affect the pseudokinase domain or a proximal region ("exon 12" mutations) but not the kinase domain.

Abnormal activation of JAK1 has also been noted in MF patients (Quintas-Cardama et al 2010). In addition to alterations in JAK1 and JAK2, alterations in other members of the JAK pathway have been detected in MPN patients. These alterations include a somatic activating mutation in the JAK2-associated thrombopoietin receptor gene MPL at codon 515 (*MPL W515L/K*) and various mutations in LNK, a negative regulator of JAK/STAT signaling (Oh 2010, Patnaik 2010) and mutations in CALR (Kampfl 2013, Nangalia 2013, Chachoua 2016). Clearly, JAK pathway dysregulation, regardless of mutational status, is a key pathophysiological feature of MPNs.

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 develo ped 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.

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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); also EU and other countries have recently approved JAKAVI for the treatment of adult patients with polycythemia vera (PV) resistant to or intolerant of hydroxyurea. 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 (Appendix 6).

1.2.1.1 Non-clinical experience

1.2.1.1.1 Ruxolitinib preclinical safety

Ruxolitinib has been evaluated in safety pharmacology, repeat dose toxicity, genotoxicit y, reproductive toxicity and carcinogenicity studies. Target organs associated with the pharmacological action of ruxolitinib in repeat dose studies include bone marrow, peripheral blood and lymphoid tissues. Infections generally associated with immunosupp ression were noted in dogs. The potential for ruxolitinib to cause adverse alterations in respiratory, neurologic, and cardiovascular parameters in humans is low.

Ruxolitinib was not teratogenic but was associated with increases in post-implantation loss and decreases in fetal weights. No effects were noted on fertility. In a pre - and post-natal development study, there were no adverse findings for fertility indices and maternal and embryofetal survival, growth, and developmental parameters. Ruxolitinib was not mutagenic or clastogenic. Ruxolitinib was not carcinogenic in the Tg.rasH2 transgenic mouse model nor in a 2-year study in rats.

Additional toxicology and safety pharmacology information is available in the [Investigator Brochure].

1.2.1.2 Clinical experience

1.2.1.2.1 Ruxolitinib pharmacokinetics

Fifteen Phase I , nine Phase II and three Phase III clinical studies (two in MF, one in PV) provided clinical pharmacology data on ruxolitinib in healthy volunteers and in patients with MF, ET, PV, subjects with renal or hepatic impairment, prostate cancer, pancreatic cancer, multiple myeloma (MM) or rheumatoid arthritis (RA).

Oral absorption of ruxolitinib is rapid and nearly complete, with ≥95% absorption indicating high *in vivo* permeability in the human gastrointestinal tract, consistent with a Biopharmaceutical Classification System (BCS) Class I compound. Mean peak plasma concentration (C_{max}) is achieved 1-2 h post-dose. The effect of food on ruxolitinib exposure is minimal and is not expected to be clinically significant; as a result, the drug may be administered either with or without food.

Dose proportional exposure is observed between 5 and 200 mg dose range with linear pharmacokinetics (PK). Plasma protein binding is approximately 97% *in vitro*. There is

[redacted]

moderate distribution to organs and tissues with no long-term retention of drug-related material in preclinical species and limited drug penetration into the central nervous system (CNS) or across the blood-brain barrier. There was >95% [^{14}C] drug recovery in a mass balance study with 74% and 22% of the dose excreted in urine and feces of healthy subjects, respectively. Less than 1% of the administered dose is recovered in urine and feces as unchanged parent drug. The mean terminal elimination half-life ($T_{1/2}$) is ~3 h with no appreciable accumulation of either parent or metabolites with twice daily dosing.

Metabolism is predominantly via the cytochrome P450 isozyme CYP3A4 to yield oxygenated and subsequent conjugated metabolites. Oxidative metabolites of ruxolitinib retain pharmacological activity albeit with one half to one fifth of the activity of the parent compound. *Ex vivo* pharmacokinetic/pharmacodynamic (PK/PD) analysis indicates that the total of 8 active metabolites contribute to 18% of the overall PD activity of ruxolitinib.

When administering ruxolitinib with strong CYP3A4 inhibitors, the total daily dose should be reduced by approximately 50%.

No dose adjustment is necessary when co-administering ruxolitinib with strong CYP3A4 inducers. No dose adjustment is necessary when co-administering ruxolitinib with CYP3A4 substrates. Ruxolitinib did not decrease the exposure of a fixed dose oral contraceptive metabolized via the CYP3A4 pathway, thus demonstrating lack of CYP3A4 induction potential.

In patients with severe (creatinine clearance (Clcr) <30 mL/min) and moderate renal impairment (Clcr = 30-59 mL/min), the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice a day. Patients on hemodialysis should initiate ruxolitinib with a single dose of 15 mg or 20 mg based on platelet counts on day of hemodialysis with subsequent doses only on hemodialysis days and following each hemodialysis session. Ruxolitinib doses should be titrated based on individual safety and efficacy.

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

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

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

1.2.1.2.2 Ruxolitinib clinical safety in healthy volunteers

The safety profile for ruxolitinib in the Phase I development program was assessed in over 370 subjects for single or repeat doses. Ruxolitinib has been administered to 40 subjects with various degrees of renal impairment and 32 subjects with various degrees of hepatic impairment. Additionally, a DDI study with methotrexate was completed in 18 RA patients.

[redacted]

AEs were, in general, mild and resolved without interventions. In the first-in-human study one subject had hyponatremia after receiving 5 mg ruxolitinib. The hyponatremia was assesse d as severe in intensity, unrelated to study medication, reversed within 5 days, and was reported as serious adverse event (SAE).

In the repeat-dose study in healthy subjects, the dose-limiting AE was neutropenia, which occurred at a dose of 50 mg b.i.d. Neutropenia as an AE was noted in three subjects, all receiving the highest dose of ruxolitinib, 50 mg b.i.d. Neutropenia at the Grade 4 level, assessed as severe, led to study drug discontinuation on Day 5 in one subject, and was reported as an SAE. Neutrophil count returned to a normal level 12 days after the final dose of study medication. In two other subjects, neutropenia was Grade 1 or 2, and resolved with dose interruption or during continued dosing. The AE profile was similar for single - and multiple- dose studies, and no differences were observed between males and females. The most frequent (≥2 subjects) treatment-emergent AEs (TEAEs) occurring in the Phase I multiple- dose study were: neutropenia (4.2%), dizziness (2.8%), headache (2.8%) and nausea (2 .8%). Overall, in healthy volunteer studies where frequent sampling of the neutrophil count was performed, a transient, reversible decrease in neutrophil count was frequently seen following dosing, which reversed after 12-24 h off drug.

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

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

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

1.2.1.2.3 Ruxolitinib clinical safety and efficacy in phase I/II/III trials

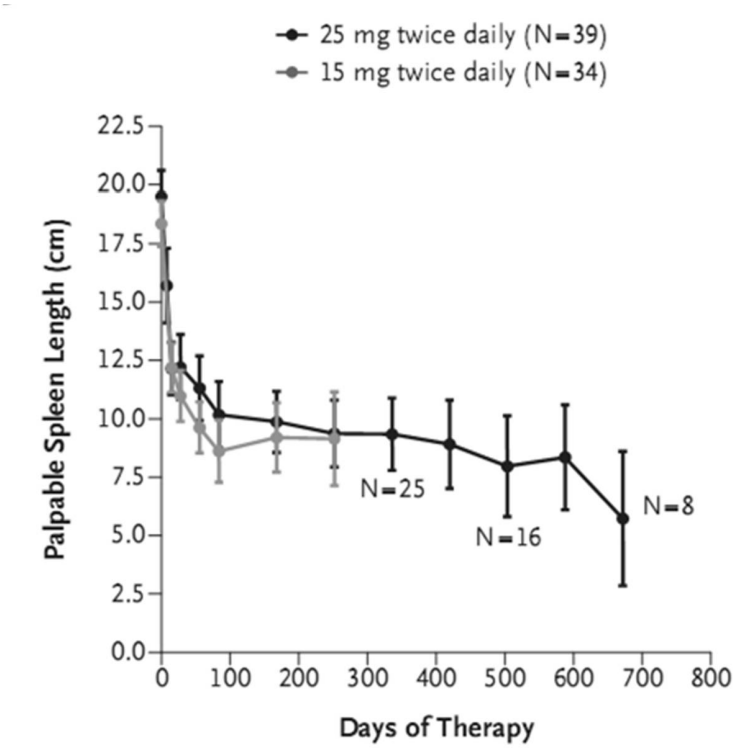
Phase I/II study of INC424 in patients with primary, post-PV, or post-ET MF

Study INCB 18424-251 is a completed Phase I/ II open-label study of orally administered INC424 (ruxolitinib) in patients with PMF, PPV MF and PET MF. A total of 153 patients were enrolled at the following oral dosing levels/regimens: starting dose of 25 mg BID followed by escalation up to 50 mg BID; once daily (QD) dosing ranging from 25 mg QD to 200 mg QD. The maximum tolerated doses were identified as 25 mg BID or 100 mg QD, based on dose-limiting thrombocytopenia. In the Phase II component of the trial additional dosing schedules were also evaluated including 25 mg BID (with a reduction to 10 mg BID after 2 cycles [months] of therapy); 10 mg BID, with dose escalation permitted after 3 cycles (months) of therapy; 10 mg BID (in patients with a baseline platelet count of 100 - 200 x 10^9/L); and 15 mg BID (in patients with a baseline platelet count of > 200 x 10^9/L) with dose increases to 25 mg BID (in 5 mg increments). Data from the completed Study INCB 18424 - 251 demonstrate marked and durable reductions in spleen size. In this study spleen size was measured as palpable length below the left costal margin. Figure 1-1 illustrates the mean reduction in absolute spleen size (measured by palpation) for patients receiving 15 mg BID and 25 mg BID, and Figure 1-2 mean reduction in absolute spleen size (measured by

[redacted]

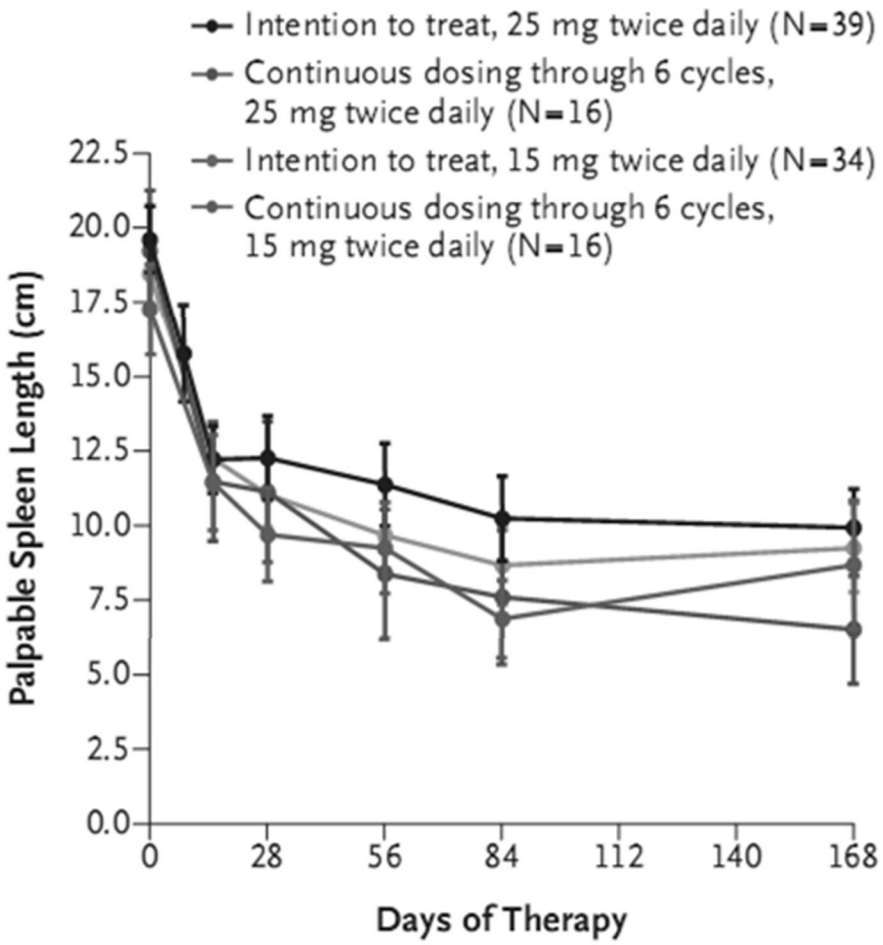
palpation) for patients receiving their originally assigned dose for at least 6 months (Verstovsek 2010b).

Figure 1-1 Reduction in palpable spleen length in patients receiving different doses of ruxolitinib (Verstovsek 2010b)



[redacted]

Figure 1-2 Reduction in palpable spleen length according to ruxolitinib dose when maintained for at least 6 months (Verstovsek 2010b)



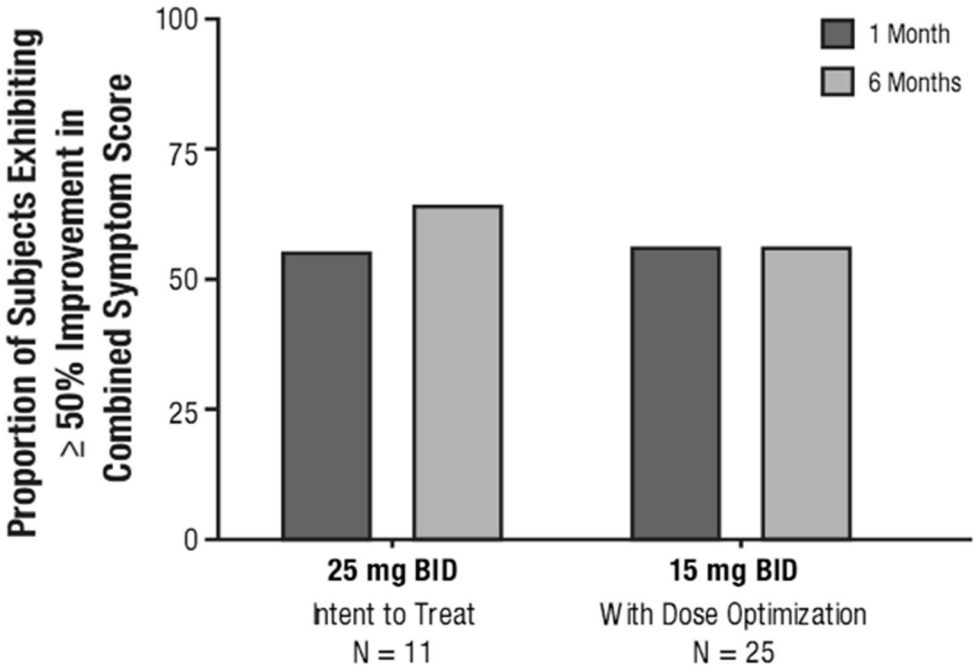
As noted in Figure 1-2, BID regimens are associated with a prompt decrease in spleen size. Response rates have been demonstrated to be greatest in the BID dosing cohort, with reduced responses in the 50 mg PO QD dosing cohort, and lowest in the 10 mg PO BID dosing cohort (Verstovsek 2010b). The majority of patients had a ≥ 25% reduction in spleen size on therapy (70% in 10 mg BID cohort; 82% in 15 mg BID dosing cohort; 77% in the 25 mg BID cohort). Responses occurred quickly, within 1-2 months of therapy and appear durable (> 1 year in 16 patients for whom data were available at 1.5 years and all 8 patients for whom data were available at 2 years). Best responses were greatest in the 25 mg BID dosing cohort (among patients starting at 25 mg BID and maintaining that dosing schedule), although dose interruptions were common (60%) primarily due to thrombocytopenia. Based on this profile an initial dose of 15 mg ruxolitinib BID is recommended. Spleen reduction occurred regardless of presence/absence of the *JAK2*V617F mutation (data not shown). Progressive MPN are associated with weight loss and cachexia. Dysregulation and abnormal elevation of a variety of pro-inflammatory cytokines may produce a hypercatabolic state which contributes to the weight loss and wasting seen in patients with MF. After an initial weight loss

[redacted]

(presumably due to the rapid decrease in splenomegaly and hepatomegaly and loss of ascites and/or pleural effusions) there is a gain in total body weight that appears to be dose-dependent. Weight gains are present in most patients, including those with body mass index at baseline in the lowest quartile (body mass index below ~ 22).

Improvements in QoL were rapidly demonstrated, typically within 1 month of therapy. The Modified Myelofibrosis Symptom Assessment Form (MFSAF) developed by Mesa et al, and based on an international internet-based survey of over 1000 patients with MPD, was used to probe a range of constitutional symptoms related to splenomegaly (including impaired ability to move around and early satiety) and elevated cytokines (including fatigue, night sweats and pruritus) (Mesa 2007). Most patients in the 10 to 25 mg BID dose groups demonstrated a ≥ 50% improvement in total or individual symptom scores per the MF -SAF, which assesses constitutional symptoms including fatigue, night sweats, and pruritus (Figure 1-3). These responses were durable through 6 months of therapy. Symptomatic improvements were similar among the 10, 15, and 25 mg BID dose groups, with improvements in abdominal discomfort and pain accompanying the reduction in spleen size. Additionally, patients started to gain weight as early as after 2 c ycles of therapy, with patients in the lowest quartile for body mass index at baseline gaining more weight than those in the highest quartile. Functional improvements in the ability to walk were observed; patients improved their walking ability by 34, 57, and 71 m after 1, 3, and 6 months, respectively (Verstovsek 2010b).

Figure 1-3 Improvements in combined MFSAF score on ruxolitinib



In summary, ruxolitinib is associated with prompt and marked reduction in spleen size, gains in total body weight, improvement in ECOG status PS and improvement in constitutional symptoms that can be debilitating in this patient population. Re fer to the IB and (Verstovsek 2010b) for more complete information. Ruxolitinib has been well tolerated by this aged

[redacted]

population with advanced disease. Nonhematologic adverse events were uncommon and included diarrhea (5.9%), fatigue (4.3%), headache (3.3%), peripheral edema (2.6%), pain in extremities (2.6%), urinary tract infections (2.6%), dizziness (2.6%), dyspnea (2.6%), asthenia (2%), fever (2%), cardiac murmur (2%), musculoskeletal pain (2%), peripheral neuropathy (2%), edema (2%), anxiety (2%), insomnia (2%), epistaxis (2%), flatulence (2%), and nausea (2%). The majority of these were Grade 1/ 2 CTCAE toxicity. Grade 3/ 4 nonhematologic toxicity included fatigue (1.3%), asthenia (2%), fever (0.7%), anxiety (1.3%) and insomnia (1.3%). Hematologic toxicity consisted primarily of anemia and thrombocytopenia. Thrombocytopenia appeared to be dose related occurring less frequently in the 15 mg BID group (3% Grade 3) than the 25 mg BID group (23% Grade 3; 6 % Grade 4). Thrombocytopenia was not related to JAK V617F mutational status. Grade 3 thrombocytopenia occurred in 10% of patients receiving 10 mg BID of ruxolitinib, 3% of patients receiving 15 mg BID of ruxolitinib, 23% of patients receiving 25 mg BID of ruxolitinib, 60% of patients receiving 50 mg BID of ruxolitinib, 0% of patients receiving 25 mg QD of ruxolitinib, 27% of patients receiving 50 mg QD of ruxolitinib; 33% of patients receiving 100 mg QD; and 0% of patients receiving 200 mg QD of ruxolitinib . Thrombocytopenia of Grade 4 severity occurred in 0% of patients receiving 10 mg BID of ruxolitinib, 0% of patients receiving 15 mg BID of ruxolitinib, 6% of patients receiving 25 mg BID of ruxolitinib, 20% of patients receiving 50 mg BID of ruxolitinib, 0% of patients receiving 25 mg QD of ruxolitinib, 9% of patients receiving 50 mg QD of ruxolitinib, 0% of patients receiving 100 mg QD of ruxolitinib, and 33% of patients receiving 200 mg QD of ruxolitinib. Thrombocytopenia occurred more frequently in patients with lower baseline platelet counts ($< 200 \times 10^9$/L), and was reversible within 1 to 3 weeks after dose interruption and/or reduction. New onset anemia occurring in patients who were not transfusion dependent at baseline occurred in 23% of patients across all dosing intervals, and was most common in the 25 mg BID dosing cohort (27%) and least common in the 15 mg BID dosing cohort (8%). Anemia, though dose dependent, largely reflects the low Hgb status at baseline in this disease population.

SAEs occurred in 59 (39%) patients, of which 12 were assessed as at least possible related to study drug, including bone marrow suppression, febrile neutropenia, syncope, progression to CMMoL, B-cell lymphoma, pharyngotonsilitis, pharyngitis, myalgia, sinusitis, and cerebral hemorrhage. Of related SAEs reported in the study to date, the most frequent are those reflecting inhibition of bone marrow function(s) (i.e., thrombocytopenia) and activation of inflammatory cytokines when the inhibitory influence of ruxolitinib i s removed due to drug interruption or discontinuation. See (Verstovsek, 2010b) for complete details on INC424/ ruxolitinib clinical study findings.

Fourteen patients discontinued study drug participation due to death, disease progression, unacceptable toxicity, or intercurrent illness. Four of 14 discontinuations were thought to be "possibly related to study drug, and included the following: (a) a [redacted] year -old [redacted] patient suffering from intracerebral hemorrhage without thrombocytopenia and associated death on day 374 of study drug dosed at 25 mg PO BID; (b) [redacted] year -old [redacted] with disease progression to CMMoL (evidence of CMMoL at screening) on day 147 of 25 mg p.o. BID; (c) [redacted] year old [redacted] developed grade 3 thrombocytopenia on day 278 on 50 mg p.o. BID; an d (d) a [redacted] year-old [redacted] developed grade 3 thrombocytopenia on day 57 on 50 mg p.o. BID.

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During 2 or more years of follow-up, a number of patients discontinued study drug treatment including the following: withdrawal of consent, investigators decision to discontinue treatment, or other reasons (n = 24); progressive disease (n = 4); toxic effects (n = 2); intercurrent illness (n = 3), and death (n = 5). A total of 17 patients died during the follow -up period of which 5 died on treatment, and 3 died within 30 days of study treatment discontinuation.

Phase 1b study of ruxolitinib in patients with MF and baseline platelet counts between 50 x 10^9/L and less than or equal to 99 x 10^9/L

A phase Ib study of ruxolitinib to investigate the safety of ruxolitinib and es tablish the maximum safe starting dose in patients with MF who have baseline platelet counts ≥ 50,000/µL to 99,000/µL is currently ongoing (Gisslinger 2012). The (Evaluating Ruxolitinib in Patients with Low Baseline Platelet Counts Diagnosed With Myelofibrosis) study is a single-arm, open-label, dose-finding study in adult patients with PMF, PET-MF, or PPV MF. This study consists of two periods: (a) core study period (day 1 to week 24), and (b) an extension period (beyond week 24). There are two different dosing strata based on baseline platelet counts (Stratum 1: 75,000/µL to 99,000/µL starting dose is 5 mg BID; Stratum 2: 50,000/µL to 74,000/µL). A preliminary analysis based on an unplanned data cutoff d ate of May 16, 2012 was presented at the European Hematology Association meeting in June 2012. An updated analysis was presented at the American Society of Hematology meeting in December 2012 (Harrison 2012). The data (n=20; PMF n=14, PPV=MF n=5, PET-MF n=1) demonstrates that in this phase 1b study of ruxolitinib in thrombocytopenic patients with MF, no DLT has occurred at the first 2 dose levels in patients with platelet counts of 50,000/µL to 99,000/µL. Ruxolitinib has been generally well tolerated, similar to the tolerability reported in the previous studies, and no patient has discontinued because of thrombocytopenia. No patient has had platelet counts below 20,000/ µL. No Grade 3/4 hemorrhagic events were reported. Treatment with ruxolitinib led to spleen length reductions from baseline in 17 of 20 patients and three patients have experienced complete resolution of palpable splenomegaly as best response on study.

Phase II study of ruxolitinib in patients with low baseline platelet counts (50 x 10^9/L to 100 x 10^9/L)

A 24-week, open-label phase II study of ruxolitinib to investigate the efficacy, hematologic effects and dose of ruxolitinib in patients with MF, PPV-MF, and PET-MF and baseline platelet counts of 50,000 to 100,000/ µL is ongoing (INCB018424 -258) (Talpaz 2012a). The starting dose of ruxolitinib is 5 mg p.o. BID with dose escalation with adequate platelet count by 5 mg once daily (i.e. 5 mg p.o. AM and 10 mg p.o.PM) every 4 weeks to a maximum of 10 mg BID. Further dose escalation requires evidence of suboptimal efficacy. An initial report with data from 41 evaluable patients was presented at the American Society of Hematology meeting in December 2012. Among patients who completed 24 weeks of treatment, most were receiving ruxolitinib dose of 10 mg p.o. BID or higher. No patients have discontinued treatment due to adverse events. Bleeding related events were reported in 7 patients (17.1%). Grade 1 bruising events (contusion n=2 and ecchymosis n=3) were reported in 7 patients. Other bleeding events were reported in 4 patients (subdural hematoma secondary to fall, hematochezia, hemorrhoidal hemorrhage and epistaxis; all grade 1 except grade 2

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hematochezia).Phase III ruxolitinib clinical trials (controlled MF study with oral JAK inhibitor treatment [COMFORT; (INCB 18424-351 and CINC424A2352)])

The results from two Phase III studies in myelofibrosis (COMFORT-I, COMFORT-II) demonstrate the effectiveness of ruxolitinib in patients with PMF, PPV-MF and PET-MF. The results of these two studies were consistent, demonstrating statistically significant ($p < 0.0001$) differences in rates of ≥35% spleen volume reduction compared with either placebo or an investigator's selection of best available therapy (BAT). Although, the time point for the primary endpoint (spleen volume reductions) were different in COMFORT-I (at Week 24) and COMFORT-II (at Week 28) the mean reduction in spleen volume is similar at Week 24 (31.6% vs. 29.2%, COMFORT-I and COMFORT-II, respectively).

The COMFORT-I trial is a randomized, double-blind, placebo-controlled Phase III study of the oral JAK1/JAK2 inhibitor ruxolitinib in 309 patients with PMF, PPV MF, or PET -MF. Patients from 89 sites in the USA, Canada and Australia were randomized 1:1 to receive either ruxolitinib (15 mg PO BID or 20 mg PO BID depending on baseline platelet count) or placebo. The primary endpoint of the study was the proportion of patients achieving ≥35% reduction in spleen volume from baseline to Week 24 as measured by MRI (or CT scan in applicable patients) and the secondary endpoints included: duration of maintenance of a ≥35% reduction from baseline in spleen volume among patients initially randomized to recei ve ruxolitinib, and the proportion of patients with ≥50% reduction in total symptom score from baseline to Week 24 as measured by the modified MFSAF v2.0 diary.

A total of 309 patients were enrolled in the study, with 155 randomized to ruxolitinib and 154 to placebo. The groups were matched for baseline characteristics; the majority of patients had high-risk disease (61.2%). Patients were eligible to cross-over in this study, and 36 patients in the placebo group (23.4%) crossed over to ruxolitinib. The data cutoff date was 2-Nov-2010, the date of last patient last visit.

Significantly more patients in the ruxolitinib group had a reduction in spleen volume (≥35%) at week 24 (41.9% vs. 0.7%; $P<.0001$). A reduction in spleen volume for ≥48 weeks was maintained in 67% patients who achieved a response on ruxolitinib. More patients receiving ruxolitinib had an improvement of ≥50% in the total symptom score at 24 weeks compared to placebo (45.9% vs. 5.3%, $P<0.001$). Patient's receiving ruxolitinib also had improvements in each symptom assessed on the MF-SAF. Overall survival was a secondary endpoint of COMFORT-I. Ten deaths occurred in the ruxolitinib group vs. 14 deaths in the placebo group (hazard ratio, 0.67; 95% CI, 0.30 to 1.50; $P = 0.33$). A survival analysis based on a planned data cutoff with 4 additional months of follow-up (median follow-up, 51 weeks) revealed a significant survival advantage for patients who received ruxolitinib (13 deaths in the ruxolitinib group (8.4%) vs. 24 deaths in the placebo group (15. 6%) (Hazard ratio, 0.50; 95% confidence interval, 0.25 to 0.98; $P = 0.04$).

Ruxolitinib was well tolerated in COMFORT-I, with most Grade 3/4 nonhematologic toxicities occurring in less than 6% patients: fatigue 5.2%, diarrhea 1.9%, dyspnea 1.3%, dizziness 0.6%, vomiting 0.6%, arthralgia 1.9%, pyrexia 0.6%, and abdominal pain 2.6% (Verstovsek 2012). Hematologic toxicity consisted primarily of anemia and thrombocytopenia. Grade 3/4 anemia occurred in 45.2% patients, Grade 3/4 thrombocytopenia occurred in 12.9% patients, and Grade 3/4 neutropenia occurred less frequently in 7.1% of patients.

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Approximately half of the Grade 3/4 anemia and thrombocytopenia events occur during the first 8 weeks of therapy. Treatment with ruxolitinib enabled 41.2% to become transfusion independent. Anemia and thrombocytopenia was manageable, and thrombocytopenia generally responded to dose reduction or temporary dosing interruption. Thirteen deaths occurred in the ruxolitinib group vs. 24 deaths in the placebo group (HR, 0.50; 95% confidence interval, 0.25 to 0.98; $P = 0.04$). The rate of discontinuation of the study drug because of AEs was 11.0% in the ruxolitinib group vs. 10.6% in the placebo group.

The COMFORT-II study (Study INCB 18424-352) is an open-label, randomized, active-comparator trial that compared ruxolitinib therapy to best currently available therapy (BAT) [as determined by the investigator for each individual patient randomized to the control group] in 219 adult patients with PMF, PPV-MF or PET-MF. The control group therapy could also consist of no therapy (i.e., "watchful waiting"), or a combination of agents. COMFORT -II assessed the impact of therapy on spleen length; evaluated durability of response; and gave additional data on the long-term safety of ruxolitinib use. Patients were randomized in a 2:1 ratio of ruxolitinib:BAT. At randomization, patients were stratified by IPSS prognostic category as having either two prognostic risk factors (intermediate -2 risk), or three or more prognostic risk factors (high risk). In COMFORT-II, the randomized treatment phase started on Study Day 1 and continued until the patient met defined criteria for disease progression. During this phase, all patients in both arms underwent an objective evaluation of spleen length using MRI or CT. The percentage of patients achieving a 35% reduction in spleen volume at 48 weeks was the primary endpoint for efficacy. MRI was the primary modality of spleen length (volume) measurement. Patients who were not candidates for MRI (including at sites where MRI is unavailable) were evaluated with sequential CT. Spleen volume was assessed by a central reader. While investigators were able to follow spleen length by palpation, results of MRI (or CT) spleen volume assessments were only to be made known to the investigator if a patient had reached a protocol-defined criterion for disease progression based upon increase in spleen volume. Patients having reached this endpoint were eligible to continue study participation in the extension phase, and if originally randomized to the control group, could cross over to receive ruxolitinib if they met safety requirements.

The rates of leukemic-free survival, progression-free survival, overall survival, and durability of response will be determined and compared between the randomized treatment groups, using data from both the randomized treatment phase and extension phase. Additional assessments will include analysis of *JAK* mutation status, cytokine levels, and change in symptoms as assessed by the EORTC QLQ-C30 and MFSAF v 2.0 questionnaires.

In the COMFORT-II trial (Harrison 2012), 28% of the patients in the ruxolitinib group had ≥35% reduction in spleen volume at week 48 vs. 0% in the BAT group ($P < 0.0001$); the corresponding percentages at week 24 were 32% and 0% ($P < 0.001$). The mean palpable spleen length (48 weeks) had decreased by 56% with ruxolitinib but had increased by 4% with BAT. The median duration of response with ruxolitinib was not reached, with 80% of patients still having a response at a median follow-up of 12 months. Ruxolitinib treatment was associated with an improvement in overall quality-of-life measures and a reduction in symptoms associated with MF. The most common hematologic abnormalities (≥ Grade 3) were thrombocytopenia and anemia, which were managed with a dose reduction, interruption of treatment, or transfusion. One patient in each group discontinued treatment due to

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thrombocytopenia, and none discontinued due to anemia. Non-hematologic AEs were rare and mostly grade 1 or 2. Two cases of AML were reported with the best available therapy. ruxolitinib was also well tolerated in the COMFORT-II trial, with most Grade 3/4 non-hematologic toxicities occurring in < 3% patients: diarrhea 1%, asthenia 1%, dyspnea 1%, pyrexia 2%, nausea 1%, arthralgia 1%, fatigue 1%, pain in extremity 1%, abdominal pain 3%, headache 1%, and back pain 2%. Thrombocytopenia and anemia occurred more frequently in the patients receiving ruxolitinib vs. BAT, although these events rarely led to treatment discontinuation (1 patient in each group discontinued the study due to thrombocytopenia) and were generally manageable with dose modifications, transfusions of packed red ce lls, or both. AEs leading to dose modification with ruxolitinib occurred in 41% patients. Only 5% of the patients receiving ruxolitinib required dose interruptions or reductions due to anemia and 1% due to neutropenia.

When pooling the results of COMFORT-I and COMFORT-II to examine safety of ruxolitinib, the incidence of headache was more frequent in ruxolitinib-treated patients (13.6% vs. 6.0% on placebo and 5.5% on BAT). Most AEs of headache were Grade 1 or 2. Similarly, dizziness (12.0% vs. 6.6% on placebo and 6.8% on BAT) was more frequent in ruxolitinib-treated patients, again mostly Grade 1 or 2. When adjusted for patient -year exposure, the differences were still present for headache and dizziness. Weight increase was also more frequent in ruxolitinib-treated patients than in the control groups (9.6% vs. 1.3% on placebo and 1.4% on BAT). Although some of these patients had co-reported AEs of edema, many had a past medical history of weight loss and the weight gain usually gradually accumulated over the course of one year of treatment. The majority of weight gain AEs were Grade 1 and 2. It is worth noting that weight gain may be a beneficial effect in patients with MF, given the catabolic nature of the disease and the frequency of weight loss reported as a constitutional symptom.

Other events with increased frequency in the ruxolitinib arms included bruising (2.6% vs. 1.3% on placebo in [COMFORT-I, INCB 18424-351] only), contusion (8.6% vs. 5.3% on placebo and 1.4% on BAT), urinary tract infection (7.3% vs. 4.6% on placebo and 2.7% on BAT), herpes zoster (4.0% vs. 0.7% on placebo and 0% on BAT) and flatulence (3.3% vs. 1.3% on placebo and 0% on BAT). Abdominal pain was more frequent in the control groups than in the ruxolitinib group (43% on placebo and 13.7% on BAT vs. 12% on ruxolitinib), as were weight decrease (8.6% on placebo and 8.2% on BAT vs. 1% on ruxolitinib , early satiety (8.6% on placebo and 0% on BAT vs. 0.3% on ruxolitinib) and splenic infarction (6.0% on placebo and 0% on BAT vs. 1.0% on ruxolitinib).

The most frequently occurring Grade 3 and 4 AEs regardless of study drug relationship were hematologic including anemia (14%) and thrombocytopenia (8%) (Source: 120 day safety update-Table 2.1-1.4 in [Investigator Brochure]). Non-hematologic Grade 3-4 AEs were infrequent and rarely reported more frequently than in the control arms. Two patients (0.7%) had febrile neutropenia. In general, the pattern of AEs was similar between the two ruxolitinib arms in both studies, although there were some differences in frequency for specific AEs.

In the ruxolitinib-treated Phase III population, the overall frequency of AEs leading to study drug discontinuation was 11%. This frequency was similar across both studies. None of the AEs leading to discontinuation was reported in more than two patients in any group. In the ruxolitinib-treated Phase III population, the overall frequency of AEs requiring dose reduction

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or interruption was 59.8%. This frequency was higher than in the control groups (placebo: 27.2%, BAT: 15.1%). The most frequently reported AEs requiring dose reduction or interruption in ruxolitinib treated patients were thrombocytopenia (36.9%), platelet count decrease (7.6%) and anemia (5.6%). The high frequency for thrombocytopenia is due to protocol-mandated dose reductions and interruptions. Although there were no protocol specified guidelines for dose reductions secondary to anemia, some investigators chose to reduce a patient's dose in the setting of anemia to minimize this particular cytopenia. The frequency of these AEs was higher than in the control groups. All other AEs requiring dose reduction or interruption occurred with a frequency of 1.3% or less in the ruxolitinib treated patients. There are no data from the use of ruxolitinib in pregnant women. Animal studies have shown that ruxolitinib is embryotoxic and foetotoxic. Teratogenicity was not observed in rats or rabbits; however, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans.The potential risk for humans is unknown. As a precautionary measure, the use of ruxolitinib during pregnancy is contraindicated. Women of child-bearing potential should use effective contraception.

The most frequently reported adverse drug reactions were thrombocytopenia and anemia. Hematological adverse reactions (any Common Terminology Criteria for Adverse Events [CTCAE] Grade) included anemia (82.4%), thrombocytopenia (69.8%) and neutropenia (16.6 %). Anemia, thrombocytopenia and neutropenia are dose related effects. The three most frequent non-hematological adverse reactions were bruising (21.6%), dizziness (15.3%) and headache (14.0%). The three most frequent non-hematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (18.6%) and hypercholesterolemia (16.9%).

Long-term follow-up of 5 years in patients with MF in the COMFORT studies has shown safety and tolerability consistent with previous findings and no new safety signals ha ve emerged (Verstovsek 2016, Harrison 2016).

2 Rationale

2.1 Study rationale and purpose

Ruxolitinib, a potent and selective inhibitor of JAK1 and JAK2 is indicated for treatment of disease-related splenomegaly or symptoms in adult patients with myelofibrosis (MF). Ruxolitinib effectively treats MF symptoms, spleen enlargement, and provides an overall survival benefit compared to placebo or best supportive care. Thrombocytopenia has been observed in patients with MF treated with ruxolitinib and is one of the key dose -limiting toxicity. Transient hemoglobin drops have also been observed in MF patients treated with ruxolitinib and typically reach a nadir between weeks 8 and 12, returning to levels close to baseline towards week 24.

While anemia was adequately managed for patients to continue in the phase III trials by dose adjustments and supportive interventions instituted at Investigator's discretion, the phase III study protocols did not define any specific dose modifications for patients with new onset or continuing anemia. Many events of Grade 3/4 anemia were treated with transfusions, therefore the proportion of patients receiving transfusions on study peaked around Week 12 of

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treatment and then declined to levels similar to the control groups, mirroring the profile for Grade 3/4 anemia incidence (Verstovsek 2012).

Anemia is one of the diagnostic criteria for myelofibrosis and a known adverse prognostic factor. In the International and Dynamic International Prognostic Scoring Systems, Hb levels of <100 g/L at the time of diagnosis and during the course of disease, respectively, have been shown to have a significant negative impact on overall survival (OS). However, both scoring systems were derived and validated prior to the availability of ruxolitinib; additional analyses from COMFORT studies characterized the effect of ruxolitinib treatment on the Hb dynamics and did assess its impact on OS (Al Ali 2016); consistent with validated prognostic models, baseline anemia was associated with decreased OS in the COMFORT studies. Treatment with ruxolitinib improved OS as compared with the control arm regardless of baseline anemia status. Notably, post baseline anemia that occurred on ruxolitinib therapy did not impact OS and was manageable with dose adjustments and RBC transfusions concluding that early onse t ruxolitinib-related anemia does not have the same deleterious effect as disease-related anemia. (Gupta 2015)

Considering the typical hemoglobin level for many MF patients is already at the Grade 0/Grade 1 border (hemoglobin of 10 g/dL), assessment of a dose regimen that might provide clinically meaningful symptomatic and spleen size reduction benefits of ruxolitinib while lessening the degree of worsening hemoglobin levels is warranted.

Current label recommendation on starting doses in MF are 5, 15 or 20 mg BID, depending on platelet counts 50-100 $\times 10^9$/L, 100-200 $\times 10^9$/L or >200 $\times 10^9$/L respectively, regardless of hemoglobin level at baseline.

There is increasing literature suggesting the use of lower starting doses with up titrations depending on safety and efficacy in patients with anemia (Tabarroki 2013, Cervantes 2014, Reilly 2014, Harrison 2013, Ho 2015).

This multicenter phase II open label single arm study proposes to prospectively evalu ate a starting dose of ruxolitinib 10 mg BID for 12 weeks with subsequent up titrations of 15mg BID and 20 mg BID in anemic myelofibrosis patients defined as a baseline hemoglobin < 10 g/dL (Please see Figure 6-1 for details). The trial will evaluate if this alternative dosing approach achieves spleen reduction and symptom improvement to levels consistent with those reported in previous clinical trials but with an improved tolerability assessed by inciden ce of adverse events and transfusion requirements.

2.2 Rationale for the study design

The COMFORT studies compared the effects of ruxolitinib with placebo or best available therapy, respectively and showed that ruxolitinib treatment significantly reduced splenomegaly and provided marked improvements in MF-related symptoms and quality-of- life (QOL) measures compared with controls, regardless of JAK2V617F mutational status. The clinical benefit and safety of ruxolitinib treatment in COMFORT -I and COMFORT-II have been maintained with subsequent longer-term follow-up. As anticipated, the effect of JAK2 inhibition on hematopoiesis resulted in dose-dependent anemia and thrombocytopenia. The majority of these cytopenias occurred in the first 8 to 12 weeks of treatment, and they were generally manageable with dose reductions and/or red blood cell transfusions.

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There is increasing literature suggesting the use of a 10 mg BID starting dose with subsequent up titrations depending on safety and efficacy in patients with anemia at the time of treatment initiation with ruxolitinib (Tabarroki 2013, Cervantes 2014, Reilly 2014, Harrison 2013, Ho 2015). This dosing approach for anemic MF patients will be systematically studied in this prospective multicenter phase II open label single arm trial to determine if the levels of spleen length reduction and symptom improvement are consistent with those reported in previous clinical trials with ruxolitinib in patients with anemia and doses according to platelet counts at the moment of treatment initiation, and whether this lower starting dose and up titration approach may minimize the initial hemoglobin and platelet declines and transfusion requirements. The efficacy and safety of ruxolitinib with starting doses based on platelet counts in MF patients including those with anemia at baseline have been well studi ed and characterized in several clinical trials (COMFORT I, COMFORT II, JUMP).

This is an open-label, single-arm study of treatment with ruxolitinib for 48 weeks in patients who presents with transfusion dependent or independent anemia at screening defined as an hemoglobin <10 g/dL.

Ruxolitinib will be self-administered as BID oral treatment. The starting dose is 10 mg BID for all enrolled patients and gradual up titrations will start at week 12 determined by the level of efficacy achieved and the tolerability.

2.3 Rationale for dose and regimen selection

Phase I/II trials evaluated a number of different doses and schedules of ruxolitinib. Based on these, two phase III trials evaluated the efficacy and safety of ruxolitinib versus placebo in COMFORT I and versus BAT in COMFORT II in a population of patients with primary and secondary MF. In both phase III trials a starting dose of 20 mg orally BID wa s administered for patients with platelet counts from 200,000/ µL and a lower starting dose of 15 mg orally BID in patients with baseline platelet counts from 100,000 to 200,000/ µL.

Additional studies generated clinical data on the efficacy and tolerability of ruxolitinib in patients with MF and platelet counts from 50,000 to 100,000/µL. A starting dose of 5 mg BID with subsequent optional up titrations every 4 weeks by dose increments of 5 mg OD was evaluated in a phase II open label single arm study INC B18424-258 in a population of patients with platelet counts from 50,000 to 100,000/µL. Similarly, an expanded access program and phase IIIb study CINC424A2401 (JUMP) that recruited more than 2200 patients allowed the inclusion of patients with low platelet counts (50,000 to 100,000/µL) to be treated with a 5 mg BID starting dose.

Furthermore, a Phase Ib study (EXPAND) evaluating the safety and MTD of ruxolitinib in patients with lower baseline platelet counts (50,000– 100,000/µL) suggests that higher doses of ruxolitinib can be safely administered to patients with lower baseline platelet count. The maximum safe starting dose in this ongoing study was reported to be 15 mg BID for patients with platelet counts from 75,000 to 100,000/µL and 10 mg BID for patien ts with platelet counts from 50,000 to 75,000/µL.

Anemia may be ameliorated by lowering the dose of ruxolitinib or by concomitant use of erythropoietin stimulating agents and/or anabolic steroids (Reilly 2014). This approach may make particular sense in patients with anemia at the moment of treatment initiation with ruxolitinib in order to avoid further hemoglobin decrease, the need of blood transfusions or have them more frequently in patients already receiving regular transfusions for anemia.

An alternative strategy to start patients at 10 mg BID and titrate the dose up according to tolerability and response (Cervantes 2014, Harrison 2013) has anecdotally suggested improved tolerance and reduced adverse events yielding fewer treatment discontinuations and has been already included in treatment guidelines (Ho 2015, Reilly 2014).

Based on the above, a starting dose of 10 mg BID will be assigned to patients recruited in this phase II open label single arm study followed by gra dual up titrations starting at week 12, based on efficacy and safety at the different evaluation visits. This approach assumes that starting at a lower dose may impact the rate of the initial hemoglobin decline and the nadir, by decreasing the level of JAK-mediated inhibition of hematopoiesis.

2.4 Rationale for choice of combination drugs

Not Applicable.

2.5 Rationale for choice of comparators drugs

Not applicable.

[redacted]

2.6 Risks and benefits

The primary clinical risks with ruxolitinib treatment are the potential consequ ences of decreased hematopoietic proliferation secondary to the inhibition of growth factor pathways associated with JAK2 inhibition. Dose-dependent, reversible thrombocytopenia has been observed in patients with MF and represents the DLT. Anemia and, less frequently, neutropenia have also been observed in patients with MF treated with ruxolitinib. Increased rates of infection and anemia are potential risks of myelosuppression, and there are other consequences of anemia including the burden and risks of transfusion.

Of note, the dosing approach proposed in this study may decrease the risk of patients developing cytopenias compared to the standard dose approach utilized in the two phase III pivotal studies.

A dose escalation starting at week 12 aims to achieve a maintenance dose for each patient that maximizes the benefits from ruxolitinib while keeping the treatment well tolerated. The main potential benefit of the proposed dosing approach in the study resides in achieving similar levels of efficacy seen in previous clinical trial experiences with an improved safety and tolerability profile expressed by lower rates of cytopenias and transfusion requirements.

Appropriate eligibility criteria, as well as specific dose modification and stopping rules, are included in this protocol. The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as and close clinical monitoring. There may be unforeseen risks with ruxolitinib which could be serious. Please refer to the latest [Investigator Brochure].

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To determine the spleen length response rate at week 24.	Proportion of patients achieving a 50% reduction in spleen length at week 24.	
Secondary		Refer to Section 10.5.1
To evaluate safety.	Safety will be assessed by • Frequency and severity of adverse events and serious adverse events and AEs leading to discontinuations. • Changes in hematology/biochemistry parameters over time.	
To determine the spleen length response rate at week 48.	Proportion of patients achieving a 50% reduction in spleen length at week 48.	
To evaluate the effect of ruxolitinib on spleen length.	Percent change from baseline in spleen length over time.	
To evaluate the effect of ruxolitinib on symptoms.	Summary of the Modified MFSAF v2.0 and MF-7 over time.	
To evaluate the effect of ruxolitinib on Patient Global Impression of Change (PGIC).	PGIC at each visit where measured.	
To evaluate the effect of ruxolitinib on transfusion requirements.	Summary of transfusions over time. For Transfusion Dependent (TD)* patients, the following will be analyzed: • Transfusion independence (TI) rate (requiring no transfusion for ≥12 weeks at any time). • Transfusion response rate (not TD: having 5 or less transfusion for ≥12 weeks at any time).	

[redacted]

[redacted]

[redacted]

[redacted]

4 Study design

4.1 Description of study design

This is a multicenter phase II, open label, single arm study to assess the efficacy and safety of ruxolitinib in patients with Primary Myelofibrosis (PMF), Post-Polycythemia Vera-Myelofibrosis (PPV-MF), or Post-Essential Thrombocythemia Myelofibrosis (PET-MF) who have splenomegaly that is equal to or greater than 5 cm below the left costal margin and with anemia defined by Hb less than 10 g/dL.

The target number of patients for this trial is 50.

Screening

Screening evaluations should be performed to determine the eligibility for the study and establish a baseline prior to dosing, and should be conducted between Day -28 and Day -1. However platelet and hemoglobin counts should be performed within a maximum of 7 days from the first dose of ruxolitinib. See Section 7 for complete screening and assessment details.

Treatment Period

All patients who consent to study participation will start treatment with ruxolitinib upon meeting all study eligibility criteria and none of the exclusion criteria. The treatment period commences on Day 1 (day of first dose of study drug). Patients will have study visits at Day 1 and at Weeks 4, 8, 12, 16, 20, 24, and every 12 weeks thereafter.

Patients will be treated with ruxolitinib 10 mg BID for the first 12 weeks and up titrations thereafter. See Section 6.1.1 for details.

Patients will receive treatment on this trial as long as they benefit from it until 48 weeks after Last Patient First Treatment date.

End of Study Treatment (EoT)

Patients may be discontinued from treatment with the study drug earlier due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the patient.

Patients who in the opinion of the investigator are still deriving clinical benefit from ruxolitinib may continue treatment with commercial ruxolitinib according to local regulations in countries with commercially available ruxolitinib.

Should ruxolitinib not be available to patients commercially after the end of treatment visit, every effort will be made to continue provision of ruxolitinib off study. Novartis will have a transition plan in place to ensure that patients have access to ruxolitinib without delays to treatment.

[redacted]

Safety Follow up period

The safety follow up period is 30 days after the last dose of study treatment. All patients must have safety evaluations for 30 days, after the last dose of study treatment. Data collected should be added to the Adverse Events CRF and the Concomitant Medications CRF.

4.2 Timing of interim analyses and design adaptations

Not applicable.

4.3 Definition of end of study

The end of the study (last patient last visit) will occur after completion of the last follow up visit of the last patient on treatment with ruxolitinib.

Patients who in the opinion of the investigator are still deriving clinical benefit from ruxolitinib may continue treatment with commercial ruxolitinib according to local regulations in countries with commercially available ruxolitinib.

Should ruxolitinib not be available to patients commercially after the end of treatment visit, every effort will be made to continue provision of ruxolitinib off study. Novartis will have a transition plan in place to ensure that patients have access to ruxolitinib without delays to 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 and the same assessments should be performed as described in Section 7 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

Adult Primary Myelofibrosis (PMF), Post-Polycythemia Vera-Myelofibrosis (PPV-MF), or Post-Essential Thrombocythemia Myelofibrosis (PET-MF) patients with splenomegaly at baseline that is equal to or greater than 5 cm below the left costal margin and with anemia at baseline defined by Hb less than 10 g/dL will be eligible to participate in this trial.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies.

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

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

[redacted]

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

1. Male or female patients aged ≥ 18 years of age.
2. Patients must be diagnosed with PMF, according to the 2016 revised International Standard Criteria (Arber et al. 2016), PPV MF or PET-MF (Barosi 2008), irrespective of JAK2 mutation status.
3. Patients with palpable splenomegaly that is equal to or greater than 5 cm below the left costal margin.
4. Patients with a hemoglobin less than 10 g/dL
5. Patients with a history of transfusions must have a documented transfusion record in the previous 12 weeks to baseline.
6. Patients with an ECOG performance status of 0, 1, or 2.
7. Patients with a peripheral blood blast percentage count of < 10%.
8. Patients must have recovered or stabilized sufficiently from any adverse drug reactions associated with prior treatments before beginning treatment with ruxolitinib.

5.3 Exclusion criteria

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

1. Patients with prior treatment with any JAK1 or JAK2 inhibitor.
2. Patients with known hypersensitivity to ruxolitinib or other JAK1/JAK2 inhibitors, or to their excipients.
3. Patients eligible for hematopoietic stem cell transplantation (suitable candidate and a suitable donor is available).
4. Patients with inadequate bone marrow reserve at baseline as demonstrated by at least one of the following:
   a. ANC that is ≤ 1,000/µL.
   b. Platelet count that is <50,000/µL without the assistance of growth factors, thrombopoietic factors or platelet transfusions.
   c. Hemoglobin count that is ≤ 6.5 g/dL despite transfusions.
5. Patients with severely impaired renal function defined by:
   Creatinine clearance less than 30 mL/min.
6. Patients with inadequate liver function defined by any of these:
   a. Total bilirubin ≥ 2.5 x ULN and subsequent determination of direct bilirubin ≥ 2.5 x ULN;
   b. Alanine aminotransferase (ALT) > 2.5 x ULN;
   c. Aspartate aminotransferase (AST) > 2.5 x ULN.
7. Patients being treated concurrently with a strong (potent) systemic inhibitor or inducer of CYP3A4 at the time of Screening.
8. Presence of active bacterial, fungal, parasitic, or viral infection which requires therapy.
9. Known history of human immunodeficiency virus (HIV) infection or other immunodeficiency syndromes such as X-linked agammaglobulinemia and common variable immune deficiency.

[redacted]

10. Acute viral hepatitis or active chronic hepatitis B or C infection. Patients with *inactive* chronic infection (without viral replication) can be enrolled (See Section 7.2.2.7)

11. History of progressive multifocal leuko-encephalopathy (PML).
12. 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).
13. History or current diagnosis of uncontrolled or significant cardiac disease, including any of the following:
    a. Myocardial infarction within last 6 months
    b. Uncontrolled congestive heart failure
    c. Unstable angina within last 6 months
    d. Clinically significant (symptomatic) cardiac arrhythmias (e.g. bradyarrhythmias, sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker)
14. Significant concurrent, uncontrolled medical condition which, in the investigator's opinion, would jeopardize the safety of the patient or compliance with the protocol.
15. Patients 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.
16. Patients with a history of malignancy in the past 3 years, except for treated early stage squamous or basal cell carcinoma.
17. Patients who are unable to comprehend or are unwilling to sign an ICF.
18. Pregnant or nursing (lactating) women
19. 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:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    b. 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
    c. Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient.
    d. 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)

[redacted]

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

6 Treatment

6.1 Study treatment

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

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
INC424/ruxolitinib	5mg Tablet for oral use	Starting dose 10 mg bid (2 tablets of INC424 5mg, approximately 12 hours apart: morning and night), to be increased or decreased per standardized dosing paradigm and not to exceed 25 mg bid.	Twice Daily (BID),unless instructed to temporarily withhold dosing for safety

INC424 (ruxolitinib) 10 mg BID (2 tablets of INC424 5mg) will be self-administered as starting dose for treatment of anemic MF patients. This dose will be maintained for the first 12 weeks and titrated up thereafter unless they have met criteria for dose hold or dose reduction.

Ruxolitinib should be taken orally, approximately 12 hours apart (morning and night) without regards to food. Ruxolitinib will be self-administered by the patient in an outpatient setting, and each investigator should instruct the patient to take the study drug as per protocol. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the appropriate case report form (CRF).

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

See Section 6.3

[redacted]

6.1.5 Treatment duration

The planned minimum duration of treatment is 48 weeks. Patients may be discontinued from treatment with the study drug earlier due to unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or the patient.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

Phase I/II trials evaluated a number of different doses and schedules of ruxolitinib. Based on these, two phase III trials evaluated the efficacy and safety of ruxolitinib versus placebo in COMFORT I and versus BAT in COMFORT II in a population of patients with primary and secondary MF. In both phase III trials a starting dose of 20 mg orally BID was administered for patients with platelet counts from 200,000/ µL and a lower starting dose of 15 mg orally BID in patients with baseline platelet counts from 100,000 to 200,000/ µL.

Additional studies generated clinical data on the efficacy and tolerability of ruxolitinib in patients with MF and platelet counts from 50,000 to 100,000/µL. A starting dose of 5 mg BID with subsequent optional up titrations every 4 weeks by dose increments of 5 mg OD was evaluated in a phase II open label single arm study INCB18424-258 in a population of patients with platelet counts from 50,000 to 100,000/µL. Similarly, an expanded access program and phase IIIb study CINC424A2401 that recruited more than 2200 patients allowed the inclusion of patients with low platelet counts (50,000 to 100,000/µL) to be treated with a 5 mg BID starting dose.

Furthermore, a Phase Ib study (EXPAND) evaluating the safety and MTD of ruxolitinib in patients with lower baseline platelet counts (50,000– 100,000/µL) suggests that higher doses of ruxolitinib can be safely administered to patients with lower baseline platelet count. The maximum safe starting dose in this ongoing study was reported to be 15 mg BID for patients with platelet counts from 75,000 to 100,000/µL and 10 mg BID for patients with platelet counts from 50,000 to 75,000/µL.

Anemia may be ameliorated by lowering the dose of ruxolitinib or by concomitant use of erythropoietin stimulating agents and/or anabolic steroids (Reilly 2014). This approach may make particular sense in patients with anemia at the moment of treatment initiation with ruxolitinib in order to avoid further hemoglobin decrease, the need of blood transfusions or have them more frequently in patients already receiving regular transfusions for anemia.

An alternative strategy to start patients at 10 mg BID and titrate the dose up according to tolerability and response (Cervantes 2014, Harrison 2013) has anecdotally suggested improved tolerance and reduced adverse events yielding fewer treatment discontinuations and has been already included in treatment guidelines (Ho 2015, Reilly 2014).

Based on the above, a starting dose of 10 mg BID will be assigned to patients recruited in this phase II open label single arm study followed by gradual up titrations starting at week 12, based on efficacy and safety at the different evaluation visits. This approach assumes that starting at a lower dose may impact the rate of the initial hemoglobin decline and the nadir, by decreasing the level of JAK-mediated inhibition of hematopoiesis.

[redacted]

6.2.2 Provisional dose levels

Not Applicable.

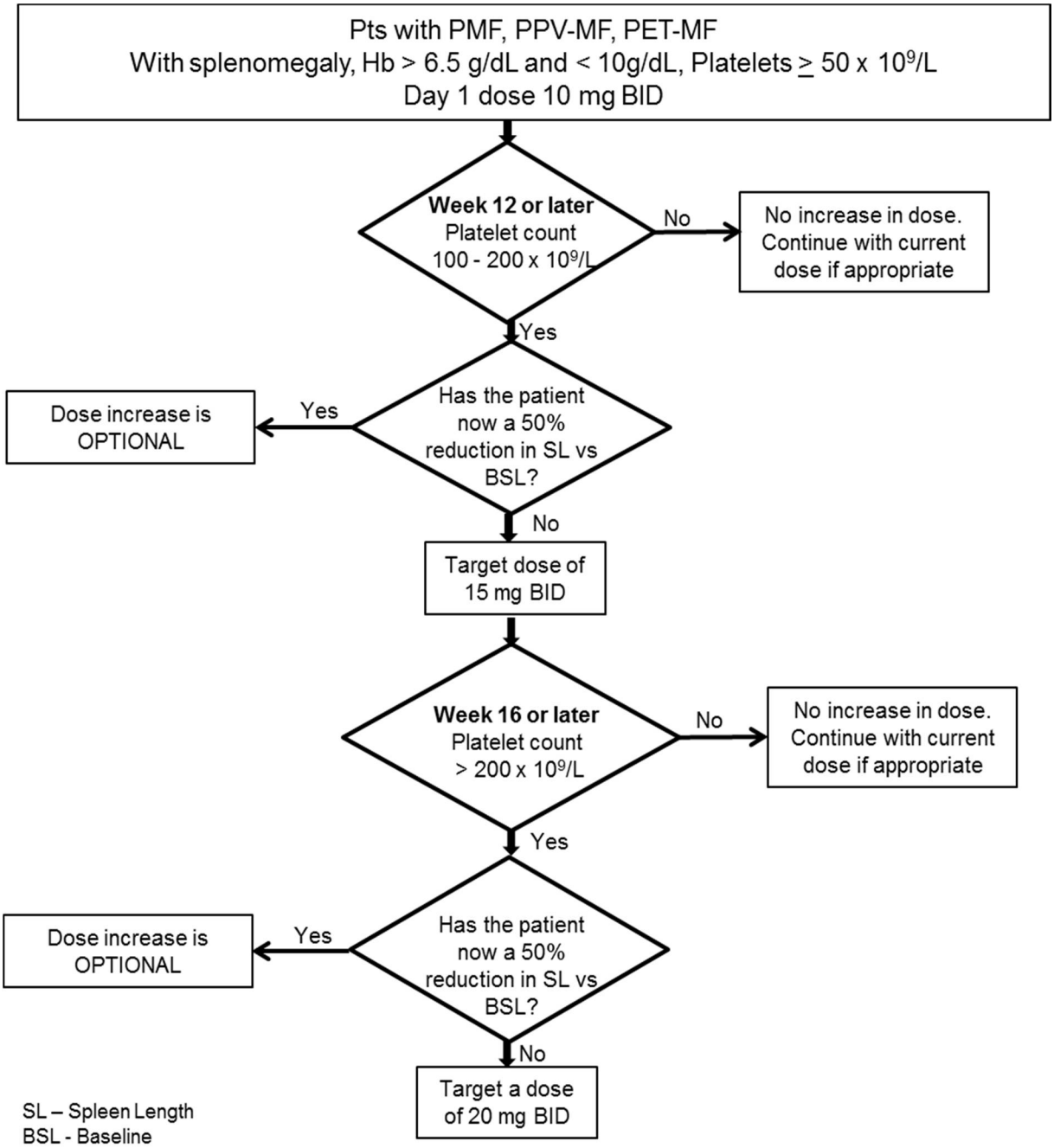
6.2.3 Guidelines for dose escalations

Dose up titrations will be based on efficacy and platelet counts provided that ANC is >500 µL and Hb level is ≥ 6.5 g/dL as follows:

- A dose of 15 mg BID should be targeted in patients with platelet count ≥ 100 x 10^9/L and ≤ 200 x 10^9/L from week 12. This dose increase is optional for patients that achieved a ≥ 50% reduction in spleen length at this visit relative to Baseline.
- A dose of 20 mg BID should be targeted in patients with platelet count ≥ 200 x 10^9/L from week 16. This dose increase is optional for patients that achieved a ≥ 50% reduction in spleen length at this visit relative to Baseline.
- Maximum dose allowed in the study is 25 mg BID and may be used from Week 20 in patients that did not achieve a 50% reduction in spleen length relative to Baseline and provided that platelet count is ≥ 200 x 109/L at this visit.
- Patients who did not qualify for a dose increase at Week 12, may qualify for an increase at week 16 (from 10 mg BID to 15 mg BID). In that case, the Week 12 dose increase rules will apply. Similarly, patients who did not qualify for a dose increase at Week 16, may qualify for an increase later (from 15 mg BID to 20 mg BID). In that case, the Week 16 dose increase rules will apply.

[redacted]

Figure 6-1 Dosing Up-titration Diagram



6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow patients to continue the study treatment. These dose changes must be recorded on the Dosage Administration Record CRF.

6.3.1.1 Dose modification for hematologic toxicity

For all patients who receive ruxolitinib, there are mandatory dose decreases or dose interruptions for declining platelet counts, hemoglobin or ANC levels that might be observed while on ruxolitinib therapy. Deviations to mandatory dose interruptions and/or reductions are not allowed.

Doses may be titrated based on safety. Dosing must be held if platelet counts decline below 25,000/μL or if ANC that is ≤ 500/μL or Hemoglobin is ≤ 6.5 g/dL despite transfusions, while receiving ruxolitinib.

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

Table 6-2 Dose modifications for hematologic toxicity

The instructions provided in this table and the criteria for dose reduction / interruption are used to determine a protocol deviation.

Hematology Value at time of decline:	**Dose at the time of decline**				
	25 mg BID	20 mg BID	15 mg BID	10 mg BID	5 mg BID
	Dose reduction to				
Platelet < 125,000 /μL	20 mg BID	20 mg BID	15 mg BID	10 mg BID	5 mg BID
Platelet < 100,000 /μL	15 mg BID	15 mg BID	15 mg BID	10 mg BID	5 mg BID
Platelet < 75,000 /μL	10 mg BID	10 mg BID	10 mg BID	10 mg BID	5 mg BID
Platelet < 50,000 /μL	5 mg BID	5 mg BID	5 mg BID	5 mg BID	5 mg BID
Platelet < 25,000 /μL	Treatment must be interrupted.				
Hemoglobin ≤ 6.5 g/dL despite transfusions	Treatment must be interrupted.				
Absolute neutrophil count < 0.5 x 109/L	Treatment must be interrupted.				

6.3.1.2 Dose modification for renal impairment

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

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).

[redacted]

6.3.1.3 Dose modification for hepatic impairment

Patients diagnosed with hepatic impairment while receiving ruxolitinib should be carefully monitored and may need to have their dose reduced to avoid adverse drug reactions.

Patients diagnosed with hepatic impairment while receiving ruxolitinib should have complete blood counts, including a white blood cell count differential (neutrophils, lymphocytes, eosinophils, basophils, monocytes, and blast cells), monitored at least every one to two weeks for the first 6 weeks after initiation of therapy with ruxolitinib and as clinically indicated thereafter once their liver function and blood counts have been stabilized. ruxolitinib dose can be titrated to reduce the risk of cytopenia.

6.3.1.4 Dose reduction for non-hematological safety

Although study guidelines provide for dose reduction/interruption for the management of hematologic or non-hematologic toxicities that occur during the course of the study, the investigator should determine whether permanent discontinuation of study drug is necessary.

6.3.2 Optional dose tapering strategy in the event of study drug discontinuation

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

When a decision is made to permanently discontinue ruxolitinib therapy for reasons other than low platelet counts or ANC levels, a dose tapering strategy may be considered, based on evaluation of the condition of the patient, 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 adverse drug reactions of discontinuation. Short-term courses of corticosteroids have been used to moderate the withdrawal of ruxolitinib 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 with utilization of a tapering strategy, regardless of the use of concomitant medications, safety data will continue to be assessed in accordance with the protocol until the end of ruxolitinib administration and in the event of an AE through resolution of the AE.

6.3.3 Dose interruption and discontinuation of study drug

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of adverse drug reaction that may have an unclear relationship to study drug. Except in cases of emergency or for protocol mandated holds for ANC, hemoglobin or platelet count, it is

recommended that the investigator consult with the Sponsor medical monitor (or other representative of the Sponsor) before temporarily interrupting therapy.

Study drug may be held by the investigator at any time if there is concern about patient safety, and for all aspects of the conduct of the protocol the safety of the individual patient is paramount. Treating investigators may employ any means necessary to ensure patient safety, particularly in medical circumstances not anticipated by this protocol. Dosing must be halted immediately if any of the following occur:

- Platelet counts fall below 25,000/μL
- ANC levels fall below 500/μL
- Hemoglobin cannot be maintained ≥6.5 g/dL despite the use of transfusion therapy

Dosing may be reinstated following dose holding as detailed in Section 6.3.6. In order to provide sufficient data to make the dose adjustment decisions, it is recommended that hematology parameters be obtained at least weekly for platelet count < 100,000/μL or ANC < 1000/μL and at least two times weekly for platelet count < 50,000/μL or ANC < 500/μL. (Note: patients with platelet counts of < 10,000/μL should be hospitalized, unless local or national practice does not permit it).

If a patient on a dose-hold requires frequent testing for safety parameters, these tests may be performed at a local laboratory. If the study drug is interrupted for any reason for more than 8 weeks, dosing may not be restarted, except in the case of splenectomy, for which a maximum 12 week period of study drug interruption is permitted. Although study guidelines provide for dose reduction/interruption for the management of hematologic or non-hematologic toxicities that occur during the course of the study, the following guidelines should be used to determine whether permanent discontinuation of study drug is necessary.

6.3.4 Discontinuation of study drug for hematologic toxicity:

Study drug MUST be permanently discontinued if the lowest allowed dose (5 mg BID or 5 mg QD with concomitant CYP3A4 inhibitor) is not tolerated due to the following:

- Platelets cannot be maintained ≥ 25,000/μL.
- Absolute neutrophil count cannot be maintained ≥500/μL.
- Hemoglobin cannot be maintained ≥6.5 g/dL despite the use of transfusion therapy.

In the event that any patient permanently discontinues the study drug, regardless of reason, reasonable efforts should be made to have the patient return for an early termination visit and have the End of Treatment evaluations and Safety Follow up evaluations completed.

The date the patient discontinued the study drug and the specific reason for discontinuation will be recorded in the eCRF. This will include reasons such as discontinued due to disease worsening or withdrawn due to adverse event. This information will be used to summarize the reasons for study withdrawal.

6.3.5 Restarting or reinstituting previous dose

Dosing of ruxolitinib may be restarted or increased following recovery of platelet counts and/or ANC to acceptable levels as illustrated in Table 6-3. The objective for restarting or

[redacted]

escalating after a reduction for safety is to find the highest safe dose of ruxolitinib for each patient, with increases in dose generally not more than in increments of 5 mg BID and not more often than every 2 weeks. Similarly, ANC levels that decline to < 500/µL necessitate immediate dose interruption (Section 6.3.1.1). ANC level recovery to 500 /µL and above but less than 750/µL will allow dosing to be restarted at 5 mg BID, and ANC levels between 750/µL, but < 1000/µL may restart at 10 mg BID. Absolute neutrophil count level increases to above 1000/µL will allow a further dose increase.

After restarting using the guidelines in Table 6-3, if it is found that a patient cannot tolerate the lowest allowed dose (5mg BID, or 5mg QD with concomitant CYP3A4 inhibitor, see Section 6.4.2) without platelets falling below 25,000/µL, neutrophils falling below 500/µL, or Hgb falling below 6.5g/dL despite the use of transfusion therapy, drug must be permanently discontinued (Section 6.3.1.1).

Table 6-3 Restarting or reinstituting previous ruxolitinib dose after safety interruptions or dose reductions

Current Platelet Count after interruption or reduction	**Maximum Dose for Restarting or reinstituting previous dose after interruption or reduction**
< 25,000/µL	Continue hold
25,000/µL to < 50,000/µL	5 mg BID
50,000/µL to < 75,000/µL	10 mg BID
75,000/µL to < 125,000/µL	15 mg BID
≥125,000/µL	20 mg BID
Current ANC Level after interruption or reduction	**Dose Restart or Dose Increase Guidelines**
< 500/µL	Continue hold
500 to < 750/µL	5 mg BID for at least 2 weeks; if stable, may increase to 10 mg BID
750 to < 1000/µL	10 mg BID for at least 2 weeks; if stable, may increase to 15 mg BID
1000 to < 1500/µL	15 mg BID for at least 2 weeks; if stable may increase to 20 mg BID
≥1500/µL	20 mg BID
NOTE: Whether the dose interruption occurred because of neutropenia, thrombocytopenia or both, when restarting, both the platelet count and ANC must be considered to determine the restart dose, with the lower calculated dose being used.	

6.3.6 Treatment of investigational drug overdose

There is no known antidote for ruxolitinib overdose. Overdose will be defined as the use of ruxolitinib in doses in excess of that specified in the protocol. . Patients overdosed should be treated with appropriate supportive care until recovery. Use of ruxolitinib in doses in excess of that specified in the protocol should not be recorded in the eCRFs as an AE of 'Overdose'. An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE and SAE forms in the eCRFs. An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the eCRFs. An overdose without associated symptoms should not be recorded as an AE in the eCRFs.

[redacted]

6.4 Concomitant medications

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

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. At each visit, the patient must be asked about any new medications he/she is or has taken. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the appropriate CRF.

All medications taken ≤ 30 days prior to study entry should be recorded on the appropriate Case Report Form (eCRF). All prior medications used to treat PMF, PPV MF, or PET-MF will be recorded. All concomitant treatments during the trial will also be recorded in the eCRF.

The following restrictions apply during the study:

- No other investigational therapy should be given to patients.
- No anticancer agents other than the study medication (ruxolitinib) should be given to patients until disease progression or withdrawal from the study. If such agents are required for a patient then the patient must first be withdrawn from the study.

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:

- In patients for whom warfarin or heparin use will be initiated, the degree of thrombocytopenia should be considered, coagulation parameters monitored, and dose of anticoagulant adjusted accordingly. If anticoagulation is required during ruxolitinib administration, low molecular weight heparin is preferred, particularly in patients who are: elderly, history of CHF, diabetic, hepatic or renal disease, or atrial fibrillation (first episode).
- Low dose aspirin (≤150 mg/day) and non-steroidal anti-inflammatory agents (acetaminophen, ibuprofen) may be used. Aspirin doses > 150 mg are prohibited.
- Inducers or inhibitors of the metabolizing enzyme CYP3A4 (Appendix 5)
- When concomitant administration of a strong (potent) inhibitor of CYP3A4 metabolizing enzymes or dual CYP2C9/CYP3A4 inhibitors (Appendix 5) is required for patient management, the dose of ruxolitinib tablets 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 dose is not practical..
    - Note: No dose adjustment of ruxolitinib is needed for use with topical ketoconazole.

[redacted]

- 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 (Appendix 5) are co-administered with study treatment.
- Granulocyte growth factors are not allowed while study treatment is being administered but may be used for severe neutropenia at the Investigator's discretion while study medication is being withheld.
- Certain herbal supplements see Appendix 5 are prohibited. Because the composition, pharmacokinetics and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is strongly discouraged during the study however if used during the trial please ensure the treatment is entered on the proper eCRF page (see Section 6.4.1).

6.4.3 Prohibited concomitant therapy

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

- Concomitant use of another JAK inhibitor.
- 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 until treatment discontinuation is prohibited.
- Use of hydroxyurea, interferon, thalidomide, busulfan, lenalidomide, or anagrelide is not permitted at any time during participation in the study. These medications should be discontinued prior to Day 1 of ruxolitinib therapy. All adverse events attributed to these medications should be resolved prior to Day 1 of ruxolitinib treatment.
- Potent inducers of CYP3A4 (Appendix 5) are not permitted.
- Aspirin in doses exceeding 150 mg per day is prohibited.

6.4.4 Use of Bisphosphonates (or other concomitant agents)

Not applicable.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject 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 Subject No. available to the investigator through the Oracle Clinical RDC interface.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must

[redacted]

not be reused for any other patient and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition page.

IRT must be notified within 2 days that the patient fails to start treatment.

6.5.2 Treatment assignment or randomization

The investigational treatment ruxolitinib will be provided to all participants and no randomization processes will apply.

6.5.3 Treatment blinding

All study participants will receive single arm study medication, therefore blinding is 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.

6.6.1 Study treatment packaging and labeling

Study treatment, ruxolitinib, will be provided as global clinical open supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Study treatment labels will be in the local language and comply with the legal requirements of each country, and will include storage conditions, a unique medication number (corresponding to study treatment and strength) but no information about the patient.

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label.

Responsible site personnel will identify the study treatment package(s) to dispense by the medication number(s) assigned by IRT to the patient. Site personnel will add the patient number on the label. The label has 2-parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document (Drug Label Form) for that patient's unique patient number.

6.6.2 Drug supply and storage

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

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

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

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log.

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. 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.

- All doses taken by the patient and all dose changes or interruptions during the study must be recorded on the DAR eCRF.
- The investigator or his/her designee must keep documentation (overall drug accountability for the study as well as individual study drug accountability for each patient) of tablets administered, tablets used, dose changes, and dates dispensed.
- Drug accountability will be monitored by the field monitor during site visits and at the completion of the study.

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

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation. No CRF will be used as a source document.

[redacted]

Table 7-1 Visit evaluation schedule

Evaluation	Category	Protocol Section	Screening	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 36	Week 48	Every 12 weeks thereafter (wk 60, 72, 84, etc)	End of study treatment (EoT)	30 Day Safety Follow up
Day of Visit			-28 to -1	1	28	56	84	112	140	168	252	336	420, 504, 598, etc.,	-	
Visit Windows					+/- 7 days						+/- 14 days				
Obtain Informed Consent	D	7.1.2	X												
Eligibility Checklists(s)	S	7.1.2.1	X												
Disposition –Screening CRF	D	7.1.2.2	X												
IRT Registration	D	7.1.2.1	X												
Patient history															
Demography	D	7.1.2.3	X												
Inclusion/exclusion criteria	D	7.1.2.1	X												
Medical History	D	7.1.2.3	X												
Diagnosis of PMF, PPV MF, and PET-MF includes bone marrow biopsy with grading of fibrosis	D	7.1.2.3	X												
MF Treatment history	D	7.1.2.3	X												
Transfusions since last visit	D	7.2.2.3	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	D	7.1.2.3	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

Evaluation	Category	Protocol Section	Screening	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 36	Week 48	Every 12 weeks thereafter (wk 60, 72, 84, etc)	End of study treatment (EoT)	30 Day Safety Follow up
Day of Visit			-28 to -1	1	28	56	84	112	140	168	252	336	420, 504, 598, etc.,	-	
Visit Windows					+/- 7 days						+/- 14 days				
Physical examination	S	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X
Measurement of spleen by palpation	D	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance status	D	7.2.2.6	X	X	X	X	X	X	X	X	X	X	X	X	
Height	D	7.2.2.5	X												
Weight	D	7.2.2.5	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	D	7.2.2.4	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments															
Hematology	D	7.2.2.7	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	D	7.2.2.7	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]															
Viral Hepatitis (testing as indicated in Section 7.2.2.7 during trial for patients with inactive chronic infection)	D	7.2.2.7	X												

[redacted]

Evaluation	Category	Protocol Section	Screening	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 36	Week 48	Every 12 weeks thereafter (wk 60, 72, 84, etc)	End of study treatment (EoT)	30 Day Safety Follow up
Day of Visit			-28 to -1	1	28	56	84	112	140	168	252	336	420, 504, 598, etc.,	-	
Visit Windows					+/- 7 days						+/- 14 days				
Pregnancy test serum	D	7.2.2.7	X											X	
Pregnancy test urine	D	7.2.2.7		X	X	X	X	X	X	X	X	X	X		
Safety															
Adverse events	D	8.1	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient reported Outcomes															
Myelofibrosis 7 Item Symptom Scale (MF-7)	D	7.2.6	X	X	X	X	X	X	X	X	X	X	X	X	
Modified MFSAF v2.0	D	7.2.6	X	X	X	X	X	X	X	X	X	X	X	X	
Patient Global Impression of Change (PGIC)	D	7.2.6			X	X	X	X	X	X	X	X	X	X	
Study Drug administration	D	6.1.1		X	X	X	X	X	X	X	X	X	X		
End of Phase Disposition	D	7.1.4												X	

[redacted]

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 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 28 day screening period.

Re-screening of patients will be allowed, if all entry criteria are not met during the screening period (-28 days to -1 day). Re-screening should only occur after a patient has failed screening. The same patient ID number should be used to rescreen.

Rescreening of patients is permissible at the discretion of the investigator i.e., a patient is screened and is found to be ineligible, they may be rescreened at a later date and entered onto the study provided **all** inclusion and **no** exclusion criteria are met. Rescreening should not occur more often than every 7 days.

7.1.2.1 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,

Following registering in the IRT for screening, patient eligibility will be checked by the Sponsor once all screening procedures are completed. The eligibility check form will be sent from the site to the Sponsor either via fax or email for evaluation. Upon confirmation of eligibility, the Sponsor will return the signed eligibility check form via fax or email to the site.

The investigator site will then contact the IRT to be allowed to assign treatment to the patient. Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 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).

[redacted]

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.

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

7.1.2.3 Patient demographics and other baseline characteristics

Data to be collected on patient characteristics at screening include:

- Demography (including: date of birth, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)
- Relevant medical history including: Myelofibrosis diagnosis (Appendix 3) and disease history, Prior MF Medications (Treatment history), and transfusion history.
- 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.

7.1.3 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 48 weeks after Last Patient First Treatment date or the patient is discontinued for other reasons as indicated in Section 7.1.4.

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

Visit windows of ± 7 days from scheduled study assessments will apply from Week 4 visit up to Week 24 and ± 14 days for visits after Week 24.

7.1.4 Discontinuation of study treatment

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

[redacted]

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

In addition to mandatory dose interruptions and/or reductions of Study treatment listed in Section 6.3, study treatment may also be discontinued under the following circumstances:

- Consent is withdrawn
- Further participation would be injurious to the patient's health or well-being in the investigator's medical judgment
- The study is terminated
- Disease progression
- Pregnancy
- Unacceptable toxicity
- The following deviations from the prescribed dose regimen for study treatment . If the study drug is interrupted for any reason for more than 8 weeks, dosing may not be restarted, except in the case of splenectomy, for which a maximum 12 week period of study drug interruption is permitted.
- Use of prohibited treatment refer to Appendix 5
- Any other protocol deviation that results in a significant risk to the patient's safety
- Discontinuation from the study for any other reason per the Investigator's judgement

Adverse events requiring discontinuation are listed in Section 6.3.4.

Patients who discontinue study treatment should undergo an end of study treatment visit and then enter the follow-up epoch or period.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

7.1.4.1 Replacement policy

Not applicable.

7.1.5 Withdrawal of consent

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

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

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

Study treatment must be discontinued and no further assessments conducted.

[redacted]

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

7.1.6 Follow up for safety evaluations

All patients must have safety evaluations for 30 days after the last dose of study treatment.

Data collected should be added to the Adverse Events CRF and the Concomitant Medications CRF.

Follow-up evaluations

The following evaluations will be performed within 30 days after the last dose of study treatment. The following procedures will be performed and all observations will be recorded in the eCRF:

- Review of concomitant medications.
- Review of transfusion history
- A complete physical examination will be performed, including body weight and measurement of spleen by palpation.
- Vital signs to be performed in a sitting position after 5 minutes of rest)
- Blood sampling for serum chemistry and hematology tests.
- Record adverse events.

7.1.7 Lost to follow-up

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

7.2 Assessment types

7.2.1 Efficacy assessments

Assessments for efficacy will consist of spleen length measurement, transfusion requirements, symptom scores using Myelofibrosis 7 Item Symptom Scale, Separate question on Inactivity to compute Modified MFSAF v2.0 and PGIC.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing described below as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

[redacted]

7.2.2.1 Physical examination

A comprehensive physical examination will be performed. The comprehensive physical examination will include the following organ/body system assessments: general appearance, skin; HEENT (head, eyes, ears, nose and throat); thyroid; lungs; cardiovascular; abdomen (liver, spleen); lymph nodes; neurological examination, assessment of edema and extremities. A targeted physical examination will be performed at each visit that will include body systems as indicated by patient symptoms, AEs, prior physical examinations, or other findings as determined by the investigator.

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 begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.2.2 Spleen Measurement

The physical examination will include a measurement of spleen length.

The edge of the spleen shall be determined by palpation, measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion. The spleen should be measured in the same manner at all visits.

7.2.2.3 Transfusion requirements

At the screening visit, information on all prior transfusions (Whole blood - PRBC) performed during the last 12 weeks prior to screening will be collected and recorded in the appropriate eCRF.

At each subsequent visit, all transfusions (Whole blood - PRBC) performed since the last visit will collected and recorded in the appropriate eCRF.

7.2.2.4 Vital signs

Vital signs include blood pressure and body temperature measurement.

7.2.2.5 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1.

7.2.2.6 Performance status

ECOG Performance status scale (Appendix 2) will be used in the timepoints as described in the Table 7-1.

7.2.2.7 Laboratory evaluations

Clinical laboratory tests (hematology, clinical chemistry, viral hepatitis and pregnancy testing) will be performed at the center where the patient is enrolled (local laboratory).

[redacted]

All patients will have samples of blood collected on the days noted in the Visit Evaluation Schedule Table 7-1. Table 7-2 provides a complete list of laboratory tests that will be performed at the local laboratory.

Hepatitis B testing – At screening, HBV infection status testing will be done for HB-sAG and anti HB-c antibody. If HB-sAG is negative and anti HB-c antibody is negative, the patient can be enrolled.

If HB-sAG is positive and/or anti HB-c antibody is positive, the site will determine per local procedures if infection is active (with viral replication) or inactive (without viral replication). Possible test include, for instance, serology testing for HB-eAG and PCR for HBV DNA.

Patients with active HBV infection (with viral replication) are not eligible for enrollment.

Patients with inactive HBV infection (without viral replication) can be enrolled. Monitoring of these patients for reactivation by regular testing, using the same test is required **every 12 weeks**. Treatment in case of reactivation will be as per local procedure. This information will be collected in the eCRF.

Hepatitis C testing – At screening, HCV infection status will be assessed by the means of anti HCV antibody screen. The patient can be enrolled if anti HCV antibody is negative. If anti HCV antibody is positive then HCV RNA by PCR will be performed.

Patients with active HCV infection (with viral replication) are not eligible for enrollment.

Patients with inactive HCV infection (without viral replication) can be enrolled. Monitoring of these patients for reactivation is required by means of HCV RNA by PCR at regular intervals as per the local practice. This information will be collected in the eCRF.

Table 7-2 Local Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, RBC Morphology,Blasts, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred , %s are acceptable).
Chemistry	Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Total Bilirubin, Total Cholesterol, LDL Cholesterol, HDL Cholesterol, Total Protein, Triglycerides (fasting), Blood Urea Nitrogen (BUN) or Urea, Uric Acid Amylase, Lipase, Glucose (fasting)
Viral Hepatitis	For hepatitis B: HB-sAG and anti HB-c antibody at screening. For Hepatitis C: anti HCV antibody at screening. For patients with inactive infection, testing every 12 weeks for reactivation (for HBV) and at regular intervals as per the local practice (for HCV).
Pregnancy Test	A serum pregnancy test should be performed at screening and EOT visit, while at all other timepoints, urinary pregnancy tests are sufficient.

[redacted]

7.2.2.8 Radiological examinations

Not applicable.

7.2.2.9 Cardiac assessments

Not applicable.

7.2.2.10 Tolerability

Not applicable

7.2.3 Pharmacokinetics

Not applicable

[redacted]

[redacted]

[redacted]

7.2.5 Resource utilization

Not applicable.

7.2.6 Patient reported outcomes

Patients with MF often experience significant symptoms that interfere with their quality of life (QoL) including, fatigue, early satiety, pruritus, weight loss, weakness and night sweats. The effect of ruxolitinib on patient symptoms and QoL will be measured using several assessment tools including but not limited to the MF-7, Modified MFSAF v2.0 and the Patient Global Impression of Change (PGIC). All questionnaires are patient-reported outcomes (PROs). The PRO questionnaires provided electronically (ePRO) are to be completed by the patient. The site will review for completeness.

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

1. MF-7
2. Separate question on Inactivity to compute Modified MFSAF v2.0
3. PGIC

Patient Reported Outcomes will be collected according to the Visit Schedule outlined in Table 7-1. The patient should be given sufficient space and time to complete the PRO questionnaires.

[redacted]

The site personnel should check the questionnaires for completeness and ask the patient to complete any missing responses. The original questionnaire will be kept with the patient's file as the source document.

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

MF-7

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

Modified MFSAF v2.0 – Computed through a separate Question on Inactivity

A separate question on Inactivity (Appendix 4) will measure the severity of this symptom on a scale from 0 (absent) to 10 (worst imaginable) and will allow the computation of the MFSAF v2.0 questionnaire results, as 6 out of 7 items in the latter PRO are in overlap with MF7 (they also share same 0-10 range Likert scale and ascending order, absent to worst imaginable).

PGIC

The Patient Global Impression of Change (PGIC; Appendix 4) is comprised of a single question intended to measure a patient's perspective of improvement or deterioration over time relative to treatment. The PGIC uses a seven-point scale where one (1) equals very much improved and seven (7) equals very much worse.

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).

[redacted]

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

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient 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 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 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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

[redacted]

necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

All patients who have AEs, whether considered associated with the use of the investigational product or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the AE result in death, a full pathologist's report should be supplied if and when available.

SAEs must be reported as outlined in Section 8.2.2. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

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

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

8.1.3 Adverse events of special interest

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,

[redacted]

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 additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes 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.

Any SAEs experienced after the 30 day safety evaluation follow-up should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site

Follow-up information is submitted in the same way as the original SAE 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

[redacted]

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 Pregnancies

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

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

8.4 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.

8.5 Data Monitoring Committee

Not applicable

8.6 Steering Committee

The steering committee will be established comprising investigators participating in the trial, i.e. not being members of the DMC and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

9 Data collection and management

9.1 Data confidentiality

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

- What protected health information (PHI) will be collected from patients 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/patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients 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 patient 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 (Patient 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 Patient Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the patient 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.

PPI [redacted]

Data for PROs: will be collected by the patient electronically and transferred to the ePRO vendor. The data will be sent electronically to Novartis (or a designated CRO). The site will enter information regarding sample collection in the eCRF.

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

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel 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.

All [redacted] IVRS and PRO Samples and/or data will be processed centrally and the results will be sent electronically to Novartis.

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

10 Statistical methods and data analysis

The primary analysis will be performed when all enrolled patients have completed the week 24 visit or have discontinued from the study prior to week 24.

[redacted]

The final analysis will occur at the end of the study. All available data from all patients will be analyzed and summarized in a final CSR.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment (ruxolitinib) has been assigned and who received one dose of study treatment (ruxolitinib).

10.1.2 Safety set

The Safety Set is the same as the FAS.

10.1.3 Per-Protocol set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who had no major protocol deviation.

Any protocol deviations potentially leading to exclusion from the PPS will be specified in the study Statistical Analysis Plan (SAP). This population will be used as supportive analyses for the primary efficacy endpoint.

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.

10.1.6.1 Efficacy/evaluable set

Not applicable.

10.2 Patient demographics/other baseline characteristics

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

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

Relevant medical histories and current medical at baseline will be summarized separately for ongoing and historical medical conditions by system organ class and preferred term, for the FAS.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The Safety set will be used for the analyses below.

The duration of exposure to study treatment, as well as the actual dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure), cumulative dose and average daily dose of ruxolitinib will be summarized by means of descriptive statistics using the safety set.

The number of patients with dose adjustments (dose changes/interruption) and the reasons will be summarized for the Safety set and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of ruxolitinib will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by means of frequency counts and percentages. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed.

10.4 Primary objective

The primary objective of this study is to determine the spleen length response rate at week 24.

10.4.1 Variable

The primary efficacy variable for this study is the proportion of patients achieving a 50% reduction in spleen length at Week 24.

10.4.2 Statistical hypothesis, model, and method of analysis

The assessment of primary efficacy of study treatment will be based on the calculation of observed proportion of patients with spleen length response at Week 24 and its posterior distribution using a Beta-binomial model. The FAS will be used for the primary analysis. Study treatment will be declared efficacious if the following criteria are met:

a. Observed proportion of patients with ≥50% reduction in spleen length at Week 24 ≥25%
b. Probability of true response rate ≤15% (considered not clinically meaningful) is less than 10%

With 50 patients, criteria ‘a’ and ‘b’ will be met if the observed responder rate is ≥25%, i.e., at least 13 patients out of 50 patients have a response at Week 24 which will give a probability of “not being clinically meaningful (response ≤15%)” of 0.0243.

The primary analysis will be performed when all the enrolled patients have been treated with ruxolitinib for 24 weeks or discontinued prior to week 24. The point estimate of the proportion of patients achieving ≥50% reduction in spleen length at Week 24 along with corresponding exact 95% confidence interval using Clopper and Pearson exact method will be presented.

[redacted]

10.4.3 Handling of missing values/censoring/discontinuations

For the primary analysis, patients with missing baseline spleen length will be excluded from the analysis as change from baseline cannot be calculated.

Patients with missing spleen length at Week 24 or who withdraw earlier from the study will be considered as a non-responder.

10.4.4 Supportive and Sensitivity analyses

The primary analysis (as described in Section 10.4.2) will also be repeated on the PPS. Furthermore, the primary endpoint will be analyzed on patients with non-missing spleen length at both baseline and week 24.

10.5 Secondary objectives

All secondary efficacy analyses will be performed on the FAS, unless otherwise specified. All safety related endpoints will be analyzed on the Safety set unless otherwise specified.

10.5.1 Secondary efficacy objective(s)

The spleen length response rate at Week 48 will be evaluated. The point estimate of the proportion of patients achieving ≥50% reduction in spleen length at Week 48 along with corresponding exact 95% confidence interval using Clopper and Pearson exact method will be presented.

Percent change from baseline in spleen length over time will be evaluated to assess the effect of ruxolitinib on spleen length. The analysis will be performed for each visit and at end of treatment. This parameter is computed by dividing the difference of spleen length at assessment time and at baseline by the length at baseline multiplied by one hundred.

To evaluate the effect of ruxolitinib on transfusion requirements, the following will be summarized:

- Number and percentage of transfusions over time
- Proportion of patients who are transfusion dependent (TD). Transfusion dependence is defined as per IWG MRT criteria: 6 or more transfusions in 12 weeks prior to baseline.
- For transfusion dependent (TD) patients, the following will be analyzed:
  - transfusion independence (TI) rate (requiring no transfusion for ≥12 weeks at any time)
  - transfusion response rate (not TD: having 5 or less transfusion for ≥12 weeks at any time)

10.5.2 Other secondary efficacy objectives

Not applicable.

[redacted]

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, unless specified otherwise.

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

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

The safety summary tables will include only assessments collected within 30 days after study treatment discontinuation and assessments on or prior to the data cut-off date for ongoing patients, unless otherwise specified.

All data, regardless of the observation period, will be listed and assessments collected in the pre-treatment and post-treatment period will be flagged in all the listings.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs.

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), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events leading to treatment discontinuations during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized by system organ class and preferred term.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the post-treatment period will be flagged.

AEs will be assessed according to the Common Terminology Criteria for AEs (CTCAE version 4.03). AEs will be coded using the latest MedDRA terminology version during the time of data analyses.

10.5.3.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

[redacted]

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for laboratory tests:

- Changes from baseline in hematology/biochemistry parameters over time.
- Listing of all laboratory data (including hematology, biochemistry, and urinary laboratory test with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v4.03

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v4.03 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v4.03,

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

In addition to the above mentioned tables and listings, figures plotting time course of raw or change in laboratory tests over time or box plots will be specified in the SAP and TLF shells.

10.5.3.4 Other safety data

Vital signs (including weight) and ECOG performance status will be summarized.

Vital signs

Data on vital signs (including weight) will be tabulated and listed, notable values will be flagged.

The following summaries will also be provided:

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

ECOG Performance Status

The following summaries will also be provided:

- shift tables comparing the baseline performance score with the worst result during post-baseline will be summarized.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

Not applicable.

[redacted]

10.5.4 Pharmacokinetics

Not applicable.

[redacted]

10.5.6 Resource utilization

Not applicable.

10.5.7 Patient-reported outcomes

The Myelofibrosis 7 Item Symptom Scale (MF-7) along with Modified MFSAF v2.0 (computed through the addition of a separate question on Inactivity to the data captured with MF7) and the PGIC will be primarily used to collect electronically the patient's disease- related symptoms and patient impression of change. 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. The FAS will be used for analyzing PRO data. Descriptive statistics (e.g., mean, median) will be used to summarize the scored scales at each scheduled assessment time point for the Myelofibrosis 7 Item Symptom Scale (MF-7) and the Modified MFSAF v2.0 score.

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. The number and percentage of patients in each PGIC response category at selected time points will be summarized.

[redacted]

[redacted]

[redacted]

10.7 Interim analysis

No formal interim analysis is planned for this trial.

The primary analysis will be performed after all patients have completed Week 24 or discontinued prior to Week 24. Any other interim updates may be provided to fulfill regulatory obligations, to comply with post-approval commitments or for publication purposes.

The final analysis will occur at the end of the study. All available data from all patients will be analyzed and summarized in a final CSR.

[redacted]

10.8 Sample size calculation

Approximately 50 patients will be enrolled in this study. Success at Week 24 will be declared if the following criteria are met:

a. Observed proportion of patients with ≥50% reduction in spleen length at Week 24 ≥25%
b. Probability of true response rate ≤15% (considered not clinically meaningful) is less than 10%

With 50 patients, criteria 'a' and 'b' will be met if the observed responder rate is ≥ 25%, i.e. if at least 13 patients out of 50 patients have a response at Week 24.

Sample size	No. of responders	Observed responder rate (%)	Probability of true responder rate ≤15%
N=50	11	22	0.1014
	12	24	0.0520
	13	**26**	**0.0243**
	14	28	0.0104
	15	30	0.0041
	16	32	0.0015

The operating characteristics of the design are presented in the table below. This table shows probability for positive conclusion (i.e. success criteria met at the end of study) under different true responder rates. When the true responder rate at Week 24 is ≤ 15%, the probability of positive conclusion is ≤ 10% (false success rate). The probability of success is > 90% when the true responder rate at Week 24 is 35%.

Sample size	True responder rate (%)	Probability of positive conclusion
N=50	15	0.0301
	20	0.1861
	25	0.4890
	30	0.7771
	35	0.9339
	40	0.9867
	45	0.9982
	50	0.9998

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.

[redacted]

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicines, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion..

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

According to Novartis policy, authors of publication will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

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

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or

evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

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

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

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

11.7 Confidentiality of study documents and patient records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must

be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

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

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14 Appendices

14.1 Appendix 1 - Diagnostic criteria for PMF, PPV MF, and PET-MF

Criteria for post-polycythemia vera myelofibrosis (Barosi 2008)
Required criteria: 1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria (Tefferi2007b) 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 (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly 4. Development of ≥1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5ºC)
[a]Grade 2–3 according to the European classification: [3] diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3–4 according to the standard classification: [4] diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis. [b]Below the reference range for appropriate age, sex and altitude considerations.

Criteria for post-essential thrombocythemia myelofibrosis (Barosi 2008)
Required criteria: 1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria (Tefferi 2007b) 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] and a ≥2mg ml^{-1} decrease from baseline hemoglobin level 2. A leukoerythroblastic peripheral blood picture 3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly 4. Increased LDH (above reference level) 5. Development of ≥1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (> 37.5ºC)
[a]Grade 2–3 according to the European classification: [3] diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3–4 according to the standard classification: [4] diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis. [b]Below the reference range for appropriate age, sex and altitude considerations.

[redacted]

Diagnostic criteria for primary myelofibrosis (Arber et al., 2016)

Criteria for the diagnosis of primary myelofibrosis (PMF)

Diagnosis of overt PMF requires meeting all three major criteria, and at least one minor criterion
Major Criteria
1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3* 2. Not meeting WHO criteria for ET, PV, *BCR-ABL1*+ CML, myelodysplastic syndromes, or other myeloid neoplasms 3. Presence of *JAK2, CALR* or *MPL* mutation or in the absence of these mutations, presence of another clonal marker** or absence of reactive myelofibrosis***
Minor Criteria
Presence of at least one of the following, confirmed in two consecutive determinations: a. Anemia not attributed to a comorbid condition b. Leukocytosis >11 x 109/L c. Palpable splenomegaly d. LDH increased to above upper normal limit of institutional reference range e. Leukoerythroblastos
* Grading of myelofibrosis: Semiquantitative grading of BM fibrosis (MF) with minor modifications concerning collagen and osteosclerosis (Fiber density should be assessed only in hematopoietic areas): MF-0 Scattered linear reticulin with no intersections (cross-overs) corresponding to normal BM MF-1 Loose network of reticulin with many intersections, especially in perivascular areas MF-2 Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis (In grades MF-2 or MF-3 an additional trichrome stain is recommended) MF-3 Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis (In grades MF-2 or MF-3 an additional trichrome stain is recommended) ** in the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (e.g.*ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1*) are of help in determining the clonal nature of the disease *** BM fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies

14.2 Appendix 2 - Eastern Cooperative Oncology Group performance status

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

[redacted]

14.3 Appendix 3 - Bone marrow biopsy evaluation (Arber et al., 2016) (when performed, they are not mandatory)

Fibrosis density should be assessed in hematopoietic areas. Grading of myelofibrosis: Semi quantitative grading of BM fibrosis (MF) with minor modifications concerning collagen and osteosclerosis*

Fibrosis Grade	Description
MF-0	Scattered linear reticulin with no intersections (cross-overs) corresponding to normal BM
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis**
* Fiber density should be assessed only in hematopoietic areas ** In grades MF-2 or MF-3 an additional trichrome stain is recommended	

14.4 Appendix 4 - Patient reported outcomes – Questionnaires

MF-7 Myelofibrosis 7 Item Symptom Scale

Myelofibrosis 7 Item Symptom Scale (MF-7)	
Symptom	**0 to 10 Ranking**
Select the one number that describes the worst severity you have experienced with each of the following in the past 24 hours	
Tiredness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Filling up quickly when you eat	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night Sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Pain under ribs on left side	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Modified MFSAF v2.0 - addition of Question on Inactivity

During the past 24hrs, what was the worst degree of inactivity (including work and social activities) you had due to MF?

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

Patient Global Impression of Change (PGIC)

Instructions: Circle the answer that is most appropriate.

Since the start of the treatment you've received in this study, your myelofibrosis (MF) symptoms are:

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

[redacted]

14.5 Appendix 5 - List of CYP3A4 inhibitors and inducers

Table 14-1 List of CYP3A4 inhibitors and inducers

Category	Drug Names
Strong inhibitors[a] of CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice[1], idelalisib, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, LCL161, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, troleandomycin,
Moderate inhibitors[b] of CYP3A	amprenavir, aprepitant, atazanavir, atazanavir/ritonavir,, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporin, duranavir, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, faldaprevilr, fluconazole[2], fosamprenavir, grapefruit juice[1], imatinib, lomitapide, netupitant,nilotinib, schisandra sphenanthera[3], tofisopam, verapamil
Strong inducers[c] of CYP3A	avasimibe, carbamazepine, enzalutamide, mitotane,phenytoin, rifampin, St. John's wort[3], rifabutin, phenobarbital,
Moderate inducers[d] of CYP3A	bosentan, efavirenz, etravirine, genistein[3], lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat[4], talviraline[4], thioridazine, tipranavir, ,

The list of CYP inhibitors and inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table (Flockhart 2007) 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]

14.6 Appendix 6 - Jakavi Summary of Product Characteristics

14.6.1 ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg ruxolitinib (as phosphate).

Excipient with known effect:

Each tablet contains 71.45 mg lactose monohydrate.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Round curved white to almost white tablets of approximately 7.5 mm in diameter with “NVR” debossed on one side and “L5” debossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Myelofibrosis (MF)

Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

Polycythaemia vera (PV)

Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

4.2 Posology and method of administration

Jakavi treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.

[redacted]

A complete blood cell count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi.

Complete blood count, including a white blood cell count differential, should be monitored every 2-4 weeks until Jakavi doses are stabilised, and then as clinically indicated (see section 4.4).

Posology

Starting dose

The recommended starting dose of Jakavi in myelofibrosis is 15 mg twice daily for patients with a platelet count between 100,000/mm^3 and 200,000/mm^3 and 20 mg twice daily for patients with a platelet count of >200,000/mm^3. The recommended starting dose of Jakavi in polycythaemia vera is 10 mg given orally twice daily.

There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm^3 and <100,000/mm^3. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously.

Dose modifications

Doses may be titrated based on safety and efficacy. Treatment should be discontinued for platelet counts less than 50,000/mm^3 or absolute neutrophil counts less than 500/mm^3. In PV, treatment should also be interrupted when haemoglobin is below 8 g/dl. After recovery of blood counts above these levels, dosing may be re-started at 5 mg twice daily and gradually increased based on careful monitoring of complete blood cell count, including a white blood cell count differential.

Dose reductions should be considered if the platelet count decreases below 100,000/mm^3, with the goal of avoiding dose interruptions for thrombocytopenia. In PV, dose reductions should also be considered if haemoglobin decreases below 12 g/dl and is recommended if it decreases below 10 g/dl.

If efficacy is considered insufficient and blood counts are adequate, doses may be increased by a maximum of 5 mg twice daily, up to the maximum dose of 25 mg twice daily.

The starting dose should not be increased within the first four weeks of treatment and thereafter no more frequently than at 2-week intervals.

The maximum dose of Jakavi is 25 mg twice daily.

Dose adjustment with concomitant strong CYP3A4 inhibitors or fluconazole

When Jakavi is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily (see section 4.5). Avoid the concomitant use of Jakavi with fluconazole doses greater than 200 mg daily.

More frequent monitoring (e.g. twice a week) of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended while on strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes.

[redacted]

Special populations

Renal impairment

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

In patients with severe renal impairment (creatinine clearance less than 30 ml/min) the recommended starting dose based on platelet count for MF patients should be reduced by approximately 50% to be administered twice daily. The recommended starting dose for PV patients with severe renal impairment is 5 mg twice daily. Patients should be carefully monitored with regard to safety and efficacy during Jakavi treatment.

There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis. Pharmacokinetic/pharmacodynamic simulations based on available data in this population suggest that the starting dose for MF patients with ESRD on haemodialysis is a single dose of 15-20 mg or two doses of 10 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. A single dose of 15 mg is recommended for MF patients with platelet count between 100,000/mm^3 and 200,000/mm^3. A single dose of 20 mg or two doses of 10 mg given 12 hours apart is recommended for MF patients with platelet count of >200,000/mm^3. Subsequent doses (single administration or two doses of 10 mg given 12 hours apart) should be administered only on haemodialysis days following each dialysis session.

The recommended starting dose for PV patients with ESRD on haemodialysis is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. These dose recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration (see section 5.2).

Hepatic impairment

In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice daily. Subsequent doses should be adjusted based on careful monitoring of safety and efficacy. Patients diagnosed with hepatic impairment while receiving Jakavi should have complete blood counts, including a white blood cell count differential, monitored at least every one to two weeks for the first 6 weeks after initiation of therapy with Jakavi and as clinically indicated thereafter once their liver function and blood counts have been stabilised. Jakavi dose can be titrated to reduce the risk of cytopenia.

Older people (≥65 years)

No additional dose adjustments are recommended for older people.

Paediatric population

The safety and efficacy of Jakavi in children aged up to 18 years have not been established. No data are available (see section 5.1).

[redacted]

Treatment discontinuation

Treatment may be continued as long as the benefit-risk remains positive. However the treatment should be discontinued after 6 months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy.

It is recommended that, for patients who have demonstrated some degree of clinical improvement, ruxolitinib therapy be discontinued if they sustain an increase in their spleen length of 40% compared with baseline size (roughly equivalent to a 25% increase in spleen volume) and no longer have tangible improvement in disease-related symptoms.

Method of administration

Jakavi is to be taken orally, with or without food.

If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Myelosuppression

Treatment with Jakavi can cause haematological adverse drug reactions, including thrombocytopenia, anaemia and neutropenia. A complete blood count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi. Treatment should be discontinued in patients with platelet count less than 50,000/mm^3 or absoute neutrophil count less than 500/mm^3 (see section 4.2).

It has been observed that patients with low platelet counts (<200,000/mm^3) at the start of therapy are more likely to develop thrombocytopenia during treatment.

Thrombocytopenia is generally reversible and is usually managed by reducing the dose or temporarily withholding Jakavi (see sections 4.2 and 4.8). However, platelet transfusions may be required as clinically indicated.

Patients developing anaemia may require blood transfusions. Dose modifications or interruption for patients developing anaemia may also be considered.

Patients with a haemoglobin level below 10.0 g/dl at the beginning of the treatment have a higher risk of developing a haemoglobin level below 8.0 g/dl during treatment compared to patients with a higher baseline haemoglobin level (79.3% versus 30.1%). More frequent monitoring of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended for patients with baseline haemoglobin below 10.0 g/dl.

Neutropenia (absolute neutrophil count <500) was generally reversible and was managed by temporarily withholding Jakavi (see sections 4.2 and 4.8).

[redacted]

Complete blood counts should be monitored as clinically indicated and dose adjusted as required (see sections 4.2 and 4.8).

Infections

Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Tuberculosis has been reported in patients receiving Jakavi for MF. Before starting treatment, patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. Jakavi therapy should not be started until active serious infections have resolved. Physicians should carefully observe patients receiving Jakavi for signs and symptoms of infections and initiate appropriate treatment promptly (see section 4.8).

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakavi. The effect of Jakavi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

Herpes zoster

Physicians should educate patients about early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported with Jakavi treatment for MF. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.

Non-melanoma skin cancer

Non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and Merkel cell carcinoma, have been reported in patients treated with ruxolitinib. Most of these patients had histories of extended treatment with hydroxyurea and prior NMSC or pre-malignant skin lesions. A causal relationship to ruxolitinib has not been established. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Special populations

Renal impairment

The starting dose of Jakavi should be reduced in patients with severe renal impairment. For patients with end-stage renal disease on haemodialysis the starting dose for MF patients should be based on platelet counts (see section 4.2). Subsequent doses (single dose of 20 mg

[redacted]

or two doses of 10 mg given 12 hours apart in MF patients; single dose of 10 mg or two doses of 5 mg given 12 hours apart in PV patients) should be administered only on haemodialysis days following each dialysis session. Additional dose modifications should be made with careful monitoring of safety and efficacy (see sections 4.2 and 5.2).

Hepatic impairment

The starting dose of Jakavi should be reduced by approximately 50% in patients with hepatic impairment. Further dose modifications should be based on the safety and efficacy of the medicinal product (see sections 4.2 and 5.2).

Interactions

If Jakavi is to be co-administered with strong CYP3A4 inhibitors or dual inhibitors of CYP3A4 and CYP2C9 enzymes (e.g. fluconazole), the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily (for monitoring frequency see sections 4.2 and 4.5).

The concomitant use of cytoreductive therapies or haematopoietic growth factors with Jakavi has not been studied. The safety and efficacy of these co-administrations are not known (see section 4.5).

Withdrawal effects

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

Excipients

Jakavi contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Ruxolitinib is eliminated through metabolism catalysed by CYP3A4 and CYP2C9. Thus, medicinal products inhibiting these enzymes can give rise to increased ruxolitinib exposure.

Interactions resulting in dose reduction of ruxolitinib

CYP3A4 inhibitors

Strong CYP3A4 inhibitors (such as, but not limited to, boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole)

In healthy subjects co-administration of Jakavi (10 mg single dose) with a strong CYP3A4 inhibitor, ketoconazole, resulted in ruxolitinib C_{max} and AUC that were higher by 33% and

[redacted]

91%, respectively, than with ruxolitinib alone. The half-life was prolonged from 3.7 to 6.0 hours with concurrent ketoconazole administration.

When administering Jakavi with strong CYP3A4 inhibitors the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily. Patients should be closely monitored (e.g. twice weekly) for cytopenias and dose titrated based on safety and efficacy (see section 4.2).

Dual CYP2C9 and CYP3A4 inhibitors

50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole). Avoid the concomitant use of Jakavi with fluconazole doses greater than 200 mg daily.

Enzyme inducers

CYP3A4 inducers (such as, but not limited to, avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St.John's wort (Hypericum perforatum))

Patients should be closely monitored and the dose titrated based on safety and efficacy (see Section 4.2).

In healthy subjects given ruxolitinib (50 mg single dose) following the potent CYP3A4 inducer rifampicin (600 mg daily dose for 10 days), ruxolitinib AUC was 70% lower than after administration of Jakavi alone. The exposure of ruxolitinib active metabolites was unchanged. Overall, the ruxolitinib pharmacodynamic activity was similar, suggesting the CYP3A4 induction resulted in minimal effect on the pharmacodynamics. However, this could be related to the high ruxolitinib dose resulting in pharmacodynamic effects near E_{max}. It is possible that in the individual patient, an increase of the ruxolitinib dose is needed when initiating treatment with a strong enzyme inducer.

Other interactions to be considered affecting ruxolitinib

Mild or moderate CYP3A4 inhibitors (such as, but not limited to, ciprofloxacin, erythromycin, amprenavir, atazanavir, diltiazem, cimetidine)

In healthy subjects co-administration of ruxolitinib (10 mg single dose) with erythromycin 500 mg twice daily for four days resulted in ruxolitinib C_{max} and AUC that were higher by 8% and 27%, respectively, than with ruxolitinib alone.

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

Effects of ruxolitinib on other medicinal products

Substances transported by P-glycoprotein or other transporters

Ruxolitinib may inhibit P-glycoprotein and breast cancer resistance protein (BCRP) in the intestine. This may result in increased sytemic exposure of substrates of these transporters, such as dabigatran etexilate, ciclosporin, rosuvastatin and potentially digoxin. Therapeutic drug monitoring (TDM) or clinical monitoring of the affected substance is advised.

[redacted]

It is possible that the potential inhibition of P-gp and BCRP in the intestine can be minimised if the time between administrations is kept apart as long as possible.

Haematopoietic growth factors

The concurrent use of haematopoietic growth factors and Jakavi has not been studied. It is not known whether the Janus Associated Kinase (JAK) inhibition by Jakavi reduces the efficacy of the haematopoietic growth factors or whether the haematopoietic growth factors affect the efficacy of Jakavi (see section 4.4).

Cytoreductive therapies

The concomitant use of cytoreductive therapies and Jakavi has not been studied. The safety and efficacy of this co-administration is not known (see section 4.4).

A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is anticipated when combining them with Jakavi. Another study in healthy subjects indicated that Jakavi does not affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

4.6 Fertility, pregnancy and lactation

Pregnancy and contraception in females

There are no data from the use of Jakavi in pregnant women.

Animal studies have shown that ruxolitinib is embryotoxic and foetotoxic. Teratogenicity was not observed in rats or rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans (see section 5.3). The potential risk for humans is unknown. As a precautionary measure, the use of Jakavi during pregnancy is contraindicated (see section 4.3). Women of child-bearing potential should use effective contraception during the treatment with Jakavi. In case pregnancy should occur during treatment with Jakavi, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the foetus (see Section 5.3).

Breast-feeding

Jakavi must not be used during breast-feeding (see section 4.3) and breast-feeding should therefore be discontinued when treatment is started. It is unknown whether ruxolitinib and/or its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. Available pharmacodynamic/toxicological data in animals have shown excretion of ruxolitinib and its metabolites in milk (see section 5.3).

Fertility

There are no human data on the effect of ruxolitinib on fertility. In animal studies, no effect on fertility was observed.

[redacted]

4.6 Effects on ability to drive and use machines

Jakavi has no or negligible sedating effect. However, patients who experience dizziness after the intake of Jakavi should refrain from driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety assessment was based on a total of 855 patients (with MF or PV) receiving Jakavi in phase 2 and 3 studies.

Myelofibrosis

In the randomised period of the two pivotal studies, COMFORT-I and COMFORT-II, the median duration of exposure to Jakavi was 10.8 months (range 0.3 to 23.5 months). The majority of patients (68.4%) were treated for at least 9 months. Of 301 patients, 111 (36.9%) had a baseline platelet count of between 100,000/mm^3 and 200,000/mm^3 and 190 (63.1%) had a baseline platelet count of >200,000/mm^3.

In these clinical studies, discontinuation due to adverse events, regardless of causality, was observed in 11.3% of patients.

The most frequently reported adverse drug reactions were thrombocytopenia and anaemia.

Haematological adverse drug reactions (any Common Terminology Criteria for Adverse Events [CTCAE] grade) included anaemia (82.4%), thrombocytopenia (69.8%) and neutropenia (16.6%).

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (21.3%), dizziness (15.3%) and headache (14.0%).

The three most frequent non-haematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (19.9%) and hypercholesterolaemia (16.9%). In phase 3 clinical studies in MF, neither CTCAE grade 3 or 4 hypercholesterolaemia, raised aspartate aminotransferase nor CTCAE grade 4 raised alanine aminotransferase were observed.

Long-term safety: As expected with an extended follow-up period, the cumulative frequency of some adverse events increased in the evaluation of the 3-year follow-up safety data (median duration of exposure of 33.2 months in COMFORT-I and COMFORT-II for patients initially randomised to ruxolitinib) from 457 patients with myelofibrosis treated with ruxolitinib during the randomised and extension periods of the two pivotal phase 3 studies. This evaluation included data from patients that were initially randomised to ruxolitinib (N=301) and patients that received ruxolitinib after crossing over from control treatment arms (N=156). With these updated data, therapy discontinuation due to adverse events was observed in 17.1% of patients treated with ruxolitinib.

Polycythaemia vera

The safety of Jakavi was assessed in 110 patients with PV in an open-label, randomised, controlled phase 3 RESPONSE study. The adverse drug reactions listed below reflect the initial study period (up to week 32) with equivalent exposure to ruxolitinib and Best Available Therapy (BAT), corresponding to a median duration of exposure to Jakavi of 7.8 months. The mean age of patients receiving Jakavi was around 60 years.

[redacted]

Discontinuation due to adverse events, regardless of causality, was observed in 3.6% of patients treated with Jakavi and 1.8% of patients treated with best available therapy.

Haematological adverse reactions (any CTCAE grade) included anaemia (43.6%) and thrombocytopenia (24.5%). Anaemia or thrombocytopenia CTCAE grade 3 and 4 were reported in respectively 1.8% or 5.5%.

The three most frequent non-haematological adverse reactions were dizziness (15.5%), constipation (8.2%) and herpes zoster (6.4%).

The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) were hypercholesterolaemia (30.0%), raised alanine aminotransferase (22.7%) and raised aspartate aminotransferase (20.9%). These were all CTCAE grade 1 and 2 with the exception of one CTCAE grade 3 raised alanine aminotransferase event.

Long-term safety: Patients had a median duration of exposure to Jakavi of 18.6 months (range 0.3 to 35.9 months). With longer exposure, frequency of adverse events increased; however no new safety findings emerged. When adjusted for exposure, the adverse event rates were generally comparable with those observed during the initial study period.

Tabulated summary of adverse drug reactions from clinical studies

In the clinical study programme the severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1 = mild, grade 2 = moderate, grade 3 = severe and grade 4=life-threatening.

Adverse drug reactions from clinical studies (Table 14-2) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 14-2 Frequency category of adverse drug reactions reported in the phase 3 studies (COMFORT-I, COMFORT-II, RESPONSE)

Adverse drug reaction	Frequency category for MF patients	Frequency category for PV patients
Infections and infestations		
Urinary tract infections[a,d]	Very common	Common
Herpes zoster[a,d]	Common	Common
Tuberculosis[e]	Uncommon	-
Blood and lymphatic system disorders[b,d]		
Anaemia[b]	-	-
CTCAE[c] grade 4 (<6.5g/dl)	Very common	Uncommon
CTCAE[c] grade 3 (<8.0 – 6.5g/dl)	Very common	Uncommon

[redacted]

Adverse drug reaction	Frequency category for MF patients	Frequency category for PV patients
Any CTCAE[c] grade	Very common	Very common
Thrombocytopenia[b]		
CTCAE[c] grade 4 (<25,000/mm^3)	Common	Uncommon
CTCAE[c] grade 3 (50,000 – 25,000/mm^3)	Common	Common
Any CTCAE[c] grade	Very common	Very common
Neutropenia[b]		
CTCAE[c] grade 4 (<500/mm^3)	Common	-
CTCAE[c] grade 3 (<1,000 – 500/mm^3)	Common	-
Any CTCAE[c] grade	Very common	-
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)	Very common	Very common
Intracranial bleeding	Common	-
Gastrointestinal bleeding	Common	-
Bruising	Very common	Very common
Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)	Common	Very common
Metabolism and nutrition disorders		
Weight gain[a]	Very common	Common
Hypercholesterolaemia[b] CTCAE[c] grade 1 and 2	Very common	Very common
Hypertriglyceridaemia[b] CTCAE[c] grade 1	-	Very common
Nervous system disorders		
Dizziness[a]	Very common	Very common
Headache[a]	Very common	-
Gastrointestinal disorders		
Flatulence[a]	Common	-
Constipation[a]	-	Common
Hepatobiliary disorders		
Raised alanine aminotransferase[b]		

[redacted]

Adverse drug reaction	Frequency category for MF patients	Frequency category for PV patients
CTCAE[c] grade 3 (> 5x – 20 x ULN)	Common	Uncommon
Any CTCAE[c] grade	Very common	Very common
Raised aspartate aminotransferase[b]		
Any CTCAE[c] grade	Very common	Very common
Vascular disorders		
Hypertension[a]	-	Very common

[a]Frequency is based on adverse event data.
- A subject with multiple occurrence of an adverse drug reaction (ADR) is counted only once in that ADR category.
- ADRs reported are on treatment or up to 28 days post treatment end date.

[b]Frequency is based on laboratory values.
- A subject with multiple occurrences of an ADR is counted only once in that ADR category.
- ADRs reported are on treatment or up to 28 days post treatment end date.

[c]Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening
[d]These ADRs are discussed in the text.
[e]Frequency is based on all patients exposed to ruxolitinib in clinical studies (N=4755)

Upon discontinuation, MF patients may experience a return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In clinical studies in MF the total symptom score for MF symptoms gradually returned to baseline value within 7 days after dose discontinuation (see Section 4.4).

Description of selected adverse drug reactions

Anaemia

In phase 3 clinical studies in MF, median time to onset of first CTCAE grade 2 or higher anaemia was 1.5 months. One patient (0.3%) discontinued treatment because of anaemia.

In patients receiving Jakavi mean decreases in haemoglobin reached a nadir of approximately 10 g/litre below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 5 g/litre below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy.

In the randomised, placebo-controlled study COMFORT-I 60.6% of Jakavi-treated MF patients and 37.7% of placebo-treated MF patients received red blood cell transfusions during randomised treatment. In the COMFORT-II study the rate of packed red blood cell transfusions was 53.4% in the Jakavi arm and 41.1% in the best available therapy arm.

In the randomised period of the pivotal studies, anaemia was less frequent in PV patients than in MF patients (43.6% versus 82.4%). In the PV population, the CTCAE grade 3 and 4 events were reported in 1.8%, while in the MF patients the frequency was 42.56%.

Thrombocytopenia

In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm^3

[redacted]

was 14 days. During the randomised period, platelet transfusions were administered to 4.7% of patients receiving Jakavi and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakavi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm^3 to 200,000/mm^3 before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm^3 (64.2% versus 38.5%).

In the randomised period of the pivotal studies, the rate of patients experiencing thrombocytopenia was lower in PV (24.5%) patients compared to MF (69.8%) patients. The frequency of severe (i.e. CTCAE grade 3 and 4) thrombocytopenia was lower in PV (5.5%) than in MF (11.6%) patients.

Neutropenia

In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 neutropenia, the median time to onset was 12 weeks. During the randomised period, dose holding or reductions due to neutropenia were reported in 1.0% of patients, and 0.3% of patients discontinued treatment because of neutropenia.

In the randomised period of the pivotal study in PV patients, neutropenia was reported in two patients (1.8%) of which one patient developed CTCAE grade 4 neutropenia.

Bleeding

In the phase 3 pivotal studies in MF bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 32.6% of patients exposed to Jakavi and 23.2% of patients exposed to the reference treatments (placebo or best available therapy). The frequency of grade 3-4 events was similar for patients treated with Jakavi or reference treatments (4.7% versus 3.1%). Most of the patients with bleeding events during the treatment reported bruising (65.3%). Bruising events were more frequently reported in patients taking Jakavi compared with the reference treatments (21.3% versus 11.6%). Intracranial bleeding was reported in 1% of patients exposed to Jakavi and 0.9% exposed to reference treatments. Gastrointestinal bleeding was reported in 5.0% of patients exposed to Jakavi compared to 3.1% exposed to reference treatments. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage and haematuria) were reported in 13.3% of patients treated with Jakavi and 10.3% treated with reference treatments.

In the randomised period of the pivotal study in PV patients, bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 20% of patients treated with Jakavi and 15.3% patients receiving best available therapy. Bruising was reported in similar frequencies in Jakavi and BAT arms (10.9% versus 8.1%). No intracranial bleeding or gastrointestinal haemorrhage events were reported in patients receiving Jakavi. One patient treated with Jakavi experienced a grade 3 bleeding event (post-procedural bleeding); no grade 4 bleeding was reported. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage, gingival bleeding) were reported in 11.8% of patients treated with Jakavi and 6.3% treated with best available therapy.

Infections

In the phase 3 pivotal studies in MF, grade 3 or 4 urinary tract infection was reported in 1.0% of patients, herpes zoster in 4.3% and tuberculosis in 1.0%. In phase 3 clinical studies sepsis was reported in 3.0% of patients. An extended follow-up of patients treated with ruxolitinib showed no trends towards an increase in the rate of sepsis over time.

In the randomised period of the pivotal study in PV patients, one (0.9%) CTCAE grade 3 and no grade 4 urinary tract infection was reported. The rate of herpes zoster was slightly higher in PV (6.4%)

[redacted]

patients than in MF (4.0%) patients. There was one report of CTCAE grade 3 post-herpetic neuralgia amongst the PV patients.

Increased systolic blood pressure

In the phase 3 pivotal clinical studies in MF an increase in systolic blood pressure of 20 mmHg or more from baseline was recorded in 31.5% of patients on at least one visit compared with 19.5% of the control-treated patients. In COMFORT-I (MF patients) the mean increase from baseline in systolic BP was 0-2 mmHg on Jakavi versus a decrease of 2-5 mmHg in the placebo arm. In COMFORT-II mean values showed little difference between the ruxolitinib-treated and the control-treated MF patients.

In the randomised period of the pivotal study in PV patients, the mean systolic blood pressure increased by 0.65 mmHg in the Jakavi arm versus a decrease of 2 mmHg in the BAT arm.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known antidote for overdoses with Jakavi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anaemia and thrombocytopenia. Appropriate supportive treatment should be given.

Haemodialysis is not expected to enhance the elimination of ruxolitinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE18

Mechanism of action

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 (IC_{50} values of 3.3 nM and 2.8 nM for JAK1 and JAK2 enzymes, respectively). These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.

Myelofibrosis and polycythaemia vera are myeloproliferative neoplasms known to be associated with dysregulated JAK1 and JAK2 signalling. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK-STAT pathway, gain-of-function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signalling regardless of JAK2V617F mutation status. Activating mutations in JAK2 (V617F or exon 12) are found in >95% of PV patients.

Ruxolitinib inhibits JAK-STAT signalling and cell proliferation of cytokine-dependent cellular models of haematological malignancies, as well as of Ba/F3 cells rendered

[redacted]

cytokine-independent by expressing the JAK2V617F mutated protein, with IC_{50} ranging from 80-320 nM.

Pharmacodynamic effects

Ruxolitinib inhibits cytokine-induced STAT3 phosphorylation in whole blood from healthy subjects, MF patients and PV patients. Ruxolitinib resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 8 hours in both healthy subjects and MF patients, indicating no accumulation of either parent or active metabolites.

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNFα, IL-6 and CRP in subjects with MF were decreased following treatment with ruxolitinib. MF patients did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with PV also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with ruxolitinib.

In a thorough QT study in healthy subjects, there was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up to a supratherapeutic dose of 200 mg, indicating that ruxolitinib has no effect on cardiac repolarisation.

Clinical efficacy and safety

Myelofibrosis

Two randomised phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with MF (primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis). In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate-2 or high risk based on the International Working Group (IWG) Consensus Criteria. The starting dose of Jakavi was based on platelet count.

COMFORT-I was a double-blind, randomised, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. The primary efficacy endpoint was proportion of subjects achieving ≥35% reduction from baseline in spleen volume at week 24 as measured by Magnetic Resonance Imaging (MRI) or Computed Tomography (CT).

Secondary endpoints included duration of maintenance of a ≥35% reduction from baseline in spleen volume, proportion of patients who had ≥50% reduction in total symptom score, changes in total symptom scores from baseline to week 24, as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary, and overall survival.

COMFORT-II was an open-label, randomised study in 219 patients. Patients were randomised 2:1 to Jakavi versus best available therapy. In the best available therapy arm, 47% of patients received hydroxyurea and 16% of patients received glucocorticoids. The primary efficacy endpoint was proportion of patients achieving ≥35% reduction from baseline in spleen volume at week 48 as measured by MRI or CT.

Secondary endpoints included proportion of patients achieving a ≥35% reduction of spleen volume from baseline at week 24 and duration of maintenance of a ≥35% reduction from baseline spleen volume.

[redacted]

In COMFORT-I and COMFORT-II, patient baseline demographics and disease characteristics were comparable between the treatment arms.

Table 14-3 Percentage of patients with ≥35% reduction from baseline in spleen volume at week 24 in COMFORT-I and at week 48 in COMFORT-II (ITT)

	COMFORT-I		COMFORT-II	
	Jakavi (N=155)	**Placebo (N=153)**	**Jakavi (N=144)**	**Best available therapy (N=72)**
Time points	Week 24		Week 48	
Number (%) of subjects with spleen volume reduced by ≥35%	65 (41.9)	1 (0.7)	41 (28.5)	0
95% confidence intervals	34.1, 50.1	0, 3.6	21.3, 36.6	0.0, 5.0
p-value	<0.0001		<0.0001	

A significantly higher proportion of patients in the Jakavi group achieved ≥35% reduction from baseline in spleen volume (Table 14-3) regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (primary myelofibrosis, post-polycythaemia vera myelofibrosis, post-essential thrombocythaemia myelofibrosis).

Table 14-4 Percentage of patients with ≥35% reduction from baseline in spleen volume by JAK mutation status (safety set)

	COMFORT-I				COMFORT-II			
	Jakavi		**Placebo**		**Jakavi**		**Best available therapy**	
JAK mutation status	Positive (N=113) n (%)	Negative (N=40) n (%)	Positive (N=121) n (%)	Negative (N=27) n (%)	Positive (N=110) n (%)	Negative (N=35) n (%)	Positive (N=49) n (%)	Negative (N=20) n (%)
Number (%) of subjects with spleen volume reduced by ≥35%	54 (47.8)	11 (27.5)	1 (0.8)	0	36 (32.7)	5 (14.3)	0	0
Time point	After 24 weeks				After 48 weeks			

The probability of maintaining spleen response (≥35% reduction) on Jakavi for at least 24 weeks was 89% in COMFORT-I and 87% in COMFORT-II; 52% maintained spleen responses for at least 48 weeks in COMFORT-II.

In COMFORT-I, 45.9% subjects in the Jakavi group achieved a ≥50% improvement from baseline in the week 24 total symptom score (measured using MFSAF diary v2.0), as compared to 5.3% in the placebo group ($p<0.0001$ using chi-square test). The mean change in the global health status at week 24, as measured by EORTC QLQ C30 was +12.3 for Jakavi and -3.4 for placebo ($p<0.0001$).

In COMFORT-I, after a median follow-up of 34.3 months, the death rate in patients randomised to the ruxolitinib arm was 27.1% versus 35.1% in patients randomised to placebo; HR 0.687; 95% CI 0.459-1.029; p=0.0668.

[redacted]

In COMFORT-II, after a median follow-up of 34.7 months, the death rate in patients randomised to ruxolitinib was 19.9% versus 30.1% in patients randomised to best available treatment (BAT); HR 0.48; 95% CI 0.28-0.85; p=0.009. In both studies, the lower death rates noted in the ruxolitinib arm were predominantly driven by the results obtained in the post polycythaemia vera and post essential thrombocythaemia subgroups.

Polycythaemia vera

A randomised, open-label, active-controlled phase 3 study (RESPONSE) was conducted in 222 patients with PV who were resistant to or intolerant of hydroxyurea defined based on the European LeukemiaNet (ELN) international working group published criteria. 110 patients were randomised to the ruxolitinib arm and 112 patients to the BAT arm. The starting dose of Jakavi was 10 mg twice daily. Doses were then adjusted in individual patients based on tolerability and efficacy with a maximum dose of 25 mg twice daily. BAT was selected by the investigator on a patient-by-patient basis and included hydroxyurea (59.5%), interferon/pegylated interferon (11.7%), anagrelide (7.2%), pipobroman (1.8%) and observation (15.3%).

Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. Most patients (>80%) had received at least two phlebotomies in the last 24 weeks prior to screening. Comparative data regarding long-term survival and incidence of disease complications is missing.

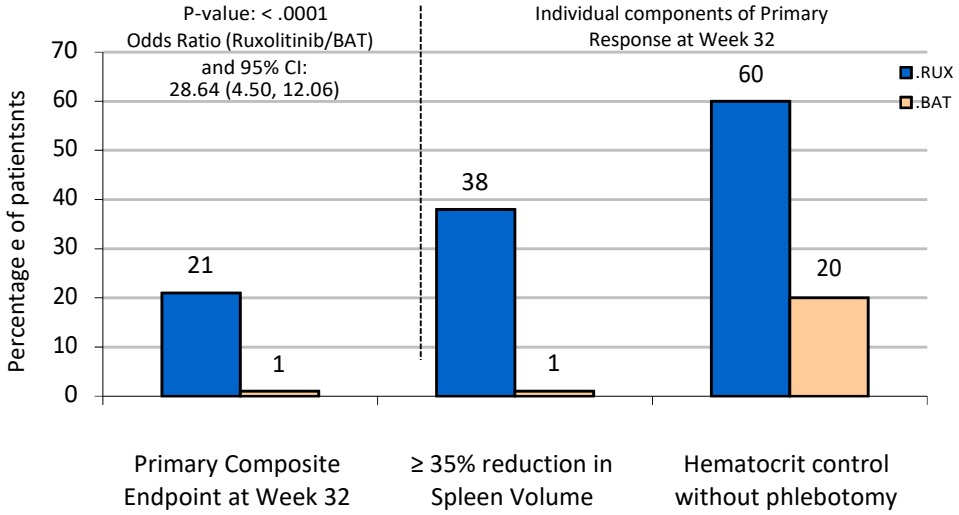
The primary composite endpoint was the proportion of patients achieving both an absence of phlebotomy eligibility (HCT control) and a ≥35% reduction in spleen volume from baseline at week 32. Phlebotomy eligibility was defined as a confirmed HCT of >45%, i.e. at least 3 percentage points higher than the HCT obtained at baseline or a confirmed HCT of >48%, depending on which was lower. Key secondary endpoints included the proportion of patients who achieved the primary endpoint and remained free from progression at week 48, as well as the proportion of patients achieving complete haematological remission at week 32.

The study met its primary objective and a higher proportion of patients in the Jakavi group achieved the primary composite endpoint and each of its individual components. Significantly more patients treated with Jakavi (20.9%) achieved a primary response (p<0.0001) compared to BAT (0.9%). Haematocrit control was achieved in 60% of patients in the Jakavi arm compared to 19.6% in the BAT arm and a ≥35% reduction in spleen volume was achieved in 38.2% of patients in the Jakavi arm compared to 0.9% in the BAT arm (Figure 14-1). 94 (83.9%) patients randomised to the BAT arm crossed over to ruxolitinib treatment at Week 32 or after, limiting the comparison between the two arms after Week 32.

Both key secondary endpoints were also met. The proportion of patients achieving a complete haematological remission was 23.6% on Jakavi compared to 8.9% on BAT (p=0.0028) and the proportion of patients achieving a durable primary response at week 48 was 19.1% on Jakavi and 0.9% on BAT.(p<0.0001).

[redacted]

Figure 14-1 Patients achieving the primary endpoint and components of the primary endpoint at week 32



Symptom burden was assessed using the MPN-SAF total symptom score (TSS) electronic patient diary, which consisted of 14 questions. At week 32, 49% and 64% of patients treated with ruxolitinib achieved a ≥50% reduction in TSS-14 and TSS-5, respectively, compared to only 5% and 11% of patients on BAT.

Treatment benefit perception was measured by the Patient Global Impression of Change (PGIC) questionnaire. 66% of patients treated with ruxolitinib compared to 19% treated with BAT reported an improvement as early as four weeks after beginning treatment. Improvement in perception of treatment benefit was also higher in patients treated with ruxolitinib at week 32 (78% versus 33%).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Jakavi in all subsets of the paediatric population for the treatment of MF (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Ruxolitinib is a Biopharmaceutical Classification System (BCS) class 1 compound, with high permeability, high solubility and rapid dissolution characteristics. In clinical studies, ruxolitinib is rapidly absorbed after oral administration with maximal plasma concentration (C_{max}) achieved approximately 1 hour post-dose. Based on a human mass balance study, oral absorption of ruxolitinib, as ruxolitinib or metabolites formed under first-pass, is 95% or greater. Mean ruxolitinib C_{max} and total exposure (AUC) increased proportionally over a single dose range of 5-200 mg. There was no clinically relevant change in the pharmacokinetics of ruxolitinib upon administration with a high-fat meal. The mean C_{max} was moderately decreased

[redacted]

(24%) while the mean AUC was nearly unchanged (4% increase) on dosing with a high-fat meal.

[redacted]

Distribution

The mean volume of distribution at steady state is approximately 75 litres in MF and PV patients. At clinically relevant concentrations of ruxolitinib, binding to plasma proteins *in vitro* is approximately 97%, mostly to albumin. A whole body autoradiography study in rats has shown that ruxolitinib does not penetrate the blood-brain barrier.

Biotransformation

Ruxolitinib is mainly metabolised by CYP3A4 (>50%), with additional contribution from CYP2C9. Parent compound is the predominant entity in human plasma, representing approximately 60% of the drug-related material in circulation. Two major and active metabolites are present in plasma representing 25% and 11% of parent AUC. These metabolites have one half to one fifth of the parent JAK-related pharmacological activity. The sum total of all active metabolites contributes to 18% of the overall pharmaco dynamics of ruxolitinib. At clinically relevant concentrations, ruxolitinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 based on *in vitro* studies. *In vitro* data indicate that ruxolitinib may inhibit P-gp and BCRP.

Elimination

Ruxolitinib is mainly eliminated through metabolism. The mean elimination half -life of ruxolitinib is approximately 3 hours. Following a single oral dose of [^{14}C]-labelled ruxolitinib in healthy adult subjects, elimination was predominately through metabolism, with 74% of radioactivity excreted in urine and 22% via faeces. Unchanged parent substance accounted for less than 1% of the excreted total radioactivity.

Linearity/non-linearity

Dose proportionality was demonstrated in the single and multiple dose studies.

Special populations

Effects of age, gender or race

Based on studies in healthy subjects, no relevant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in MF patients, no relationship was apparent between oral clearance and patient age or race. The predicted oral clearance was 17.7 l/h in women and 22.1 l/h in men, with 39% inter-subject variability in MF patients. Clearance was 12.7 l/h in PV patients, with a 42% inter-subject variability and no relationship was apparent between oral clearance and gender, patient age or race, based on a population pharmacokinetic evaluation in PV patients.

Paediatric population

The safety and effectiveness of Jakavi in paediatric patients have not been established (see section 5.1, “Paediatric population”).

Renal impairment

Renal function was determined using both Modification of Diet in Renal Disease (MDRD) and urinary creatinine. Following a single ruxolitinib dose of 25 mg, the exposure of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with

[redacted]

normal renal function. However, plasma AUC values of ruxolitinib metabolites tended to increase with increasing severity of renal impairment, and were most markedly increased in the subjects with severe renal impairment. It is unknown whether the increased metabolite exposure is of safety concern. A dose modification is recommended in patients with sev ere renal impairment and end-stage renal disease (see section 4.2). Dosing only on dialysis days reduces the metabolite exposure, but also the pharmacodynamic effect, especially on the days between dialysis.

Hepatic impairment

Following a single ruxolitinib dose of 25 mg in patients with varying degrees of hepatic impairment, the mean AUC for ruxolitinib was increased in patients with mild, moderate and severe hepatic impairment by 87%, 28% and 65%, respectively, compared to patients with normal h epatic function. There was no clear relationship between AUC and the degree of hepatic impairment based on Child-Pugh scores. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). A dose reduction of approximately 50% is recommended for patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Ruxolitinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity and reproductive toxicity studies and in a carcinogenicity study. Target organs associated with the pharmacological action of ruxolitinib in repeated dose studies include bone marrow, peripheral blood and lymphoid tissues. Infections generally associated with immunosuppression were noted in dogs. Adverse decreases in blood pressure along with increases in heart rate were noted in a dog telemetry study, and an adverse decrease in minute volume was noted in a respiratory study in rats. The margins (based on unbound C_{max}) at the non-adverse level in the dog and rat studies were 15.7-fold and 10.4-fold greater, respectively, than the maximum human recommended dose of 25 mg twice daily. No effects were noted in an evaluation of the neuropharmacological effects of ruxolitinib.

Ruxolitinib decreased foetal weight and increased post-implantation loss in animal studies. There was no evidence of a teratogenic effect in rats and rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans. No effects were noted on fertility. In a pre- and post-natal development study, a slightly prolonged gestation period, reduced number of implantation sites, and reduced number of pups delivered were observed. In the pups, decreased mean initial body weights and short period of decreased mean body weight gain were observed. In lactating rats, ruxolitinib and/or its metabolites were excreted into the milk with a concentration that was 13-fold higher than the maternal plasma concentration. Ruxolitinib was not mutagenic or clastogenic. Ruxolitinib was not carcinogenic in the Tg.rasH2 transgenic mouse model.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Cellulose, microcrystalline
- Magnesium stearate
- Silica, colloidal anhydrous

[redacted]

- Sodium starch glycolate (Type A)
- Povidone
- Hydroxypropylcellulose
- Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PCTFE/Aluminium blister packs containing 14 or 56 tablets or multipacks containing 168 (3 packs of 56) tablets.

Not all pack sizes or types may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/004-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23.08.2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

[redacted]

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg ruxolitinib (as phosphate).

Excipient with known effect:

Each tablet contains 142.90 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Round curved white to almost white tablets of approximately 9.3 mm in diameter with "NVR" debossed on one side and "L10" debossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Myelofibrosis (MF)

Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

Polycythaemia vera (PV)

Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

4.2 Posology and method of administration

Jakavi treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.

A complete blood cell count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi.

Complete blood count, including a white blood cell count differential, should be monitored every 2-4 weeks until Jakavi doses are stabilised, and then as clinically indicated (see section 4.4).

Posology

Starting dose

The recommended starting dose of Jakavi in myelofibrosis is 15 mg twice daily for patients with a platelet count between 100,000/mm^3 and 200,000/mm^3 and 20 mg twice daily for patients with a platelet count of >200,000/mm^3. The recommended starting dose of Jakavi in polycythaemia vera is 10 mg given orally twice daily.

[redacted]

There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm^3 and <100,000/mm^3. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously.

Dose modifications

Doses may be titrated based on safety and efficacy. Treatment should be discontinued for platelet counts less than 50,000/mm^3 or absolute neutrophil counts less than 500/mm^3. In PV, treatment should also be interrupted when haemoglobin is below 8 g/dl. After recovery of blood counts above these levels, dosing may be re-started at 5 mg twice daily and gradually increased based on careful monitoring of complete blood cell count, including a white blood cell count differential.

Dose reductions should be considered if the platelet count decreases below 100,000/mm^3, with the goal of avoiding dose interruptions for thrombocytopenia. In PV, dose reductions should also be considered if haemoglobin decreases below 12 g/dl and is recommended if it decreases below 10 g/dl.

If efficacy is considered insufficient and blood counts are adequate, doses may be increased by a maximum of 5 mg twice daily, up to the maximum dose of 25 mg twice daily.

The starting dose should not be increased within the first four weeks of treatment and thereafter no more frequently than at 2-week intervals.

The maximum dose of Jakavi is 25 mg twice daily.

Dose adjustment with concomitant strong CYP3A4 inhibitors or fluconazole

When Jakavi is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily (see section 4.5). Avoid the concomitant use of Jakavi with fluconazole doses greater than 200 mg daily.

More frequent monitoring (e.g. twice a week) of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended while on strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes.

Special populations

Renal impairment

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

In patients with severe renal impairment (creatinine clearance less than 30 ml/min) the recommended starting dose based on platelet count for MF patients should be reduced by approximately 50% to be administered twice daily. The recommended starting dose for PV patients with severe renal impairment is 5 mg twice daily. Patients should be carefully monitored with regard to safety and efficacy during Jakavi treatment.

There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis. Pharmacokinetic/pharmacodynamic simulations based on available data in this population suggest that the starting dose for MF patients with ESRD on haemodialysis is a single dose of 15-20 mg or two doses of 10 mg given 12 hours apart, to be

[redacted]

administered post-dialysis and only on the day of haemodialysis. A single dose of 15 mg is recommended for MF patients with platelet count between 100,000/mm^3 and 200,000/mm^3. A single dose of 20 mg or two doses of 10 mg given 12 hours apart is recommended for MF patients with platelet count of >200,000/mm^3. Subsequent doses (single administration or two doses of 10 mg given 12 hours apart) should be administered only on haemodialysis days following each dialysis session.

The recommended starting dose for PV patients with ESRD on haemodialysis is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. These dose recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration (see section 5.2).

Hepatic impairment

In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice daily. Subsequent doses should be adjusted based on careful monitoring of safety and efficacy. Patients diagnosed with hepatic impairment while receiving Jakavi should have complete blood counts, including a white blood cell count differential, monitored at least every one to two weeks for the first 6 weeks after initiation of therapy with Jakavi and as clinically indicated thereafter once their liver function and blood counts have been stabilised. Jakavi dose can be titrated to reduce the risk of cytopenia.

Older people (≥65 years)

No additional dose adjustments are recommended for older people.

Paediatric population

The safety and efficacy of Jakavi in children aged up to 18 years have not been established. No data are available (see section 5.1).

Treatment discontinuation

Treatment may be continued as long as the benefit-risk remains positive. However the treatment should be discontinued after 6 months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy.

It is recommended that, for patients who have demonstrated some degree of clinical improvement, ruxolitinib therapy be discontinued if they sustain an increase in their spleen length of 40% compared with baseline size (roughly equivalent to a 25% increase in spleen volume) and no longer have tangible improvement in disease-related symptoms.

Method of administration

Jakavi is to be taken orally, with or without food.

If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose.

[redacted]

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Myelosuppression

Treatment with Jakavi can cause haematological adverse drug reactions, including thrombocytopenia, anaemia and neutropenia. A complete blood count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi. Treatment should be discontinued in patients with platelet count less than 50,000/mm^3 or absoute neutrophil count less than 500/mm^3 (see section 4.2).

It has been observed that patients with low platelet counts (<200,000 /mm^3) at the start of therapy are more likely to develop thrombocytopenia during treatment.

Thrombocytopenia is generally reversible and is usually managed by reducing the dose or temporarily withholding Jakavi (see sections 4.2 and 4.8). However, platelet transfusions may be required as clinically indicated.

Patients developing anaemia may require blood transfusions. Dose modifications or interruption for patients developing anaemia may also be considered.

Patients with a haemoglobin level below 10.0 g/dl at the beginning of the treatment have a higher risk of developing a haemoglobin level below 8.0 g/dl during treatment compared to patients with a higher baseline haemoglobin level (79.3% versus 30.1%). More frequent monitoring of haematology parameters and of clinical signs and symptoms of Jakavi -related adverse drug reactions is recommended for patients with baseline haemoglobin below 10.0 g/dl.

Neutropenia (absolute neutrophil count <500) was generally reversible and was managed by temporarily withholding Jakavi (see sections 4.2 and 4.8).

Complete blood counts should be monitored as clinically indicated and dose adjusted as required (see sections 4.2 and 4.8).

Infections

Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Tuberculosis has been reported in patients receiving Jakavi for MF. Before starting treatment, patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. Jakavi therapy should not be started until active serious infections have resolved. Physicians should carefully observe patients receiving Jakavi for signs and symptoms of infections and initiate appropriate treatment promptly (see section 4.8).

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in

[redacted]

alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakavi. The effect of Jakavi on viral replication in patie nts with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

Herpes zoster

Physicians should educate patients about early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported with Jakavi treatment for MF. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.

Non-melanoma skin cancer

Non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and Merkel cell carcinoma, have been reported in patients treated with ruxolitinib. Most of these patients had histories of extended treatment with hydroxyurea and prior NMSC or pre -malignant skin lesions. A causal relationship to ruxolitinib has not been established. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Special populations

Renal impairment

The starting dose of Jakavi should be reduced in patients with severe renal impairment. For patients with end-stage renal disease on haemodialysis the starting dose for MF patients should be based on platelet counts (see section 4.2). Subsequent doses (single dose of 20 mg or two doses of 10 mg given 12 hours apart in MF patients; single dose of 10 mg or two doses of 5 mg given 12 hours apart in PV patients) should be administered only on haemodialysis days following each dialysis session. Additional dose modifications should be made with careful monitoring of safety and efficacy (see sections 4.2 and 5.2).

Hepatic impairment

The starting dose of Jakavi should be reduced by approximately 50% in patients with hepatic impairment. Further dose modifications should be based on the safety and efficacy of the medicinal product (see sections 4.2 and 5.2).

Interactions

If Jakavi is to be co-administered with strong CYP3A4 inhibitors or dual inhibitors of CYP3A4 and CYP2C9 enzymes (e.g. fluconazole), the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily (for monitoring frequency see sections 4.2 and 4.5).

[redacted]

The concomitant use of cytoreductive therapies or haematopoietic growth factors with Jakavi has not been studied. The safety and efficacy of these co -administrations are not known (see section 4.5).

Withdrawal effects

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

Excipients

Jakavi contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Ruxolitinib is eliminated through metabolism catalysed by CYP3A4 and CYP2C9. Thus, medicinal products inhibiting these enzymes can give rise to increased ruxolitinib exposure.

Interactions resulting in dose reduction of ruxolitinib

CYP3A4 inhibitors

Strong CYP3A4 inhibitors (such as, but not limited to, boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole)

In healthy subjects co-administration of Jakavi (10 mg single dose) with a strong CYP3A4 inhibitor, ketoconazole, resulted in ruxolitinib C_{max} and AUC that were higher by 33% and 91%, respectively, than with ruxolitinib alone. The half-life was prolonged from 3.7 to 6.0 hours with concurrent ketoconazole administration.

When administering Jakavi with strong CYP3A4 inhibitors the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily. Patients should be closely monitored (e.g. twice weekly) for cytopenias and dose titrated based on safety and efficacy (see section 4.2).

Dual CYP2C9 and CYP3A4 inhibitors

50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole). Avoid the concomitant use of Jakavi with fluconazole doses greater than 200 mg daily.

Enzyme inducers

[redacted]

CYP3A4 inducers (such as, but not limited to, avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St.John's wort (Hypericum perforatum))

Patients should be closely monitored and the dose titrated based on safety and efficacy (see section 4.2).

In healthy subjects given ruxolitinib (50 mg single dose) following the potent CYP3A4 inducer rifampicin (600 mg daily dose for 10 days), ruxolitinib AUC was 70% lower than after administration of Jakavi alone. The exposure of ruxolitinib active metabolites was unchanged. Overall, the ruxolitinib pharmacodynamic activity was similar, suggesting the CYP3A4 induction resulted in minimal effect on the pharmacodynamics. However, this could be related to the high ruxolitinib dose resulting in pharmacodynamic effects near E_{max}. It is possible that in the individual patient, an increase of the ruxolitinib dose is needed when initiating treatment with a strong enzyme inducer.

Other interactions to be considered affecting ruxolitinib

Mild or moderate CYP3A4 inhibitors (such as, but not limited to, ciprofloxacin, erythromycin, amprenavir, atazanavir, diltiazem, cimetidine)

In healthy subjects co-administration of ruxolitinib (10 mg single dose) with erythromycin 500 mg twice daily for four days resulted in ruxolitinib C_{max} and AUC that were higher by 8% and 27%, respectively, than with ruxolitinib alone.

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

Effects of ruxolitinib on other medicinal products

Substances transported by P-glycoprotein or other transporters

Ruxolitinib may inhibit P-glycoprotein and breast cancer resistance protein (BCRP) in the intestine. This may result in increased sytemic exposure of substrates of these transporters, such as dabigatran etexilate, ciclosporin, rosuvastatin and potentially digoxin. Therapeutic drug monitoring (TDM) or clinical monitoring of the affected substance is advised.

It is possible that the potential inhibition of P-gp and BCRP in the intestine can be minimised if the time between administrations is kept apart as long as possible.

Haematopoietic growth factors

The concurrent use of haematopoietic growth factors and Jakavi has not been studied. It is not known whether the Janus Associated Kinase (JAK) inhibition by Jakavi reduces the efficacy of the haematopoietic growth factors or whether the haematopoietic growth factors affect the efficacy of Jakavi (see section 4.4).

Cytoreductive therapies

The concomitant use of cytoreductive therapies and Jakavi has not been studied. The safety and efficacy of this co-administration is not known (see section 4.4).

A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is

[redacted]

anticipated when combining them with Jakavi. Another study in healthy subjects indicated that Jakavi does not affect the pharmacokinetics of an oral contracepti ve containing ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

4.6 Fertility, pregnancy and lactation

Pregnancy and contraception in females

There are no data from the use of Jakavi in pregnant women.

Animal studies have shown that ruxolitinib is embryotoxic and foetotoxic. Teratogenicity was not observed in rats or rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans (see section 5.3). The potential risk for humans is unknown. As a precautionary measure, the use of Jakavi during pregnancy is contraindicated (see section 4.3). Women of child-bearing potential should use effective contraception during the treatment with Jakavi. In case pregnancy should occur during treatment with Jakavi, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the foetus (see section 5.3).

Breast-feeding

Jakavi must not be used during breast-feeding (see section 4.3) and breast-feeding should therefore be discontinued when treatment is started. It is unknown whether ruxolitinib and/or its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. Available pharmacodynamic/toxicological data in animals have shown excretion of ruxolitinib and its metabolites in milk (see section 5.3).

Fertility

There are no human data on the effect of ruxolitinib on fertility. In animal studies, no effect on fertility was observed.

4.7 Effects on ability to drive and use machines

Jakavi has no or negligible sedating effect. However, patients who experience dizziness after the intake of Jakavi should refrain from driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety assessment was based on a total of 855 patients (with MF or PV) receiving Jakavi in phase 2 and 3 studies.

Myelofibrosis

In the randomised period of the two pivotal studies, COMFORT-I and COMFORT-II, the median duration of exposure to Jakavi was 10.8 months (range 0.3 to 23.5 months). The majority of patients (68.4%) were treated for at least 9 months. Of 301 patients, 111 (36.9%) had a baseline platelet count of between 100,000/mm^3 and 200,000/mm^3 and 190 (63.1%) had a baseline platelet count of >200,000/mm^3.

[redacted]

In these clinical studies, discontinuation due to adverse events, regardless of causality, was observed in 11.3% of patients.

The most frequently reported adverse drug reactions were thrombocytopenia and anaemia.

Haematological adverse drug reactions (any Common Terminology Criteria for Adverse Events [CTCAE] grade) included anaemia (82.4%), thrombocytopenia (69.8%) and neutropenia (16.6%).

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (21.3%), dizziness (15.3%) and headache (14.0%).

The three most frequent non-haematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (19.9%) and hypercholesterolaemia (16.9%). In phase 3 clinical studies in MF, neither CTCAE grade 3 or 4 hypercholesterolaemia, raised aspartate aminotransferase nor CTCAE grade 4 raised alanine aminotransferase were observed.

Long-term safety: As expected with an extended follow-up period, the cumulative frequency of some adverse events increased in the evaluation of the 3 -year follow-up safety data (median duration of exposure of 33.2 months in COMFORT-I and COMFORT-II for patients initially randomised to ruxolitinib) from 457 patients with myelofibrosis treated with ruxolitinib during the randomised and extension periods of the two pivotal phase 3 studies. This evaluation included data from patients that were initially randomised to ruxolitinib (N=301) and patients that received ruxolitinib after crossing over from control treatment arms (N=156). With these updated data, therapy discontinuation due to adverse events was observed in 17.1% of patients treated with ruxolitinib.

Polycythaemia vera

The safety of Jakavi was assessed in 110 patients with PV in an open-label, randomised, controlled phase 3 RESPONSE study. The adverse drug reactions listed below reflect the initial study period (up to week 32) with equivalent exposure to ruxolitinib and Best Available Therapy (BAT), corresponding to a median duration of exposure to Jakavi of 7.8 months. The mean age of patients receiving Jakavi was around 60 years.

Discontinuation due to adverse events, regardless of causality, was observed in 3.6% of patients treated with Jakavi and 1.8% of patients treated with best available therapy.

Haematological adverse reactions (any CTCAE grade) included anaemia (43.6 %) and thrombocytopenia (24.5%). Anaemia or thrombocytopenia CTCAE grade 3 and 4 were reported in respectively 1.8% or 5.5%.

The three most frequent non-haematological adverse reactions were dizziness (15.5%), constipation (8.2%) and herpes zoster (6.4%).

The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) were hypercholesterolaemia (30.0%), raised alanine aminotransferase (22.7%) and raised aspartate aminotransferase (20.9%). These were all CTCAE grade 1 and 2 with the exception of one CTCAE grade 3 raised alanine aminotransferase event.

[redacted]

Long-term safety: Patients had a median duration of exposure to Jakavi of 18.6 months (range 0.3 to 35.9 months). With longer exposure, frequency of adverse events increased; however no new safety findings emerged. When adjusted for exposure, the adverse event rates were generally comparable with those observed during the initial study period.

Tabulated summary of adverse drug reactions from clinical studies

In the clinical study programme the severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1 = mild, grade 2 = moderate, grade 3 = severe and grade 4=life-threatening.

Adverse drug reactions from clinical studies (Table14-5) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very co mmon (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 14-5 Frequency category of adverse drug reactions reported in the phase 3 studies (COMFORT-I, COMFORT-II, RESPONSE)

Adverse drug reaction	Frequency category for MF patients	Frequency category for PV patients
Infections and infestations		
Urinary tract infections[a,d]	Very common	Common
Herpes zoster[a,d]	Common	Common
Tuberculosis[e]	Uncommon	-
Blood and lymphatic system disorders[b,d]		
Anaemia[b]	-	-
CTCAE[c] grade 4 (<6.5g/dl)	Very common	Uncommon
CTCAE[c] grade 3 (<8.0 – 6.5g/dl)	Very common	Uncommon
Any CTCAE[c] grade	Very common	Very common
Thrombocytopenia[b]		
CTCAE[c] grade 4 (<25,000/mm^3)	Common	Uncommon
CTCAE[c] grade 3 (50,000 – 25,000/mm^3)	Common	Common
Any CTCAE[c] grade	Very common	Very common
Neutropenia[b]		
CTCAE[c] grade 4 (<500/mm^3)	Common	-
CTCAE[c] grade 3 (<1,000 – 500/mm^3)	Common	-

[redacted]

Any CTCAE[c] grade	Very common	-
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)	Very common	Very common
Intracranial bleeding	Common	-
Gastrointestinal bleeding	Common	-
Bruising	Very common	Very common
Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)	Common	Very common
Metabolism and nutrition disorders		
Weight gain[a]	Very common	Common
Hypercholesterolaemia[b] CTCAE[c] grade 1 and 2	Very common	Very common
Hypertriglyceridaemia[b] CTCAE[c] grade 1	-	Very common
Nervous system disorders		
Dizziness[a]	Very common	Very common
Headache[a]	Very common	-
Gastrointestinal disorders		
Flatulence[a]	Common	-
Constipation[a]	-	Common
Hepatobiliary disorders		
Raised alanine aminotransferase[b]		
CTCAE[c] grade 3 (> 5x – 20 x ULN)	Common	Uncommon
Any CTCAE[c] grade	Very common	Very common
Raised aspartate aminotransferase[b]		
Any CTCAE[c] grade	Very common	Very common
Vascular disorders		
Hypertension[a]	-	Very common

[a]Frequency is based on adverse event data.
- A subject with multiple occurrence of an adverse drug reaction (ADR) is counted only once in that ADR category.
- ADRs reported are on treatment or up to 28 days post treatment end date.

[b]Frequency is based on laboratory values.
- A subject with multiple occurrences of an ADR is counted only once in that ADR category.
- ADRs reported are on treatment or up to 28 days post treatment end date.

[c]Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening
[d]These ADRs are discussed in the text.
[e]Frequency is based on all patients exposed to ruxolitinib in clinical studies (N=4755)

Upon discontinuation, MF patients may experience a return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In clinical studies in MF the total symptom score for MF symptoms gradually returned to baseline value within 7 days after dose discontinuation (see section 4.4).

[redacted]

Description of selected adverse drug reactions

Anaemia

In phase 3 clinical studies in MF, median time to onset of first CTCAE grade 2 or higher anaemia was 1.5 months. One patient (0.3%) discontinued treatment because of anaemia.

In patients receiving Jakavi mean decreases in haemoglobin reached a nadir of approximately 10 g/litre below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 5 g/litre below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy.

In the randomised, placebo-controlled study COMFORT-I 60.6% of Jakavi-treated MF patients and 37.7% of placebo-treated MF patients received red blood cell transfusions during randomised treatment. In the COMFORT-II study the rate of packed red blood cell transfusions was 53.4% in the Jakavi arm and 41.1% in the best available therapy arm.

In the randomised period of the pivotal studies, anaemia was less frequent in PV patients than in MF patients (43.6% versus 82.4%). In the PV population, the CTCAE grade 3 and 4 events were reported in 1.8%, while in the MF patients the frequency was 42.56%.

Thrombocytopenia

In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm^3 was 14 days. During the randomised period, platelet transfusions were administered to 4.7% of patients receiving Jakavi and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakavi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm ^{3} to 200,000/mm^3 before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm^3 (64.2% versus 38.5%).

In the randomised period of the pivotal studies, the rate of patients experiencing thrombocytopenia was lower in PV (24.5%) patients compared to MF (69.8%) patients. The frequency of severe (i.e. CTCAE grade 3 and 4) thrombocytopenia was lower in PV (5.5%) than in MF (11.6%) patients.

Neutropenia

In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 neutropenia, the median time to onset was 12 weeks. During the randomised period, dose holding or reductions due to neutropenia were reported in 1.0% of patients, and 0.3% of patients discontinued treatment because of neutropenia.

In the randomised period of the pivotal study in PV patients, neutropenia was reported in two patients (1.8%) of which one patient developed CTCAE grade 4 neutropenia.

Bleeding

In the phase 3 pivotal studies in MF bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 32.6% of patients exposed to Jakavi and 23.2% of patients exposed to the reference treatments (placebo or best

[redacted]

available therapy). The frequency of grade 3-4 events was similar for patients treated with Jakavi or reference treatments (4.7% versus 3.1%). Most of the patients with bleeding events during the treatment reported bruising (65.3%). Bruising events were more frequently reported in patients taking Jakavi compared with the reference treatments (21.3% versus 11.6%). Intracranial bleeding was reported in 1% of patients exposed to Jakavi and 0.9% exposed to reference treatments. Gastrointestinal bleeding was reported in 5.0% of patients exposed to Jakavi compared to 3.1% exposed to reference treatments. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage and haematuria) were reported in 13.3% of patients treated with Jakavi and 10.3% treated with reference treatments.

In the randomised period of the pivotal study in PV patients, bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 20% of patients treated with Jakavi and 15.3% patients receiving best available therapy. Bruising was reported in similar frequencies in Jakavi and BAT arms (10.9% versus 8.1%). No intracranial bleeding or gastrointestinal haemorrhage events were reported in patients receiving Jakavi. One patient treated with Jakavi experienced a grade 3 bleeding event (post-procedural bleeding); no grade 4 bleeding was reported. Other bleeding events (including events such as epistaxis, post -procedural haemorrhage, gingival bleeding) were reported in 11.8% of patients treated with Jakavi and 6.3% treated with best available therapy.

Infections

In the phase 3 pivotal studies in MF, grade 3 or 4 urinary tract infection was reported in 1.0% of patients, herpes zoster in 4.3% and tuberculosis in 1.0%. In phase 3 clinical studies sepsis was reported in 3.0% of patients. An extended follow-up of patients treated with ruxolitinib showed no trends towards an increase in the rate of sepsis over time.

In the randomised period of the pivotal study in PV patients, one (0.9%) CTCAE grade 3 and no grade 4 urinary tract infection was reported. The rate of herpes zoster was slightly higher in PV (6.4%) patients than in MF (4.0%) patients. There was one report of CTCAE grade 3 post-herpetic neuralgia amongst the PV patients.

Increased systolic blood pressure

In the phase 3 pivotal clinical studies in MF an increase in systolic blood pressure of 20 mmHg or more from baseline was recorded in 31.5% of patients on at least one visit compared with 19.5% of the control-treated patients. In COMFORT-I (MF patients) the mean increase from baseline in systolic BP was 0-2 mmHg on Jakavi versus a decrease of 2-5 mmHg in the placebo arm. In COMFORT-II mean values showed little difference between the ruxolitinib-treated and the control-treated MF patients.

In the randomised period of the pivotal study in PV patients, the mean systolic blood pressure increased by 0.65 mmHg in the Jakavi arm versus a decrease of 2 mmHg in the BAT arm.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known antidote for overdoses with Jakavi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are

[redacted]

associated with increased myelosuppression including leukopenia, anaemia and thrombocytopenia. Appropriate supportive treatment should be given.

Haemodialysis is not expected to enhance the elimination of ruxolitinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE18

Mechanism of action

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 (IC_{50} values of 3.3 nM and 2.8 nM for JAK1 and JAK2 enzymes, respectively). These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.

Myelofibrosis and polycythaemia vera are myeloproliferative neoplasms known to be associated with dysregulated JAK1 and JAK2 signalling. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK -STAT pathway, gain-of-function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signalling regardless of JAK2V617F mutation status. Activating mutations in JAK2 (V617F or exon 12) are found in >95% of PV patients.

Ruxolitinib inhibits JAK-STAT signalling and cell proliferation of cytokine-dependent cellular models of haematological malignancies, as well as of Ba/F3 cells rendered cytokine-independent by expressing the JAK2V617F mutated protein, with IC_{50} ranging from 80-320 nM.

Pharmacodynamic effects

Ruxolitinib inhibits cytokine-induced STAT3 phosphorylation in whole blood from healthy subjects, MF patients and PV patients. Ruxolitinib resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 8 hours in both healthy subjects and MF patients, indicating no accumulation of either parent or active metabolites.

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNFα, IL-6 and CRP in subjects with MF were decreased following treatment with ruxolitinib. MF patients did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with PV also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with ruxolitinib.

In a thorough QT study in healthy subjects, there was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up to a supratherapeutic dose of 200 mg, indicating that ruxolitinib has no effect on cardiac repolarisation.

Clinical efficacy and safety

Myelofibrosis

[redacted]

Two randomised phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with MF (primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis). In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate -2 or high risk based on the International Working Group (IWG) Consensus Criteria. The starting dose of Jakavi was based on platelet count.

COMFORT-I was a double-blind, randomised, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. The primary efficacy endpoint was proportion of subjects achieving ≥35% reduction from baseline in spleen volume at week 24 as measured by Magnetic Resonance Imaging (MRI) or Computed Tomography (CT).

Secondary endpoints included duration of maintenance of a ≥35% reduction from baseline in spleen volume, proportion of patients who had ≥50% reduction in total symptom score, changes in total symptom scores from baseline to week 24, as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary, and overall survival.

COMFORT-II was an open-label, randomised study in 219 patients. Patients were randomised 2:1 to Jakavi versus best available therapy. In the best available therapy arm, 47% of patients received hydroxyurea and 16% of patients received glucocorticoids. The primary efficacy endpoint was proportion of patients achieving ≥35% reduction from baseline in spleen volume at week 48 as measured by MRI or CT.

Secondary endpoints included proportion of patients achieving a ≥35% reduction of spleen volume from baseline at week 24 and duration of maintenance of a ≥35% reduction from baseline spleen volume.

In COMFORT-I and COMFORT-II, patient baseline demographics and disease characteristics were comparable between the treatment arms.

Table 14-6 Percentage of patients with ≥35% reduction from baseline in spleen volume at week 24 in COMFORT-I and at week 48 in COMFORT-II (ITT)

	COMFORT-I		**COMFORT-II**	
	Jakavi (N=155)	**Placebo (N=153)**	**Jakavi (N=144)**	**Best available therapy (N=72)**
Time points	Week 24		Week 48	
Number (%) of subjects with spleen volume reduced by ≥35%	65 (41.9)	1 (0.7)	41 (28.5)	0
95% confidence intervals	34.1, 50.1	0, 3.6	21.3, 36.6	0.0, 5.0
p-value	<0.0001		<0.0001	

A significantly higher proportion of patients in the Jakavi group achieved ≥35% reduction from baseline in spleen volume (Table 14-6) regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (primary myelofibrosis, post-polycythaemia vera myelofibrosis, post-essential thrombocythaemia myelofibrosis).

[redacted]

Table 14-7 Percentage of patients with ≥35% reduction from baseline in spleen volume by JAK mutation status (safety set)

	COMFORT-I				COMFORT-II			
	Jakavi		Placebo		Jakavi		Best available therapy	
JAK mutation status	Positive (N=113) n (%)	Negative (N=40) n (%)	Positive (N=121) n (%)	Negative (N=27) n (%)	Positive (N=110) n (%)	Negative (N=35) n (%)	Positive (N=49) n (%)	Negative (N=20) n (%)
Number (%) of subjects with spleen volume reduced by ≥35%	54 (47.8)	11 (27.5)	1 (0.8)	0	36 (32.7)	5 (14.3)	0	0
Time point	After 24 weeks				After 48 weeks			

The probability of maintaining spleen response (≥35% reduction) on Jakavi for at least 24 weeks was 89% in COMFORT-I and 87% in COMFORT-II; 52% maintained spleen responses for at least 48 weeks in COMFORT-II.

In COMFORT-I, 45.9% subjects in the Jakavi group achieved a ≥50% improvement from baseline in the week 24 total symptom score (measured using MFSAF diary v2.0), as compared to 5.3% in the placebo group ($p<0.0001$ using chi-square test). The mean change in the global health status at week 24, as measured by EORTC QLQ C30 was +12.3 for Jakavi and -3.4 for placebo ($p<0.0001$).

In COMFORT-I, after a median follow-up of 34.3 months, the death rate in patients randomised to the ruxolitinib arm was 27.1% versus 35.1% in patients randomised to placebo; HR 0.687; 95% CI 0.459-1.029; p=0.0668.

In COMFORT-II, after a median follow-up of 34.7 months, the death rate in patients randomised to ruxolitinib was 19.9% versus 30.1% in patients randomised to best available treatment (BAT); HR 0.48; 95% CI 0.28-0.85; p=0.009. In both studies, the lower death rates noted in the ruxolitinib arm were predominantly driven by the results obtained in the post polycythaemia vera and post essential thrombocythaemia subgroups.

Polycythaemia vera

A randomised, open-label, active-controlled phase 3 study (RESPONSE) was conducted in 222 patients with PV who were resistant to or intolerant of hydroxyurea defined based on the European LeukemiaNet (ELN) international working group published criteria. 110 patients were randomised to the ruxolitinib arm and 112 patients to the BAT arm. The starting dose of Jakavi was 10 mg twice daily. Doses were then adjusted in individual patients based on tolerability and efficacy with a maximum dose of 25 mg twice daily. BAT was selected by the investigator on a patient-by-patient basis and included hydroxyurea (59.5%), interferon/pegylated interferon (11.7%), anagrelide (7.2%), pipobroman (1.8%) and observation (15.3%).

Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. Most patients (>80%) had received at

[redacted]

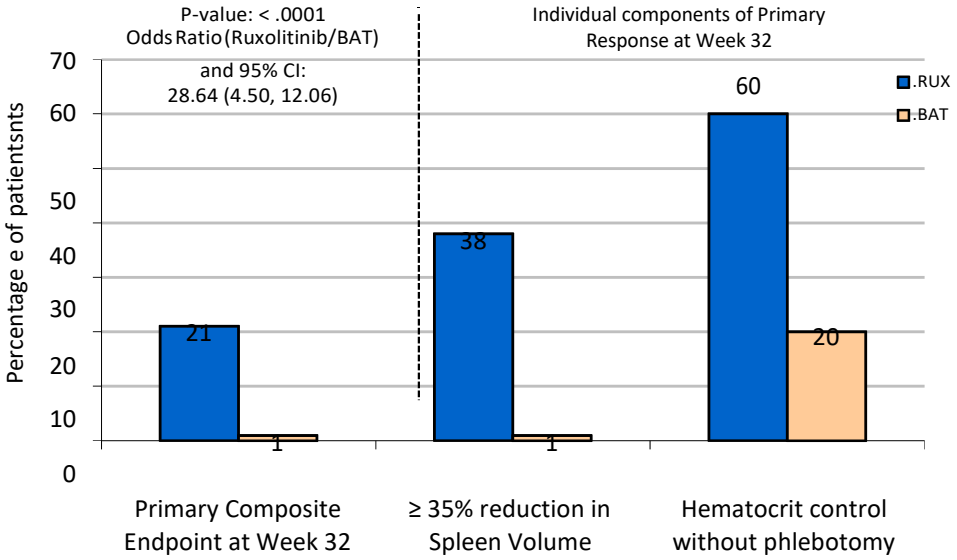
least two phlebotomies in the last 24 weeks prior to screening. Comparative data regarding long-term survival and incidence of disease complications is missing.

The primary composite endpoint was the proportion of patients achieving both an absence of phlebotomy eligibility (HCT control) and a ≥35% reduction in spleen volume from baseline at week 32. Phlebotomy eligibility was defined as a confirmed HCT of >45%, i.e. at least 3 percentage points higher than the HCT obtained at baseline or a confirmed HCT of >48%, depending on which was lower. Key secondary endpoints included the proportion of patients who achieved the primary endpoint and remained free from progression at week 48, as well as the proportion of patients achieving complete haematological remission at week 32.

The study met its primary objective and a higher proportion of patients in the Jakav i group achieved the primary composite endpoint and each of its individual components. Significantly more patients treated with Jakavi (20.9%) achieved a primary response (p<0.0001) compared to BAT (0.9%). Haematocrit control was achieved in 60% of patient s in the Jakavi arm compared to 19.6% in the BAT arm and a ≥35% reduction in spleen volume was achieved in 38.2% of patients in the Jakavi arm compared to 0.9% in the BAT arm (Figure 14-2). 94 (83.9%) patients randomised to the BAT arm crossed over to ruxolitinib treatment at Week 32 or after, limiting the comparison between the two arms after Week 32.

Both key secondary endpoints were also met. The proportion of patients achieving a complete haematological remission was 23.6% on Jakavi compared to 8.9% on BAT (p=0.0028) and the proportion of patients achieving a durable primary response at week 48 was 19.1% on Jakavi and 0.9% on BAT.(p<0.0001).

Figure 14-2 Patients achieving the primary endpoint and components ofthe primary endpoint at week 32



Symptom burden was assessed using the MPN-SAF total symptom score (TSS) electronic

[redacted]

patient diary, which consisted of 14 questions. At week 32, 49% and 64% of patients treated with ruxolitinib achieved a ≥ 50% reduction in TSS-14 and TSS-5, respectively, compared to

[redacted]

only 5% and 11% of patients on BAT.

Treatment benefit perception was measured by the Patient Global Impression of Change (PGIC) questionnaire. 66% of patients treated with ruxolitinib compared to 19% treated with BAT reported an improvement as early as four weeks after beginning treatment. Improvement in perception of treatment benefit was also higher in patients treated with ruxolitinib at week 32 (78% versus 33%).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Jakavi in all subsets of the paediatric population for the treatment of MF (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Ruxolitinib is a Biopharmaceutical Classification System (BCS) class 1 compound, with high permeability, high solubility and rapid dissolution characteristics. In clinical studies, ruxolitinib is rapidly absorbed after oral administration with maximal plasma concentration (C_{max}) achieved approximately 1 hour post-dose. Based on a human mass balance study, oral absorption of ruxolitinib, as ruxolitinib or metabolites formed under first-pass, is 95% or greater. Mean ruxolitinib C_{max} and total exposure (AUC) increased proportionally over a single dose range of 5-200 mg. There was no clinically relevant change in the pharmacokinetics of ruxolitinib upon administration with a high-fat meal. The mean C_{max} was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) on dosing with a high-fat meal.

Distribution

The mean volume of distribution at steady state is approximately 75 litres in MF and PV patients. At clinically relevant concentrations of ruxolitinib, binding to plasma proteins *in vitro* is approximately 97%, mostly to albumin. A whole body autoradiography study in rats has shown that ruxolitinib does not penetrate the blood-brain barrier.

Biotransformation

Ruxolitinib is mainly metabolised by CYP3A4 (>50%), with additional contribution from CYP2C9. Parent compound is the predominant entity in human plasma, representing approximately 60% of the drug-related material in circulation. Two major and active metabolites are present in plasma representing 25% and 11% of parent AUC. These metabolites have one half to one fifth of the parent JAK-related pharmacological activity. The sum total of all active metabolites contributes to 18% of the overall pharmacodynamics of ruxolitinib. At clinically relevant concentrations, ruxolitinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 based on *in vitro* studies. *In vitro* data indicate that ruxolitinib may inhibit P-gp and BCRP.

[redacted]

Elimination

Ruxolitinib is mainly eliminated through metabolism. The mean elimination half -life of ruxolitinib is approximately 3 hours. Following a single oral dose of [^{14}C]-labelled ruxolitinib in healthy adult subjects, elimination was predominately through metabolism, with 74% of radioactivity excreted in urine and 22% via faeces. Unchanged parent substance accounted for less than 1% of the excreted total radioactivity.

Linearity/non-linearity

Dose proportionality was demonstrated in the single and multiple dose studies.

Special populations

Effects of age, gender or race

Based on studies in healthy subjects, no relevant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in MF patients, no relationship was apparent between oral clearance and patient age or race. The predicted oral clearance was 17.7 l/h in women and 22.1 l/h in men, with 39% inter-subject variability in MF patients. Clearance was 12.7 l/h in PV patients, with a 42% inter-subject variability and no relationship was apparent between oral clearance and gender, patient age or race based on a population pharmacokinetic evaluation in PV patients.

Paediatric population

The safety and effectiveness of Jakavi in paediatric patients have not been established (see section 5.1, “Paediatric population”).

Renal impairment

Renal function was determined using both Modification of Diet in Renal Disease (MDRD) and urinary creatinine. Following a single ruxolitinib dose of 25 mg, the exposure of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites tended to increase with increasing severity of renal impairment, and were most markedly increased in the subjects with severe renal impairment. It is unknown whether the increased metabolite exposure is of safety concern. A dose modification is recommended in patient s with severe renal impairment and end-stage renal disease (see section 4.2). Dosing only on dialysis days reduces the metabolite exposure, but also the pharmacodynamic effect, especially on the days between dialysis.

Hepatic impairment

Following a single ruxolitinib dose of 25 mg in patients with varying degrees of hepatic impairment, the mean AUC for ruxolitinib was increased in patients with mild, moderate and severe hepatic impairment by 87%, 28% and 65%, respectively, compared to patients with normal hepatic function. There was no clear relationship between AUC and the degree of hepatic impairment based on Child-Pugh scores. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1 -5.0 hours versus 2.8 hours). A dose reduction of approximately 50% is recommended for patients with hepatic impairment (see section 4.2).

[redacted]

5.3 Preclinical safety data

Ruxolitinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity and reproductive toxicity studies and in a carcinogenicity study. Target organs associated with the pharmacological action of ruxolitinib in repeated dose studies include bone marrow, peripheral blood and lymphoid tissues. Infections generally associated with immunosuppression were noted in dogs. Adverse decreases in blood pressure along with increases in heart rate were noted in a dog telemetry study, and an adverse decrease in minute volume was noted in a respiratory study in rats. The margins (based on unbound C_{max}) at the non-adverse level in the dog and rat studies were 15.7-fold and 10.4-fold greater, respectively, than the maximum human recommended dose of 25 mg twice daily. No effects were noted in an evaluation of the neuropharmacological effects of ruxolitinib.

Ruxolitinib decreased foetal weight and increased post-implantation loss in animal studies. There was no evidence of a teratogenic effect in rats and rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans. No effects were noted on fertility. In a pre- and post-natal development study, a slightly prolonged gestation period, reduced number of implantation sites, and reduced number of pups delivered were observed. In the pups, decreased mean initial body weights and short period of decreased mean body weight gain were observed. In lactating rats, ruxolitinib and/or its metabolites were excreted into the milk with a concentration that was 13-fold higher than the maternal plasma concentration. Ruxolitinib was not mutagenic or clastogenic. Ruxolitinib was not carcinogenic in the Tg.rasH2 transgenic mouse model.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Cellulose, microcrystalline
- Magnesium stearate
- Silica, colloidal anhydrous
- Sodium starch glycolate (Type A)
- Povidone
- Hydroxypropylcellulose
- Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

[redacted]

6.5 Nature and contents of container

PVC/PCTFE/Aluminium blister packs containing 14 or 56 tablets or multipacks containing 168 (3 packs of 56) tablets.

Not all pack sizes or types may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/014-016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23.08.2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

[redacted]

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 15 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg ruxolitinib (as phosphate).

Excipient with known effect:

Each tablet contains 214.35 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Ovaloid curved white to almost white tablets of approximately 15.0 x 7.0 mm with "NVR" debossed on one side and "L15" debossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Myelofibrosis (MF)

Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

Polycythaemia vera (PV)

Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

4.2 Posology and method of administration

Jakavi treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.

A complete blood cell count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi.

Complete blood count, including a white blood cell count differential, should be monitored every 2-4 weeks until Jakavi doses are stabilised, and then as clinically indicated (see section 4.4).

Posology

Starting dose

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The recommended starting dose of Jakavi in myelofibrosis is 15 mg twice daily for patients with a platelet count between 100,000/mm^3 and 200,000/mm^3 and 20 mg twice daily for patients with a platelet count of >200,000/mm^3. The recommended starting dose of Jakavi in polycythaemia vera is 10 mg given orally twice daily.

There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm^3 and <100,000/mm^3. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously.

Dose modifications

Doses may be titrated based on safety and efficacy. Treatment should be discontinued for platelet counts less than 50,000/mm^3 or absolute neutrophil counts less than 500/mm^3. In PV, treatment should also be interrupted when haemoglobin is below 8 g/dl. After recovery of blood counts above these levels, dosing may be re-started at 5 mg twice daily and gradually increased based on careful monitoring of complete blood cell count, including a white blood cell count differential.

Dose reductions should be considered if the platelet count decreases below 100,000/ mm^3, with the goal of avoiding dose interruptions for thrombocytopenia. In PV, dose reductions should also be considered if haemoglobin decreases below 12 g/dl and is recommended if it decreases below 10 g/dl.

If efficacy is considered insufficient and blood counts are adequate, doses may be increased by a maximum of 5 mg twice daily, up to the maximum dose of 25 mg twice daily.

The starting dose should not be increased within the first four weeks of treatment and thereafter no more frequently than at 2-week intervals.

The maximum dose of Jakavi is 25 mg twice daily.

Dose adjustment with concomitant strong CYP3A4 inhibitors or fluconazole

When Jakavi is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily (see section 4.5). Avoid the concomitant use of Jakavi with fluconazole doses greater than 200 mg daily.

More frequent monitoring (e.g. twice a week) of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended while on strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes.

Special populations

Renal impairment

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

In patients with severe renal impairment (creatinine clearance less than 30 ml/min) the recommended starting dose based on platelet count for MF patients should be reduced by approximately 50% to be administered twice daily. The recommended starting dose for PV patients with severe renal impairment is 5 mg twice daily. Patients should be carefully monitored with regard to safety and efficacy during Jakavi treatment.

There are limited data to determine the best dosing options for patients with end -stage renal disease (ESRD) on haemodialysis. Pharmacokinetic/pharmacodynamic simulations based on available data in this population suggest that the starting dose for MF patients with ESRD on haemodialysis is a single dose of 15 -20 mg or two doses of 10 mg given 12 hours apart, to be

[redacted]

administered post-dialysis and only on the day of haemodialysis. A single dose of 15 mg is recommended for MF patients with platelet count between 100,000/mm^3 and 200,000/mm^3. A single dose of 20 mg or two doses of 10 mg given 12 hours apart is recommended for MF patients with platelet count of >200,000/mm^3. Subsequent doses (single administration or two doses of 10 mg given 12 hours apart) should be administered only on haemodialysis days following each dialysis session.

The recommended starting dose for PV patients with ESRD on haemodialysis is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. These dose recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration (see section 5.2).

Hepatic impairment

In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice daily. Subsequent doses should be adjusted based on careful monitoring of safety and efficacy. Patients diagnosed with hepatic impairment while receiving Jakavi should have complete blood counts, including a white blood cell count differential, monitored at least every one to two weeks for the first 6 weeks after initiation of therapy with Jakavi and as clinically indicated thereafter once their liver function and blood counts have been stabilised. Jakavi dose can be titrated to reduce the risk of cytopenia.

Older people (≥65 years)

No additional dose adjustments are recommended for older people.

Paediatric population

The safety and efficacy of Jakavi in children aged up to 18 years have not been established. No data are available (see section 5.1).

Treatment discontinuation

Treatment may be continued as long as the benefit-risk remains positive. However the treatment should be discontinued after 6 months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy.

It is recommended that, for patients who have demonstrated some degree of clinical improvement, ruxolitinib therapy be discontinued if they sustain an increase in their spleen length of 40% compared with baseline size (roughly equivalent to a 25% increase in spleen volume) and no longer have tangible improvement in disease-related symptoms.

Method of administration

Jakavi is to be taken orally, with or without food.

If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose.

[redacted]

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Myelosuppression

Treatment with Jakavi can cause haematological adverse drug reactions, including thrombocytopenia, anaemia and neutropenia. A complete blood count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi. Treatment should be discontinued in patients with platelet count less than 50,000/mm ^{3} or absoute neutrophil count less than 500/mm^3 (see section 4.2).

It has been observed that patients with low platelet counts (<200,000/mm^3) at the start of therapy are more likely to develop thrombocytopenia during treatment.

Thrombocytopenia is generally reversible and is usually managed by reducing the dose or temporarily withholding Jakavi (see sections 4.2 and 4.8). However, platelet transfusions may be required as clinically indicated.

Patients developing anaemia may require blood transfusions. Dose modifications or interruption for patients developing anaemia may also be considered.

Patients with a haemoglobin level below 10.0 g/dl at the beginning of the treatment have a higher risk of developing a haemoglobin level below 8.0 g/dl during treatment compared to patients with a higher baseline haemoglobin level (79.3% versus 30.1%). More frequent monitoring of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended for patients with baseline haemoglobin below 10.0 g/dl.

Neutropenia (absolute neutrophil count <500) was generally reversible and was managed by temporarily withholding Jakavi (see sections 4.2 and 4.8).

Complete blood counts should be monitored as clinically indicated and dose adjusted as required (see sections 4.2 and 4.8).

Infections

Patients should be assessed for the risk of developing serious bacte rial, mycobacterial, fungal and viral infections. Tuberculosis has been reported in patients receiving Jakavi for MF. Before starting treatment, patients should be evaluated for active and inactive (“latent”) tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. Jakavi therapy should not be started until active serious infections have resolved. Physicians should carefully observe patients receiving Jakavi for signs and symptoms of infections and initiate appropriate treatment promptly (see section 4.8).

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in

[redacted]

alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakavi. The effect of Jakavi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

Herpes zoster

Physicians should educate patients about early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported with Jakavi treatment for MF. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worseni ng symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.

Non-melanoma skin cancer

Non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and Merkel cell carcinoma, have been reported in patients treated with ruxolitinib. Most of these patients had histories of extended treatment with hydroxyurea and prior NMSC or pre -malignant skin lesions. A causal relationship to ruxolitinib has not been established. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Special populations

Renal impairment

The starting dose of Jakavi should be reduced in patients with severe renal impairment. For patients with end-stage renal disease on haemodialysis the starting dose for MF patients should be based on platelet counts (see section 4.2). Subsequent doses (single dose of 20 mg or two doses of 10 mg given 12 hours apart in MF patients; single dose of 10 mg or two doses of 5 mg given 12 hours apart in PV patients) should be administered only on haemodialysis days following each dialysis session. Additional dose modifications should be made with careful monitoring of safety and efficacy (see sections 4.2 and 5.2).

Hepatic impairment

The starting dose of Jakavi should be reduced by approximately 50% in patients with hepatic impairment. Further dose modifications should be based on the safety and efficacy of the medicinal product (see sections 4.2 and 5.2).

Interactions

If Jakavi is to be co-administered with strong CYP3A4 inhibitors or dual inhibitors of CYP3A4 and CYP2C9 enzymes (e.g. fluconazole), the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily (for monitoring frequency see sections 4.2 and 4.5).

[redacted]

The concomitant use of cytoreductive therapies or haematopoietic growth factors with Jakavi has not been studied. The safety and efficacy of these co -administrations are not known (see section 4.5).

Withdrawal effects

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

Excipients

Jakavi contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Ruxolitinib is eliminated through metabolism catalysed by CYP3A4 and CYP2C9. Thus, medicinal products inhibiting these enzymes can give rise to increased ruxolitinib exposure.

Interactions resulting in dose reduction of ruxolitinib

CYP3A4 inhibitors

Strong CYP3A4 inhibitors (such as, but not limited to, boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole)

In healthy subjects co-administration of Jakavi (10 mg single dose) with a strong CYP3A4 inhibitor, ketoconazole, resulted in ruxolitinib C_{max} and AUC that were higher by 33% and 91%, respectively, than with ruxolitinib alone. The half-life was prolonged from 3.7 to 6.0 hours with concurrent ketoconazole administration.

When administering Jakavi with strong CYP3A4 inhibitors the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily. Patients should be closely monitored (e.g. twice weekly) for cytopenias and dose titrated based on safety and efficacy (see section 4.2).

Dual CYP2C9 and CYP3A4 inhibitors

50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole). Avoid the concomitant use of Jakavi with fluconazole doses greater than 200 mg daily.

Enzyme inducers

[redacted]

CYP3A4 inducers (such as, but not limited to, avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St.John's wort (Hypericum perforatum))

Patients should be closely monitored and the dose titrated based on safety and efficacy (see section 4.2).

In healthy subjects given ruxolitinib (50 mg single dose) following the potent CYP3A4 inducer rifampicin (600 mg daily dose for 10 days), ruxolitinib AUC was 70% lower than after administration of Jakavi alone. The exposure of ruxolitinib active metabolites was unchanged. Overall, the ruxolitinib pharmacodynamic activity was similar, suggesting the CYP3A4 induction resulted in minimal effect on the pharmacodynamics. However, this could be related to the high ruxolitinib dose resulting in pharmacodynamic effects near E_{max}. It is possible that in the individual patient, an increase of the ruxolitinib dose is needed when initiating treatment with a strong enzyme inducer.

Other interactions to be considered affecting ruxolitinib

Mild or moderate CYP3A4 inhibitors (such as, but not limited to, ciprofloxacin, erythromycin, amprenavir, atazanavir, diltiazem, cimetidine)

In healthy subjects co-administration of ruxolitinib (10 mg single dose) with erythromycin 500 mg twice daily for four days resulted in ruxolitinib C_{max} and AUC that were higher by 8% and 27%, respectively, than with ruxolitinib alone.

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

Effects of ruxolitinib on other medicinal products

Substances transported by P-glycoprotein or other transporters

Ruxolitinib may inhibit P-glycoprotein and breast cancer resistance protein (BCRP) in the intestine. This may result in increased sytemic exposure of substrates of these transporters, such as dabigatran etexilate, ciclosporin, rosuvastatin and potentially digoxin. Therapeutic drug monitoring (TDM) or clinical monitoring of the affected substance is advised.

It is possible that the potential inhibition of P-gp and BCRP in the intestine can be minimised if the time between administrations is kept apart as long as possible.

Haematopoietic growth factors

The concurrent use of haematopoietic growth factors and Jakavi has not been studied. It is not known whether the Janus Associated Kinase (JAK) inhibition by Jakavi reduces the efficacy of the haematopoietic growth factors or whether the haematopoietic growth factors affect the efficacy of Jakavi (see section 4.4).

Cytoreductive therapies

The concomitant use of cytoreductive therapies and Jakavi has not been studied. The safety and efficacy of this co-administration is not known (see section 4.4).

A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is

[redacted]

anticipated when combining them with Jakavi. Another study in healthy subjects indicated that Jakavi does not affect the pharmacokinetics of an oral contrac eptive containing ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

4.6 Fertility, pregnancy and lactation

Pregnancy and contraception in females

There are no data from the use of Jakavi in pregnant women.

Animal studies have shown that ruxolitinib is embryotoxic and foetotoxic. Teratogenicity was not observed in rats or rabbits. However, the exposure margins compared to the highe st clinical dose were low and the results are therefore of limited relevance for humans (see section 5.3). The potential risk for humans is unknown. As a precautionary measure, the use of Jakavi during pregnancy is contraindicated (see section 4.3). Women of child-bearing potential should use effective contraception during the treatment with Jakavi. In case pregnancy should occur during treatment with Jakavi, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the foetus (see section 5.3).

Breast-feeding

Jakavi must not be used during breast-feeding (see section 4.3) and breast-feeding should therefore be discontinued when treatment is started. It is unknown whether ruxolitinib and/or its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. Available pharmacodynamic/toxicological data in animals have shown excretion of ruxolitinib and its metabolites in milk (see section 5.3).

Fertility

There are no human data on the effect of ruxolitinib on fertility. In animal studies, no effect on fertility was observed.

4.7 Effects on ability to drive and use machines

Jakavi has no or negligible sedating effect. However, patients who experience dizziness after the intake of Jakavi should refrain from driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety assessment was based on a total of 855 patients (with MF or PV) receiving Jakavi in phase 2 and 3 studies.

Myelofibrosis

In the randomised period of the two pivotal studies, COMFORT-I and COMFORT-II, the median duration of exposure to Jakavi was 10.8 months (range 0.3 to 23.5 months). The majority of patients (68.4%) were treated for at least 9 months. Of 301 patients, 111 (36.9%) had a baseline platelet count of between 100,000/mm^3 and 200,000/mm^3 and 190 (63.1%) had a baseline platelet count of >200,000/mm^3.

[redacted]

In these clinical studies, discontinuation due to adverse events, regardless of causality, was observed in 11.3% of patients.

The most frequently reported adverse drug reactions were thrombocytopenia and anaemia.

Haematological adverse drug reactions (any Common Terminology Criteria for Adverse Events [CTCAE] grade) included anaemia (82.4%), thrombocytopenia (69.8%) and neutropenia (16.6%).

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (21.3%), dizziness (15.3%) and headache (14.0%).

The three most frequent non-haematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (19.9%) and hypercholesterolaemia (16.9%). In phase 3 clinical studies in MF, neither CTCAE grade 3 or 4 hypercholesterolaemia, raised aspartate aminotransferase nor CTCAE grade 4 raised alanine aminotransferase were observed.

Long-term safety: As expected with an extended follow-up period, the cumulative frequency of some adverse events increased in the evaluation of the 3 -year follow-up safety data (median duration of exposure of 33.2 months in COMFORT-I and COMFORT-II for patients initially randomised to ruxolitinib) from 457 patients with myelofibrosis treated with ruxolitinib during the randomised and extension periods of the two pivot al phase 3 studies. This evaluation included data from patients that were initially randomised to ruxolitinib (N=301) and patients that received ruxolitinib after crossing over from control treatment arms (N=156). With these updated data, therapy discontinuation due to adverse events was observed in 17.1% of patients treated with ruxolitinib.

Polycythaemia vera

The safety of Jakavi was assessed in 110 patients with PV in an open-label, randomised, controlled phase 3 RESPONSE study. The adverse drug reactions listed below reflect the initial study period (up to week 32) with equivalent exposure to ruxolitinib and Best Available Therapy (BAT), corresponding to a median duration of exposure to Jakavi of 7.8 months. The mean age of patients receiving Jakavi was around 60 years.

Discontinuation due to adverse events, regardless of causality, was observed in 3.6% of patients treated with Jakavi and 1.8% of patients treated with best available therapy.

Haematological adverse reactions (any CTCAE grade) included anaemia (43.6%) and thrombocytopenia (24.5%). Anaemia or thrombocytopenia CTCAE grade 3 and 4 were reported in respectively 1.8% or 5.5%.

The three most frequent non-haematological adverse reactions were dizziness (15.5%), constipation (8.2%) and herpes zoster (6.4%).

The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) were hypercholesterolaemia (30.0%), raised alanine aminotransferase (22.7%) and raised aspartate aminotransferase (20.9%). These were all CTCAE grade 1 and 2 with the exception of one CTCAE grade 3 raised alanine aminotransferase event.

[redacted]

Long-term safety: Patients had a median duration of exposure to Jakavi of 18.6 months (range 0.3 to 35.9 months). With longer exposure, frequency of adverse events increased; howev er no new safety findings emerged. When adjusted for exposure, the adverse event rates were generally comparable with those observed during the initial study period.

Tabulated summary of adverse drug reactions from clinical studies

In the clinical study programme the severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1 = mild, grade 2 = moderate, grade 3 = severe and grade 4=life-threatening.

Adverse drug reactions from clinical studies (Table 14-8) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 14-8 Frequency category of adverse drug reactions reported in the phase 3 studies (COMFORT-I, COMFORT-II, RESPONSE)

Adverse drug reaction	Frequency category for MF patients	Frequency category for PV patients
Infections and infestations		
Urinary tract infections[a,d]	Very common	Common
Herpes zoster[a,d]	Common	Common
Tuberculosis[e]	Uncommon	-
Blood and lymphatic system disorders[b,d]		
Anaemia[b]	-	-
CTCAE[c] grade 4 (<6.5g/dl)	Very common	Uncommon
CTCAE[c] grade 3 (<8.0 – 6.5g/dl)	Very common	Uncommon
Any CTCAE[c] grade	Very common	Very common
Thrombocytopenia[b]		
CTCAE[c] grade 4 (<25,000/mm^3)	Common	Uncommon
CTCAE[c] grade 3 (50,000 – 25,000/mm^3)	Common	Common
Any CTCAE[c] grade	Very common	Very common
Neutropenia[b]		
CTCAE[c] grade 4 (<500/mm^3)	Common	-
CTCAE[c] grade 3 (<1,000 – 500/mm^3)	Common	-
Any CTCAE[c] grade	Very common	-

[redacted]

Adverse drug reaction	Frequency category for MF patients	Frequency category for PV patients
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)	Very common	Very common
Intracranial bleeding	Common	-
Gastrointestinal bleeding	Common	-
Bruising	Very common	Very common
Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)	Common	Very common
Metabolism and nutrition disorders		
Weight gain[a]	Very common	Common
Hypercholesterolaemia[b] CTCAE[c] grade 1 and 2	Very common	Very common
Hypertriglyceridaemia[b] CTCAE[c] grade 1	-	Very common
Nervous system disorders		
Dizziness[a]	Very common	Very common
Headache[a]	Very common	-
Gastrointestinal disorders		
Flatulence[a]	Common	-
Constipation[a]	-	Common
Hepatobiliary disorders		
Raised alanine aminotransferase[b]		
CTCAE[c] grade 3 (> 5x – 20 x ULN)	Common	Uncommon
Any CTCAE[c] grade	Very common	Very common
Raised aspartate aminotransferase[b]		
Any CTCAE[c] grade	Very common	Very common
Vascular disorders		
Hypertension[a]	-	Very common

[a]Frequency is based on adverse event data.
- A subject with multiple occurrence of an adverse drug reaction (ADR) is counted only once in that ADR category.
- ADRs reported are on treatment or up to 28 days post treatment end date.

[b]Frequency is based on laboratory values.
- A subject with multiple occurrences of an ADR is counted only once in that ADR category.
- ADRs reported are on treatment or up to 28 days post treatment end date.

[c]Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening

[d]These ADRs are discussed in the text.

[e]Frequency is based on all patients exposed to ruxolitinib in clinical studies (N=4755)

[redacted]

Upon discontinuation, MF patients may experience a return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In clinical studies in MF the total symptom score for MF symptoms gradually returned to baseline value within 7 days after dose discontinuation (see section 4.4).

Description of selected adverse drug reactions

Anaemia

In phase 3 clinical studies in MF, median time to onset of first CTCAE grade 2 or higher anaemia was 1.5 months. One patient (0.3%) discontinued treatment because of anaemia.

In patients receiving Jakavi mean decreases in haemoglobin reached a nadir of approximately 10 g/litre below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 5 g/litre below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy.

In the randomised, placebo-controlled study COMFORT-I 60.6% of Jakavi-treated MF patients and 37.7% of placebo-treated MF patients received red blood cell transfusions during randomised treatment. In the COMFORT-II study the rate of packed red blood cell transfusions was 53.4% in the Jakavi arm and 41.1% in the best available therapy arm.

In the randomised period of the pivotal studies, anaemia was less frequent in PV patients than in MF patients (43.6% versus 82.4%). In the PV population, the CTCAE grade 3 and 4 events were reported in 1.8%, while in the MF patients the frequency was 42.56%.

Thrombocytopenia

In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm^3 was 14 days. During the randomised period, platelet transfusions were administered to 4.7% of patients receiving Jakavi and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakavi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm^3 to 200,000/mm^3 before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm^3 (64.2% versus 38.5%).

In the randomised period of the pivotal studies, the rate of patients experiencing thrombocytopenia was lower in PV (24.5%) patients compared to MF (69.8%) patients. The frequency of severe (i.e. CTCAE grade 3 and 4) thrombocytopenia was lower in PV (5.5%) than in MF (11.6%) patients.

Neutropenia

In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 neutropenia, the median time to onset was 12 weeks. During the randomised period, dose holding or reductions due to neutropenia were reported in 1.0% of patients, and 0.3% of patients discontinued treatment because of neutropenia.

[redacted]

In the randomised period of the pivotal study in PV patients, neutropenia was reported in two patients (1.8%) of which one patient developed CTCAE grade 4 neutropenia.

Bleeding

In the phase 3 pivotal studies in MF bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 32.6% of patients exposed to Jakavi and 23.2% of patients exposed to the reference treatments (placebo or best available therapy). The frequency of grade 3-4 events was similar for patients treated with Jakavi or reference treatments (4.7% versus 3.1%). Most of the patients with bleeding events during the treatment reported bruising (65.3%). Bruising events were more frequently reported in patients taking Jakavi compared with the reference treatments (21.3% versus 11.6%). Intracranial bleeding was reported in 1% of patients exposed to Jakavi and 0.9% exposed to reference treatments. Gastrointestinal bleeding was reported in 5.0% of patients exposed to Jakavi compared to 3.1% exposed to reference treatments. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage and haematuria) were reported in 13.3% of patients treated with Jakavi and 10.3% treated with reference treatments.

In the randomised period of the pivotal study in PV patients, bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 20% of patients treated with Jakavi and 15.3% patients receiving best available therapy. Bruising was reported in similar frequencies in Jakavi and BAT arms (10.9% versus 8.1%). No intracranial bleeding or gastrointestinal haemorrhage events were reported in patients receiving Jakavi. One patient treated with Jakavi experienced a grade 3 bleeding event (post-procedural bleeding); no grade 4 bleeding was reported. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage, gingival bleeding) were reported in 11.8% of patients treated with Jakavi and 6.3% treated with best available therapy.

Infections

In the phase 3 pivotal studies in MF, grade 3 or 4 urinary tract infection was reported in 1.0% of patients, herpes zoster in 4.3% and tuberculosis in 1.0%. In phase 3 clinical studies sepsis was reported in 3.0% of patients. An extended follow-up of patients treated with ruxolitinib showed no trends towards an increase in the rate of sepsis over time.

In the randomised period of the pivotal study in PV patients, one (0.9%) CTCAE grade 3 and no grade 4 urinary tract infection was reported. The rate of herpes zoster was slightly higher in PV (6.4%) patients than in MF (4.0%) patients. There was one report of CTCAE grade 3 post-herpetic neuralgia amongst the PV patients.

Increased systolic blood pressure

In the phase 3 pivotal clinical studies in MF an increase in systolic blood pressure of 20 mmHg or more from baseline was recorded in 31.5% of patients on at least one visit compared with 19.5% of the control-treated patients. In COMFORT-I (MF patients) the mean increase from baseline in systolic BP was 0 -2 mmHg on Jakavi versus a decrease of 2-5 mmHg in the placebo arm. In COMFORT-II mean values showed little difference between the ruxolitinib-treated and the control-treated MF patients.

In the randomised period of the pivotal study in PV patients, the mean systolic blood pressure increased by 0.65 mmHg in the Jakavi arm versus a decrease of 2 mmHg in the BAT arm.

[redacted]

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known antidote for overdoses with Jakavi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anaemia and thrombocytopenia. Appropriate supportive treatment should be given.

Haemodialysis is not expected to enhance the elimination of ruxolitinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE18

Mechanism of action

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 (IC_{50} values of 3.3 nM and 2.8 nM for JAK1 and JAK2 enzymes, respectively). These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.

Myelofibrosis and polycythaemia vera are myeloproliferative neoplasms known to be associated with dysregulated JAK1 and JAK2 signalling. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK -STAT pathway, gain-of-function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signalling regardless of JAK2V617F mutation status. Activating mutations in JAK2 (V617F or exon 12) are found in >95% of PV patients.

Ruxolitinib inhibits JAK-STAT signalling and cell proliferation of cytokine-dependent cellular models of haematological malignancies, as well as of Ba/F3 cells rendered cytokine-independent by expressing the JAK2V617F mutated protein, with IC_{50} ranging from 80-320 nM.

Pharmacodynamic effects

Ruxolitinib inhibits cytokine-induced STAT3 phosphorylation in whole blood from healthy subjects, MF patients and PV patients. Ruxolitinib resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 8 hours in both healthy subjects and MF patients, indicating no accumulation of either parent or active metabolites.

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNFα, IL-6 and CRP in subjects with MF were decreased following treatment with ruxolitinib.

[redacted]

MF patients did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with PV also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with ruxolitinib.

In a thorough QT study in healthy subjects, there was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up to a supratherapeutic dose of 200 mg, indicating that ruxolitinib has no effect on cardiac repolarisation.

Clinical efficacy and safety

Myelofibrosis

Two randomised phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with MF (primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis). In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate -2 or high risk based on the International Working Group (IWG) Consensus Criteria. The starting dose of Jakavi was based on platelet count.

COMFORT-I was a double-blind, randomised, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. The primary efficacy endpoint was proportion of subjects achieving ≥35% reduction from baseline in spleen volume at week 24 as measured by Magnetic Resonance Imaging (MRI) or Computed Tomography (CT).

Secondary endpoints included duration of maintenance of a ≥35% reduction from baseline in spleen volume, proportion of patients who had ≥50% reduction in total symptom score, changes in total symptom scores from baseline to week 24, as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary, and overall survival.

COMFORT-II was an open-label, randomised study in 219 patients. Patients were randomised 2:1 to Jakavi versus best available therapy. In the best available therapy arm, 47% of patients received hydroxyurea and 16% of patients received glucocorticoids. The primary efficacy endpoint was proportion of patients achieving ≥35% reduction from baseline in spleen volume at week 48 as measured by MRI or CT.

Secondary endpoints included proportion of patients achieving a ≥35% reduction of spleen volume from baseline at week 24 and duration of maintenance of a ≥35% reduction from baseline spleen volume.

In COMFORT-I and COMFORT-II, patient baseline demographics and disease characteristics were comparable between the treatment arms.

Table 14-9 Percentage of patients with ≥35% reduction from baseline in spleen volume at week 24 in COMFORT-I and at week 48 in COMFORT-II (ITT)

	COMFORT-I		**COMFORT-II**	
	Jakavi (N=155)	**Placebo (N=153)**	**Jakavi (N=144)**	**Best available therapy (N=72)**
Time points	Week 24		Week 48	

[redacted]

Number (%) of subjects with spleen volume reduced by ≥35%	65 (41.9)	1 (0.7)	41 (28.5)	0
95% confidence intervals	34.1, 50.1	0, 3.6	21.3, 36.6	0.0, 5.0
p-value	<0.0001		<0.0001	

A significantly higher proportion of patients in the Jakavi group achieved ≥35% reduction from baseline in spleen volume (Table 14-9) regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (primary myelofibrosis, post-polycythaemia vera myelofibrosis, post-essential thrombocythaemia myelofibrosis).

Table 14-10 Percentage of patients with ≥35% reduction from baseline in spleen volume by JAK mutation status (safety set)

	COMFORT-I				**COMFORT-II**			
	Jakavi		**Placebo**		**Jakavi**		**Best available therapy**	
JAK mutation status	Positive (N=113) n (%)	Negative (N=40) n (%)	Positive (N=121) n (%)	Negative (N=27) n (%)	Positive (N=110) n (%)	Negative (N=35) n (%)	Positive (N=49) n (%)	Negative (N=20) n (%)
Number (%) of subjects with spleen volume reduced by ≥35%	54 (47.8)	11 (27.5)	1 (0.8)	0	36 (32.7)	5 (14.3)	0	0
Time point	After 24 weeks				After 48 weeks			

The probability of maintaining spleen response (≥35% reduction) on Jakavi for at least 24 weeks was 89% in COMFORT-I and 87% in COMFORT-II; 52% maintained spleen responses for at least 48 weeks in COMFORT-II.

In COMFORT-I, 45.9% subjects in the Jakavi group achieved a ≥50% improvement from baseline in the week 24 total symptom score (measured using MFSAF diary v2.0), as compared to 5.3% in the placebo group (p<0.0001 using chi-square test). The mean change in the global health status at week 24, as measured by EORTC QLQ C30 was +12.3 for Jakavi and -3.4 for placebo (p<0.0001).

In COMFORT-I, after a median follow-up of 34.3 months, the death rate in patients randomised to the ruxolitinib arm was 27.1% versus 35.1% in patients randomised to placebo; HR 0.687; 95% CI 0.459-1.029; p=0.0668.

In COMFORT-II, after a median follow-up of 34.7 months, the death rate in patients randomised to ruxolitinib was 19.9% versus 30.1% in patients randomised to best available treatment (BAT); HR 0.48; 95% CI 0.28-0.85; p=0.009. In both studies, the lower death rates noted in the ruxolitinib arm were predominantly driven by the results obtained in the post polycythaemia vera and post essential thrombocythaemia subgroups.

[redacted]

Polycythaemia vera

A randomised, open-label, active-controlled phase 3 study (RESPONSE) was conducted in 222 patients with PV who were resistant to or intolerant of hydroxyurea defined based on the European LeukemiaNet (ELN) international working group published criteria. 110 patients were randomised to the ruxolitinib arm and 112 patients to the BAT arm. The starting dose of Jakavi was 10 mg twice daily. Doses were then adjusted in individual patients based on tolerability and efficacy with a maximum dose of 25 mg twice daily. BAT was selected by the investigator on a patient-by-patient basis and included hydroxyurea (59.5%), interferon/pegylated interferon (11.7%), anagrelide (7.2%), pipobroman (1.8%) and observation (15.3%).

Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. Most patients (>80%) had received at least two phlebotomies in the last 24 weeks prior to screening. Comparative data regarding long-term survival and incidence of disease complications is missing.

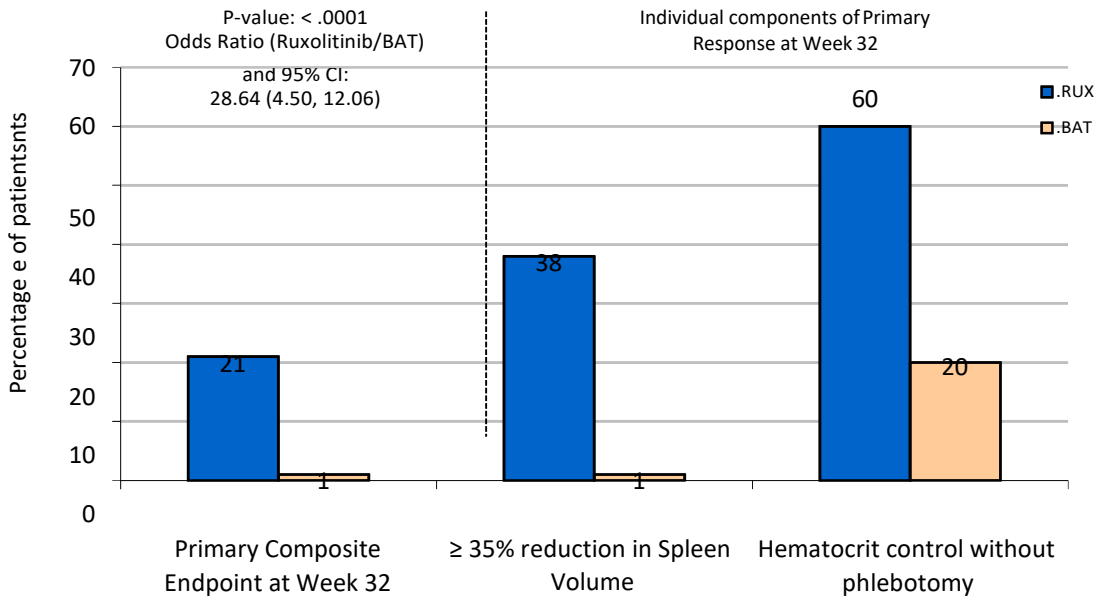
The primary composite endpoint was the proportion of patients achieving both an absence of phlebotomy eligibility (HCT control) and a ≥35% reduction in spleen volume from baseline at week 32. Phlebotomy eligibility was defined as a confirmed HCT of >45%, i.e. at least 3 percentage points higher than the HCT obtained at baseline or a confirmed HCT of >48%, depending on which was lower. Key secondary endpoints included the proportion of pa tients who achieved the primary endpoint and remained free from progression at week 48, as well as the proportion of patients achieving complete haematological remission at week 32.

The study met its primary objective and a higher proportion of patients in the Jakavi group achieved the primary composite endpoint and each of its individual components. Significantly more patients treated with Jakavi (20.9%) achieved a primary response ($p<0.0001$) compared to BAT (0.9%). Haematocrit control was achieved in 60% of patients in the Jakavi arm compared to 19.6% in the BAT arm and a ≥35% reduction in spleen volume was achieved in 38.2% of patients in the Jakavi arm compared to 0.9% in the BAT arm (Figure 14-3). 94 (83.9%) patients randomised to the BAT arm crossed over to ruxolitinib treatment at Week 32 or after, limiting the comparison between the two arms after Week 32.

Both key secondary endpoints were also met. The proportion of patients achieving a complete haematological remission was 23.6% on Jakavi compared to 8.9% on BAT ($p=0.0028$) and the proportion of patients achieving a durable primary response at week 48 was 19.1% on Jakavi and 0.9% on BAT.($p<0.0001$).

[redacted]

Figure 14-3 Patients achieving the primary endpoint and components of the primary endpoint at week 32



Symptom burden was assessed using the MPN-SAF total symptom score (TSS) electronic patient diary, which consisted of 14 questions. At week 32, 49% and 64% of patients treated with ruxolitinib achieved a ≥50% reduction in TSS-14 and TSS-5, respectively, compared to only 5% and 11% of patients on BAT.

Treatment benefit perception was measured by the Patient Global Impress ion of Change (PGIC) questionnaire. 66% of patients treated with ruxolitinib compared to 19% treated with BAT reported an improvement as early as four weeks after beginning treatment. Improvement in perception of treatment benefit was also higher in patients treated with ruxolitinib at week 32 (78% versus 33%).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Jakavi in all subsets of the paediatric population for the treatment of MF (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Ruxolitinib is a Biopharmaceutical Classification System (BCS) class 1 compound, with high permeability, high solubility and rapid dissolution characteristics. In clinic al studies, ruxolitinib is rapidly absorbed after oral administration with maximal plasma concentration (C_{max}) achieved approximately 1 hour post-dose. Based on a human mass balance study, oral absorption of ruxolitinib, as ruxolitinib or metabolites formed under first-pass, is 95% or

[redacted]

greater. Mean ruxolitinib C_{max} and total exposure (AUC) increased proportionally over a single dose range of 5-200 mg. There was no clinically relevant change in the

[redacted]

pharmacokinetics of ruxolitinib upon administration with a high-fat meal. The mean C_{max} was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) on dosing with a high-fat meal.

Distribution

The mean volume of distribution at steady state is approximately 75 litres in MF and PV patients. At clinically relevant concentrations of ruxolitinib, binding to plasma proteins *in vitro* is approximately 97%, mostly to albumin. A whole body autoradiography study in rats has shown that ruxolitinib does not penetrate the blood-brain barrier.

Biotransformation

Ruxolitinib is mainly metabolised by CYP3A4 (>50%), with additional contribution from CYP2C9. Parent compound is the predominant entity in human plasma, representing approximately 60% of the drug-related material in circulation. Two major and active metabolites are present in plasma representing 25% and 11% of parent AUC. These metabolites have one half to one fifth of the parent JAK-related pharmacological activity. The sum total of all active metabolites contributes to 18% of the overall pharm acodynamics of ruxolitinib. At clinically relevant concentrations, ruxolitinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 based on *in vitro* studies. *In vitro* data indicate that ruxolitinib may inhibit P-gp and BCRP.

Elimination

Ruxolitinib is mainly eliminated through metabolism. The mean elimination half -life of ruxolitinib is approximately 3 hours. Following a single oral dose of [^{14}C]-labelled ruxolitinib in healthy adult subjects, elimination was predominately through metabolism, with 74% of radioactivity excreted in urine and 22% via faeces. Unchanged parent substance accounted for less than 1% of the excreted total radioactivity.

Linearity/non-linearity

Dose proportionality was demonstrated in the single and multiple dose studies.

Special populations

Effects of age, gender or race

Based on studies in healthy subjects, no relevant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in MF patients, no relationship was apparent between oral clearance and patient age or race. The predicted oral clearance was 17.7 l/h in women and 22.1 l/h in men, with 39% inter-subject variability in MF patients. Clearance was 12.7 l/h in PV patients, with a 42% inter-subject variability and no relationship was apparent between oral clearance and gender, patient age or race, based on a population pharmacokinetic evaluation in PV patients.

Paediatric population

The safety and effectiveness of Jakavi in paediatric patients have not been established (see section 5.1, “Paediatric population”).

[redacted]

Renal impairment

Renal function was determined using both Modification of Diet in Renal Disease (MDRD) and urinary creatinine. Following a single ruxolitinib dose of 25 mg, the exposure of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites tended to increase with increasing severity of renal impairment, and were most markedly increased in the subjects with severe renal impairment. It is unknown whether the increased metabolite exposure is of safety concern. A dose modification is recommended in patients with severe renal impairment and end-stage renal disease (see section 4.2). Dosing only on dialysis days reduces the metabolite exposure, but also the pharmacodynamic effect, especially on the days between dialysis.

Hepatic impairment

Following a single ruxolitinib dose of 25 mg in patients with varying degrees of hepatic impairment, the mean AUC for ruxolitinib was increased in patients with mild, moderate and severe hepatic impairment by 87%, 28% and 65%, respectively, compared to patients with normal hepatic function. There was no clear relationship between AUC and the degree of hepatic impairment based on Child-Pugh scores. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1 -5.0 hours versus 2.8 hours). A dose reduction of approximately 50% is recommended for patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Ruxolitinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity and reproductive toxicity studies and in a carcinogenicity study. Target organs associated with the pharmacological action of ruxolitinib in repeated dose studies include bone marrow, peripheral blood and lymphoid tissues. Infections generally associated with immunosuppression were noted in dogs. Adverse decreases in blood pressure along with increases in heart rate were noted in a dog telemetry study, and an adverse decrease in minute volume was noted in a respiratory study in rats. The margins (based on unbound C_{max}) at the non-adverse level in the dog and rat studies were 15.7-fold and 10.4-fold greater, respectively, than the maximum human recommended dose of 25 mg twice daily. No effects were noted in an evaluation of the neuropharmacological effects of ruxolitinib.

Ruxolitinib decreased foetal weight and increased post-implantation loss in animal studies. There was no evidence of a teratogenic effect in rats and rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans. No effects were noted on fertility. In a pre- and post-natal development study, a slightly prolonged gestation period, reduced number of implantation sites, and reduced number of pups delivered were observed. In the pups, decreased mean initial body weights and short period of decreased mean body weight gain were observed. In lactating rats, ruxolitinib and/or its metabolites were excreted into the milk with a concentration that was 13-fold higher than the maternal plasma concentration. Ruxolitinib was not mutagenic or clastogenic. Ruxolitinib was not carcinogenic in the Tg.rasH2 transgenic mouse model.

[redacted]

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Cellulose, microcrystalline
- Magnesium stearate
- Silica, colloidal anhydrous
- Sodium starch glycolate (Type A)
- Povidone
- Hydroxypropylcellulose
- Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PCTFE/Aluminium blister packs containing 14 or 56 tablets or multipacks containing 168 (3 packs of 56) tablets.

Not all pack sizes or types may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/007-009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23.08.2012

[redacted]

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

[redacted]

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 20 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg ruxolitinib (as phosphate).

Excipient with known effect:

Each tablet contains 285.80 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Elongated curved white to almost white tablets of approximately 16.5 x 7.4 mm with "NVR" debossed one one side and "L20" debossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Myelofibrosis (MF)

Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

Polycythaemia vera (PV)

Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

4.2 Posology and method of administration

Jakavi treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.

A complete blood cell count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi.

Complete blood count, including a white blood cel l count differential, should be monitored every 2-4 weeks until Jakavi doses are stabilised, and then as clinically indicated (see section 4.4).

[redacted]

Posology

Starting dose

The recommended starting dose of Jakavi in myelofibrosis is 15 mg twice daily for patients with a platelet count between 100,000/mm^3 and 200,000/mm^3 and 20 mg twice daily for patients with a platelet count of >200,000/mm^3. The recommended starting dose of Jakavi in polycythaemia vera is 10 mg given orally twice daily.

There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm^3 and <100,000/mm^3. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously.

Dose modifications

Doses may be titrated based on safety and efficacy. Treatment should be discontinued for platelet counts less than 50,000/mm^3 or absolute neutrophil counts less than 500/mm^3. In PV, treatment should also be interrupted when haemoglobin is below 8 g/dl. After recovery of blood counts above these levels, dosing may be re-started at 5 mg twice daily and gradually increased based on careful monitoring of complete blood cell count, including a white blood cell count differential.

Dose reductions should be considered if the platelet count decreases below 100,000/mm^3, with the goal of avoiding dose interruptions for thrombocytopenia. In PV, dose reductions should also be considered if haemoglobin decreases below 12 g/dl and is recommended if it decreases below 10 g/dl.

If efficacy is considered insufficient and blood counts are adequate, doses may be increased by a maximum of 5 mg twice daily, up to the maximum dose of 25 mg twice daily.

The starting dose should not be increased within the first four weeks of tre atment and thereafter no more frequently than at 2-week intervals.

The maximum dose of Jakavi is 25 mg twice daily.

Dose adjustment with concomitant strong CYP3A4 inhibitors or fluconazole

When Jakavi is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily (see section 4.5). Avoid the concomitant use of Jakavi with fluconazole doses greater than 200 mg daily.

More frequent monitoring (e.g. twice a week) of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended while on strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes.

Special populations

Renal impairment

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

In patients with severe renal impairment (creatinine clearance less than 30 ml/min) the recommended starting dose based on platelet count for MF patients should be reduced by approximately 50% to be administered twice daily. The recommended starting dose for PV

[redacted]

patients with severe renal impairment is 5 mg twice daily. Patients should be carefully monitored with regard to safety and efficacy during Jakavi treatment.

There are limited data to determine the best dosing options for patients with end -stage renal disease (ESRD) on haemodialysis. Pharmacokinetic/pharmacodynamic simulations based on available data in this population suggest that the starting dose for MF patients with ESRD on haemodialysis is a single dose of 15 -20 mg or two doses of 10 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. A single dose of 15 mg is recommended for MF patients with platelet count between 100,000/mm^3 and 200,000/mm^3. A single dose of 20 mg or two doses of 10 mg given 12 hours apart is recommended for MF patients with platelet count of >200,000/mm^3. Subsequent doses (single administration or two doses of 10 mg given 12 hours apart) should be administered only on haemodialysis days following each dialysis session.

The recommended starting dose for PV patients with ESRD on haemodialysis is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. These dose recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration (see section 5.2).

Hepatic impairment

In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice daily. Subsequent doses should be adjusted based on careful monitoring of safety and efficacy. Patients diagnosed with hepatic impairment while receiving Jakavi should have complete blood counts, including a white blood cell count differential, monitored at least every one to two weeks for the first 6 weeks after initiation of therapy with Jakavi and as clinically indicated thereafter once their liver function and blood counts have been stabilised. Jakavi dose can be ti trated to reduce the risk of cytopenia.

Older people (≥65 years)

No additional dose adjustments are recommended for older people.

Paediatric population

The safety and efficacy of Jakavi in children aged up to 18 years have not been established. No data are available (see section 5.1).

Treatment discontinuation

Treatment may be continued as long as the benefit-risk remains positive. However the treatment should be discontinued after 6 months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy.

It is recommended that, for patients who have demonstrated some degree of clinical improvement, ruxolitinib therapy be discontinued if they sustain an increase in their spleen length of 40% compared with baseline size (roughly equivalent to a 25% increase in spleen volume) and no longer have tangible improvement in disease-related symptoms.

[redacted]

Method of administration

Jakavi is to be taken orally, with or without food.

If a dose is missed, the patient should not take an addit ional dose, but should take the next usual prescribed dose.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Myelosuppression

Treatment with Jakavi can cause haematological adverse drug reactions, including thrombocytopenia, anaemia and neutropenia. A complete blood count, including a white blood cell count differential, must be performed before initiating therapy with Jakavi. Treatment should be discontinued in patients with platelet count less than 50,000/mm ^{3} or absoute neutrophil count less than 500/mm^3 (see section 4.2).

It has been observed that patients with low platelet counts (<200,000 /mm^3) at the start of therapy are more likely to develop thrombocytopenia during treatment.

Thrombocytopenia is generally reversible and is usually managed by reducing the dose or temporarily withholding Jakavi (see sections 4.2 and 4.8). However, platelet transfusions may be required as clinically indicated.

Patients developing anaemia may require blood transfusions. Dose modifications or interruption for patients developing anaemia may also be considered.

Patients with a haemoglobin level below 10.0 g/dl at the beginning of the treatment have a higher risk of developing a haemoglobin level below 8.0 g/dl during treatment compared to patients with a higher baseline haemoglobin level (79.3% versus 30.1%). More frequent monitoring of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended for patients with baseline haemoglobin below 10.0 g/dl.

Neutropenia (absolute neutrophil count <500) was generally reversible and was managed by temporarily withholding Jakavi (see sections 4.2 and 4.8).

Complete blood counts should be monitored as clinically indicated and dose adjusted as required (see sections 4.2 and 4.8).

Infections

Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Tuberculosis has been reported in patients receiving Jakavi for MF. Before starting treatment, patients should be evaluated for active and inactive (“latent”) tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Prescribers are reminded of the risk

[redacted]

of false negative tuberculin skin test results, especially in patients wh o are severely ill or immunocompromised. Jakavi therapy should not be started until active serious infections have resolved. Physicians should carefully observe patients receiving Jakavi for signs and symptoms of infections and initiate appropriate treatment promptly (see section 4.8).

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakavi. The effect of Jakavi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

Herpes zoster

Physicians should educate patients about early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported with Jakavi treatment for MF. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.

Non-melanoma skin cancer

Non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and Merkel cell carcinoma, have been reported in patients treated with ruxolitinib. Most of these patients had histories of extended treatment with hydroxyurea and prior NMSC or pre -malignant skin lesions. A causal relationship to ruxolitinib has not been established. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Special populations

Renal impairment

The starting dose of Jakavi should be reduced in patients with severe renal impairment . For patients with end-stage renal disease on haemodialysis the starting dose for MF patients should be based on platelet counts (see section 4.2). Subsequent doses (single dose of 20 mg or two doses of 10 mg given 12 hours apart in MF patients; single dose of 10 mg or two doses of 5 mg given 12 hours apart in PV patients) should be administered only on haemodialysis days following each dialysis session. Additional dose modifications should be made with careful monitoring of safety and efficacy (see sections 4.2 and 5.2).

Hepatic impairment

The starting dose of Jakavi should be reduced by approximately 50% in patients with hepatic impairment. Further dose modifications should be based on the safety and efficacy of the medicinal product (see sections 4.2 and 5.2).

Interactions

[redacted]

If Jakavi is to be co-administered with strong CYP3A4 inhibitors or dual inhibitors of CYP3A4 and CYP2C9 enzymes (e.g. fluconazole), the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily (for monitoring frequency see sections 4.2 and 4.5).

The concomitant use of cytoreductive therapies or haematopoietic growth factors with Jakavi has not been studied. The safety and efficacy of these co -administrations are not known (see section 4.5).

Withdrawal effects

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

Excipients

Jakavi contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Ruxolitinib is eliminated through metabolism catalysed by CYP3A4 and CYP2C9. Thus, medicinal products inhibiting these enzymes can give rise to increased ruxolitinib exposure.

Interactions resulting in dose reduction of ruxolitinib

CYP3A4 inhibitors

Strong CYP3A4 inhibitors (such as, but not limited to, boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole)

In healthy subjects co-administration of Jakavi (10 mg single dose) with a strong CYP3A4 inhibitor, ketoconazole, resulted in ruxolitinib C_{max} and AUC that were higher by 33% and 91%, respectively, than with ruxolitinib alone. The half-life was prolonged from 3.7 to 6.0 hours with concurrent ketoconazole administration.

When administering Jakavi with strong CYP3A4 inhibitors the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily. Patients should be closely monitored (e.g. twice weekly) for cytopenias and dose titrated based on safety and efficacy (see section 4.2).

Dual CYP2C9 and CYP3A4 inhibitors

50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole). Avoid the concomitant use of Jakavi with fluconazole doses greater than 200 mg daily.

[redacted]

Enzyme inducers

CYP3A4 inducers (such as, but not limited to, avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St.John's wort (Hypericum perforatum))

Patients should be closely monitored and the dose titrated based on safety and efficacy (see section 4.2).

In healthy subjects given ruxolitinib (50 mg single dose) following the potent CYP3A4 inducer rifampicin (600 mg daily dose for 10 days), ruxolitinib AUC was 70% lower than after administration of Jakavi alone. The exposure of ruxolitinib active metabolites was unchanged. Overall, the ruxolitinib pharmacodynamic activity was similar, suggesting the CYP3A4 induction resulted in minimal effect on the pharmacodynamics. However, this could be related to the high ruxolitinib dose resulting in pharmacodynamic effects near E_{max}. It is possible that in the individual patient, an increase of the ruxolitinib dose is needed when initiating treatment with a strong enzyme inducer.

Other interactions to be considered affecting ruxolitinib

Mild or moderate CYP3A4 inhibitors (such as, but not limited to, ciprofloxacin, erythromycin, amprenavir, atazanavir, diltiazem, cimetidine)

In healthy subjects co-administration of ruxolitinib (10 mg single dose) with erythromycin 500 mg twice daily for four days resulted in ruxolitinib C_{max} and AUC that were higher by 8% and 27%, respectively, than with ruxolitinib alone.

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

Effects of ruxolitinib on other medicinal products

Substances transported by P-glycoprotein or other transporters

Ruxolitinib may inhibit P-glycoprotein and breast cancer resistance protein (BCRP) in the intestine. This may result in increased sytemic exposure of substrates of these transporters, such as dabigatran etexilate, ciclosporin, rosuvastatin and potentially digoxin. Therapeutic drug monitoring (TDM) or clinical monitoring of the affected substance is advised.

It is possible that the potential inhibition of P-gp and BCRP in the intestine can be minimised if the time between administrations is kept apart as long as possible.

Haematopoietic growth factors

The concurrent use of haematopoietic growth factors and Jakavi has not been studied. It is not known whether the Janus Associated Kinase (JAK) inhibition by Jakavi reduces the efficacy of the haematopoietic growth factors or whether the haematopoietic growth factors affect the efficacy of Jakavi (see section 4.4).

Cytoreductive therapies

The concomitant use of cytoreductive therapies and Jakavi has not been studied. The safety and efficacy of this co-administration is not known (see section 4.4).

A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral

[redacted]

CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is anticipated when combining them with Jakavi. Another study in healthy subjects indicated that Jakavi does not affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

4.6 Fertility, pregnancy and lactation

Pregnancy and contraception in females

There are no data from the use of Jakavi in pregnant women.

Animal studies have shown that ruxolitinib is embryotoxic and foetotoxic. Teratogenicity was not observed in rats or rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans (see section 5.3). The potential risk for humans is unknown. As a precautionary mea sure, the use of Jakavi during pregnancy is contraindicated (see section 4.3). Women of child-bearing potential should use effective contraception during the treatment with Jakavi. In case pregnancy should occur during treatment with Jakavi, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the foetus (see section 5.3).

Breast-feeding

Jakavi must not be used during breast-feeding (see section 4.3) and breast-feeding should therefore be discontinued when treatment is started. It is unknown whether ruxolitinib and/or its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. Available pharmacodynamic/toxicological data in animals have shown excretion of ruxolitinib and its metabolites in milk (see section 5.3).

Fertility

There are no human data on the effect of ruxolitinib on fertility. In animal studies, no effect on fertility was observed.

4.7 Effects on ability to drive and use machines

Jakavi has no or negligible sedating effect. However, patients who experience dizziness after the intake of Jakavi should refrain from driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety assessment was based on a total of 855 patients (with MF or PV) receiving Jakavi in phase 2 and 3 studies.

Myelofibrosis

In the randomised period of the two pivotal studies, COMFORT -I and COMFORT-II, the median duration of exposure to Jakavi was 10.8 months (range 0.3 to 23.5 months). The majority of patients (68.4%) were treated for at least 9 months. Of 301 patients, 111 (36.9%)

had a baseline platelet count of between 100,000/mm^3 and 200,000/mm^3 and 190 (63.1%) had a baseline platelet count of >200,000/mm^3.

In these clinical studies, discontinuation due to adverse events, regardless of causality, was observed in 11.3% of patients.

The most frequently reported adverse drug reactions were thrombocytopenia and anaemia.

Haematological adverse drug reactions (any Common Terminology Criteria for Adverse Events [CTCAE] grade) included anaemia (82.4%), thrombocytopenia (69.8%) and neutropenia (16.6%).

Anaemia, thrombocytopenia and neutropenia are dose-related effects.

The three most frequent non-haematological adverse drug reactions were bruising (21.3%), dizziness (15.3%) and headache (14.0%).

The three most frequent non-haematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (19.9%) and hypercholesterolaemia (16.9%). In phase 3 clinical studies in MF, neither CTCAE grade 3 or 4 hypercholesterolaemia, raised aspartate aminotransferase nor CTCAE grade 4 raised alanine aminotransferase were observed.

Long-term safety: As expected with an extended follow-up period, the cumulative frequency of some adverse events increased in the evaluation of the 3-year follow-up safety data (median duration of exposure of 33.2 months in COMFORT-I and COMFORT-II for patients initially randomised to ruxolitinib) from 457 patients with myelofibrosis treated with ruxolitinib during the randomised and extension periods of the two pivotal phase 3 studies. This evaluation included data from patients that were initially randomised to ruxolitinib (N=301) and patients that received ruxolitinib after crossing over from control treatment arms (N=156). With these updated data, therapy discontinuation due to adverse events was observed in 17.1% of patients treated with ruxolitinib.

Polycythaemia vera

The safety of Jakavi was assessed in 110 patients with PV in an open-label, randomised, controlled phase 3 RESPONSE study. The adverse drug reactions listed below reflect the initial study period (up to week 32) with equivalent exposure to ruxolitinib and Best Available Therapy (BAT), corresponding to a median duration of exposure to Jakavi of 7.8 months. The mean age of patients receiving Jakavi was around 60 years.

Discontinuation due to adverse events, regardless of causality, was observed in 3.6% of patients treated with Jakavi and 1.8% of patients treated with best available therapy.

Haematological adverse reactions (any CTCAE grade) included anaemia (43.6%) and thrombocytopenia (24.5%). Anaemia or thrombocytopenia CTCAE grade 3 and 4 were reported in respectively 1.8% or 5.5%.

The three most frequent non-haematological adverse reactions were dizziness (15.5%), constipation (8.2%) and herpes zoster (6.4%).

The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) were hypercholesterolaemia (30.0%), raised alanine aminotransferase (22.7%) and raised aspartate aminotransferase (20.9%). These were all CTCAE grade 1 and 2 with the exception of one CTCAE grade 3 raised alanine aminotransferase event.

Long-term safety: Patients had a median duration of exposure to Jakavi of 18.6 months (range 0.3 to 35.9 months). With longer exposure, frequency of adverse events increased; however

[redacted]

no new safety findings emerged. When adjusted for exposure, the adverse event rates were generally comparable with those observed during the initial study period.

Tabulated summary of adverse drug reactions from clinical studies

In the clinical study programme the severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1 = mild, grade 2 = moderate, grade 3 = severe and grade 4=life-threatening.

Adverse drug reactions from clinical studies (Table 14-11) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 14-11 Frequency category of adverse drug reactions reported in the phase 3 studies (COMFORT-I, COMFORT-II, RESPONSE)

Adverse drug reaction	Frequency category for MF patients	Frequency category for PV patients
Infections and infestations		
Urinary tract infections[a,d]	Very common	Common
Herpes zoster[a,d]	Common	Common
Tuberculosis[e]	Uncommon	-
Blood and lymphatic system disorders[b,d]		
Anaemia[b]	-	-
CTCAE[c] grade 4 (<6.5g/dl)	Very common	Uncommon
CTCAE[c] grade 3 (<8.0 – 6.5g/dl)	Very common	Uncommon
Any CTCAE[c] grade	Very common	Very common
Thrombocytopenia[b]		
CTCAE[c] grade 4 (<25,000/mm^3)	Common	Uncommon
CTCAE[c] grade 3 (50,000 – 25,000/mm^3)	Common	Common
Any CTCAE[c] grade	Very common	Very common
Neutropenia[b]		
CTCAE[c] grade 4 (<500/mm^3)	Common	-
CTCAE[c] grade 3 (<1,000 – 500/mm^3)	Common	-

[redacted]

Adverse drug reaction	Frequency category for MF patients	Frequency category for PV patients
Any CTCAE[c] grade	Very common	-
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)	Very common	Very common
Intracranial bleeding	Common	-
Gastrointestinal bleeding	Common	-
Bruising	Very common	Very common
Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)	Common	Very common
Metabolism and nutrition disorders		
Weight gain[a]	Very common	Common
Hypercholesterolaemia[b] CTCAE[c] grade 1 and 2	Very common	Very common
Hypertriglyceridaemia[b] CTCAE[c] grade 1	-	Very common
Nervous system disorders		
Dizziness[a]	Very common	Very common
Headache[a]	Very common	-
Gastrointestinal disorders		
Flatulence[a]	Common	-
Constipation[a]	-	Common
Hepatobiliary disorders		
Raised alanine aminotransferase[b]		
CTCAE[c] grade 3 (> 5x – 20 x ULN)	Common	Uncommon
Any CTCAE[c] grade	Very common	Very common
Raised aspartate aminotransferase[b]		
Any CTCAE[c] grade	Very common	Very common
Vascular disorders		
Hypertension[a]	-	Very common

[a]Frequency is based on adverse event data.
- A subject with multiple occurrence of an adverse drug reaction (ADR) is counted only once in that ADR category.
- ADRs reported are on treatment or up to 28 days post treatment end date.

[b]Frequency is based on laboratory values.
- A subject with multiple occurrences of an ADR is counted only once in that ADR category.
- ADRs reported are on treatment or up to 28 days post treatment end date.

[c]Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening

[d]These ADRs are discussed in the text.

[e]Frequency is based on all patients exposed to ruxolitinib in clinical studies (N=4755)

Upon discontinuation, MF patients may experience a return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In

[redacted]

clinical studies in MF the total symptom score for MF symptoms gradually returned to baseline value within 7 days after dose discontinuation (see section 4.4).

Description of selected adverse drug reactions

Anaemia

In phase 3 clinical studies in MF, median time to onset of first CTCAE grade 2 or higher anaemia was 1.5 months. One patient (0.3%) discontinued treatment because of anaemia.

In patients receiving Jakavi mean decreases in haemoglobin reached a nadir of approximately 10 g/litre below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 5 g/litre below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy.

In the randomised, placebo-controlled study COMFORT-I 60.6% of Jakavi-treated MF patients and 37.7% of placebo-treated MF patients received red blood cell transfusions during randomised treatment. In the COMFORT-II study the rate of packed red blood cell transfusions was 53.4% in the Jakavi arm and 41.1% in the best available therapy arm.

In the randomised period of the pivotal studies, anaemia was less frequent in PV patients than in MF patients (43.6% versus 82.4%). In the PV population, the CTCAE grade 3 and 4 events were reported in 1.8%, while in the MF patients the frequency was 42.56%.

Thrombocytopenia

In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm^3 was 14 days. During the randomised period, platelet transfusions were administered to 4.7% of patients receiving Jakavi and to 4.0% of patients receiving cont rol regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakavi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm ^{3} to 200,000/mm^3 before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm^3 (64.2% versus 38.5%).

In the randomised period of the pivotal studies, the rate of patients experiencing thrombocytopenia was lower in PV (24.5%) patients compared to MF (69.8%) patients. The frequency of severe (i.e. CTCAE grade 3 and 4) thrombocytopenia was lower in PV (5.5%) than in MF (11.6%) patients.

Neutropenia

In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 neutropenia, the median time to onset was 12 weeks. During the randomised period, dose holding or reductions due to neutropenia were reported in 1.0% of patients, and 0.3% of patients discontinued treatment because of neutropenia.

In the randomised period of the pivotal study in PV patients, neutropenia was reported in two patients (1.8%) of which one patient developed CTCAE grade 4 neutropenia.

Bleeding

In the phase 3 pivotal studies in MF bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 32.6% of patients exposed to Jakavi and 23.2% of patients exposed to the reference treatments (placebo or best available therapy). The frequency of grade 3-4 events was similar for patients treated with Jakavi or refer ence treatments (4.7% versus 3.1%). Most of the patients with bleeding events during the treatment reported bruising (65.3%).

Bruising events were more frequently reported in patients taking Jakavi compared with the reference treatments (21.3% versus 11.6%). Intracranial bleeding was reported in 1% of patients exposed to Jakavi and 0.9% exposed to reference treatments. Gastrointestinal bleeding was reported in 5.0% of patients exposed to Jakavi compared to 3.1% exposed to reference treatments. Other bleedin g events (including events such as epistaxis, post-procedural haemorrhage and haematuria) were reported in 13.3% of patients treated with Jakavi and 10.3% treated with reference treatments.

In the randomised period of the pivotal study in PV patients, blee ding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 20% of patients treated with Jakavi and 15.3% patients receiving best available therapy. Bruising was reported in similar frequencies in Jakavi and BAT arms (10.9% versus 8.1%). No intracranial bleeding or gastrointestinal haemorrhage events were reported in patients receiving Jakavi. One patient treated with Jakavi experienced a grade 3 bleeding event (post-procedural bleeding); no grade 4 bleeding was reported. Other bleeding events (including events such as epistaxis, post -procedural haemorrhage, gingival bleeding) were reported in 11.8% of patients treated with Jakavi and 6.3% treated with best available therapy.

Infections

In the phase 3 pivotal studies in MF, grade 3 or 4 urinary tract infection was reported in 1.0% of patients, herpes zoster in 4.3% and tuberculosis in 1.0%. In phase 3 clinical studies sepsis was reported in 3.0% of patients. An extended follow-up of patients treated with ruxolitinib showed no trends towards an increase in the rate of sepsis over time.

In the randomised period of the pivotal study in PV patients, one (0.9%) CTCAE grade 3 and no grade 4 urinary tract infection was reported. The rate of herpes zoster was slightly higher in PV (6.4%) patients than in MF (4.0%) patients. There was one report of CTCAE grade 3 post-herpetic neuralgia amongst the PV patients.

Increased systolic blood pressure

In the phase 3 pivotal clinical studies in MF an increase in systolic blood p ressure of 20 mmHg or more from baseline was recorded in 31.5% of patients on at least one visit compared with 19.5% of the control-treated patients. In COMFORT-I (MF patients) the mean increase from baseline in systolic BP was 0-2 mmHg on Jakavi versus a decrease of 2-5 mmHg in the placebo arm. In COMFORT-II mean values showed little difference between the ruxolitinib-treated and the control-treated MF patients.

In the randomised period of the pivotal study in PV patients, the mean systolic blood pressure increased by 0.65 mmHg in the Jakavi arm versus a decrease of 2 mmHg in the BAT arm.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactio ns via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known antidote for overdoses with Jakavi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anaemia and thrombocytopenia. Appropriate supportive treatment should be given.

Haemodialysis is not expected to enhance the elimination of ruxolitinib.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE18

Mechanism of action

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 (IC_{50} values of 3.3 nM and 2.8 nM for JAK1 and JAK2 enzymes, respectively). These mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.

Myelofibrosis and polycythaemia vera are myeloproliferative neoplasms known to be associated with dysregulated JAK1 and JAK2 signalling. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK -STAT pathway, gain-of-function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signalling regardless of JAK2V617F mutation status. Activating mutations in JAK2 (V617F or exon 12) are found in >95% of PV patients.

Ruxolitinib inhibits JAK-STAT signalling and cell proliferation of cytokine-dependent cellular models of haematological malignancies, as well as of Ba/F3 cells rendered cytokine-independent by expressing the JAK2V617F mutated protein, with IC_{50} ranging from 80-320 nM.

Pharmacodynamic effects

Ruxolitinib inhibits cytokine-induced STAT3 phosphorylation in whole blood from healthy subjects, MF patients and PV patients. Ruxolitinib resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 8 hours in both healthy subjects and MF patients, indicating no accumulation of either parent or active metabolites.

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNFα, IL-6 and CRP in subjects with MF were decreased following treatment with ruxolitinib. MF patients did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with PV also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with ruxolitinib.

In a thorough QT study in healthy subjects, there was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up to a supratherapeutic dose of 200 mg, indicating that ruxolitinib has no effect on cardiac repolarisation.

Clinical efficacy and safety

Myelofibrosis

Two randomised phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with MF (primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis). In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate -2 or

[redacted]

high risk based on the International Working Group (IWG) Consensus Criteria. The starting dose of Jakavi was based on platelet count.

COMFORT-I was a double-blind, randomised, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. The primary efficacy endpoint was proportion of subjects achieving ≥35% reduction from baseline in spleen volume at week 24 as measured by Magnetic Resonance Imaging (MRI) or Computed Tomography (CT).

Secondary endpoints included duration of maintenance of a ≥35% reduction from baseline in spleen volume, proportion of patients who had ≥50% reduction in total symptom score, changes in total symptom scores from baseline to week 24, as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary, and overall survival.

COMFORT-II was an open-label, randomised study in 219 patients. Patients were randomised 2:1 to Jakavi versus best available therapy. In the best available therapy arm, 47% of patients received hydroxyurea and 16% of patients received glucocorticoids. The primary efficacy endpoint was proportion of patients achieving ≥35% reduction from baseline in spleen volume at week 48 as measured by MRI or CT.

Secondary endpoints included proportion of patients achieving a ≥35% reduction of spleen volume from baseline at week 24 and duration of maintenance of a ≥35% reduction from baseline spleen volume.

In COMFORT-I and COMFORT-II, patient baseline demographics and disease characteristics were comparable between the treatment arms.

Table 14-12 Percentage of patients with ≥35% reduction from baseline in spleen volume at week 24 in COMFORT-I and at week 48 in COMFORT-II (ITT)

	COMFORT-I		**COMFORT-II**	
	Jakavi (N=155)	**Placebo (N=153)**	**Jakavi (N=144)**	**Best available therapy (N=72)**
Time points	Week 24		Week 48	
Number (%) of subjects with spleen volume reduced by ≥35%	65 (41.9)	1 (0.7)	41 (28.5)	0
95% confidence intervals	34.1, 50.1	0, 3.6	21.3, 36.6	0.0, 5.0
p-value	<0.0001		<0.0001	

A significantly higher proportion of patients in the Jakavi group achieved ≥35% reduction from baseline in spleen volume (Table 14-12) regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (primary myelofibrosis, post-polycythaemia vera myelofibrosis, post-essential thrombocythaemia myelofibrosis).

[redacted]

Table 14-13 Percentage of patients with ≥35% reduction from baseline in spleen volume by JAK mutation status (safety set)

	COMFORT-I				COMFORT-II			
	Jakavi		Placebo		Jakavi		Best available therapy	
JAK mutation status	Positive (N=113) n (%)	Negative (N=40) n (%)	Positive (N=121) n (%)	Negative (N=27) n (%)	Positive (N=110) n (%)	Negative (N=35) n (%)	Positive (N=49) n (%)	Negative (N=20) n (%)
Number (%) of subjects with spleen volume reduced by ≥35%	54 (47.8)	11 (27.5)	1 (0.8)	0	36 (32.7)	5 (14.3)	0	0
Time point	After 24 weeks				After 48 weeks			

The probability of maintaining spleen response (≥35% reduction) on Jakavi for at least 24 weeks was 89% in COMFORT-I and 87% in COMFORT-II; 52% maintained spleen responses for at least 48 weeks in COMFORT-II.

In COMFORT-I, 45.9% subjects in the Jakavi group achieved a ≥50% improvement from baseline in the week 24 total symptom score (measured using MFSAF diary v2.0), as compared to 5.3% in the placebo group ($p<0.0001$ using chi-square test). The mean change in the global health status at week 24, as measured by EORTC QLQ C30 was +12.3 for Jakavi and -3.4 for placebo ($p<0.0001$).

In COMFORT-I, after a median follow-up of 34.3 months, the death rate in patients randomised to the ruxolitinib arm was 27.1% versus 35.1% in patients randomised to placebo; HR 0.687; 95% CI 0.459-1.029; p=0.0668.

In COMFORT-II, after a median follow-up of 34.7 months, the death rate in patients randomised to ruxolitinib was 19.9% versus 30.1% in patients randomised to best available treatment (BAT); HR 0.48; 95% CI 0.28-0.85; p=0.009. In both studies, the lower death rates noted in the ruxolitinib arm were predominantly driven by the result s obtained in the post polycythaemia vera and post essential thrombocythaemia subgroups.

Polycythaemia vera

A randomised, open-label, active-controlled phase 3 study (RESPONSE) was conducted in 222 patients with PV who were resistant to or intolerant of hydroxyurea defined based on the European LeukemiaNet (ELN) international working group published criteria. 110 patients were randomised to the ruxolitinib arm and 112 patients to the BAT arm. The starting dose of Jakavi was 10 mg twice daily. Doses were then adjusted in individual patients based on tolerability and efficacy with a maximum dose of 25 mg twice daily. BAT was selected by the investigator on a patient-by-patient basis and included hydroxyurea (59.5%), interferon/pegylated interferon (11.7%), anagrelide (7.2%), pipobroman (1.8%) and observation (15.3%).

Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. Most patients (>80%) had received at

[redacted]

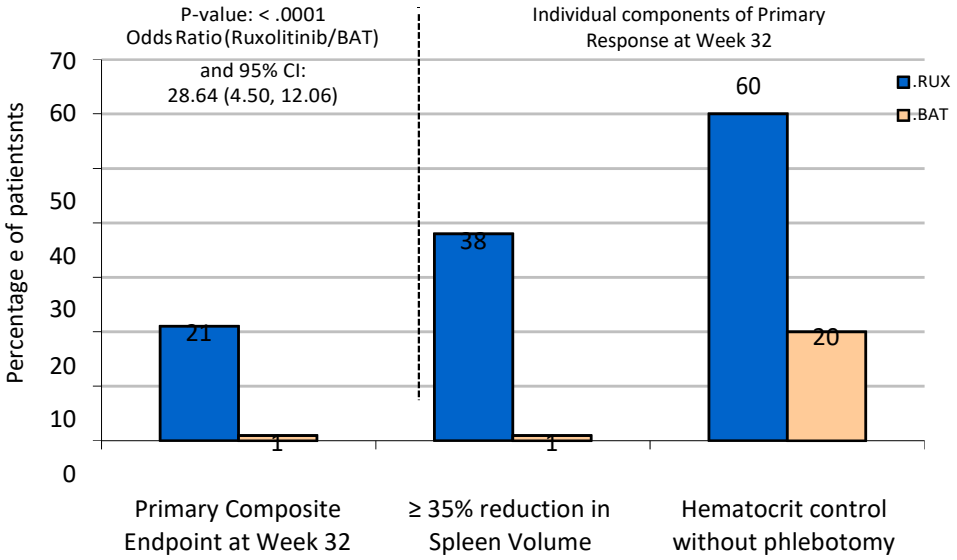
least two phlebotomies in the last 24 weeks prior to screening. Comparative data regarding long-term survival and incidence of disease complications is missing.

The primary composite endpoint was the proportion of patients achieving both an absence of phlebotomy eligibility (HCT control) and a ≥35% reduction in spleen volume from baseline at week 32. Phlebotomy eligibility was defined as a confirmed HCT of >45%, i.e. at least 3 percentage points higher than the HCT obtained at baseline or a confirmed HCT of >48%, depending on which was lower. Key secondary endpoints included the proportion of patients who achieved the primary endpoint and remained free from progression at week 48, as well as the proportion of patients achieving complete haematological remission at week 32.

The study met its primary objective and a higher proportion of patients in the Jakavi group achieved the primary composite endpoint and each of its individual components. Significantly more patients treated with Jakavi (20.9%) achieved a primary response (p<0.0001) compared to BAT (0.9%). Haematocrit control was achieved in 60% of patients in the Ja kavi arm compared to 19.6% in the BAT arm and a ≥35% reduction in spleen volume was achieved in 38.2% of patients in the Jakavi arm compared to 0.9% in the BAT arm (Figure 14-4). 94 (83.9%) patients randomised to the BAT arm crossed over to ruxolitinib tre atment at Week 32 or after, limiting the comparison between the two arms after Week 32.

Both key secondary endpoints were also met. The proportion of patients achieving a complete haematological remission was 23.6% on Jakavi compared to 8.9% on BAT (p=0.00 28) and the proportion of patients achieving a durable primary response at week 48 was 19.1% on Jakavi and 0.9% on BAT.(p<0.0001).

Figure 14-4 Patients achieving the primary endpoint and components of the primary endpoint at week 32



Symptom burden was assessed using the MPN-SAF total symptom score (TSS) electronic

[redacted]

patient diary, which consisted of 14 questions. At week 32, 49% and 64% of patients treated with ruxolitinib achieved a ≥50% reduction in TSS-14 and TSS-5, respectively, compared to

[redacted]

only 5% and 11% of patients on BAT.

Treatment benefit perception was measured by the Patient Global Impression of Change (PGIC) questionnaire. 66% of patients treated with ruxolitinib compared to 19% treated with BAT reported an improvement as early as four weeks after beginning treatment. Improvement in perception of treatment benefit was also higher in patients treated with ruxolitinib at week 32 (78% versus 33%).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Jakavi in all subsets of the paediatric population for the treatment of MF (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Ruxolitinib is a Biopharmaceutical Classification System (BCS) class 1 compound, with high permeability, high solubility and rapid dissolution characteristics. In clinical studies, ruxolitinib is rapidly absorbed after oral administration with maximal plasma concentration (C_{max}) achieved approximately 1 hour post-dose. Based on a human mass balance study, oral absorption of ruxolitinib, as ruxolitinib or metabolites formed under first-pass, is 95% or greater. Mean ruxolitinib C_{max} and total exposure (AUC) increased proportionally over a single dose range of 5-200 mg. There was no clinically relevant change in the pharmacokinetics of ruxolitinib upon administration with a high-fat meal. The mean C_{max} was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) on dosing with a high-fat meal.

Distribution

The mean volume of distribution at steady state is approximately 75 litres in MF and PV patients. At clinically relevant concentrations of ruxolitinib, binding to plasma proteins *in vitro* is approximately 97%, mostly to albumin. A whol e body autoradiography study in rats has shown that ruxolitinib does not penetrate the blood-brain barrier.

Biotransformation

Ruxolitinib is mainly metabolised by CYP3A4 (>50%), with additional contribution from CYP2C9. Parent compound is the predominant entity in human plasma, representing approximately 60% of the drug-related material in circulation. Two major and active metabolites are present in plasma representing 25% and 11% of parent AUC. These metabolites have one half to one fifth of the parent JAK-related pharmacological activity. The sum total of all active metabolites contributes to 18% of the overall pharmacodynamics of ruxolitinib. At clinically relevant concentrations, ruxolitinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 based on *in vitro* studies. *In vitro* data indicate that ruxolitinib may inhibit P-gp and BCRP.

Elimination

[redacted]

Ruxolitinib is mainly eliminated through metabolism. The mean elimination half -life of ruxolitinib is approximately 3 hours. Following a single oral dose of [^{14}C]-labelled ruxolitinib in healthy adult subjects, elimination was predominately through metabolism, with 74% of radioactivity excreted in urine and 22% via faeces. Unchanged parent substance accounted for less than 1% of the excreted total radioactivity.

Linearity/non-linearity

Dose proportionality was demonstrated in the single and multiple dose studies.

Special populations

Effects of age, gender or race

Based on studies in healthy subjects, no relevant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in MF patients, no relationship was apparent between oral clearance and patient age or race. The predicted oral clearance was 17.7 l/h in women and 22.1 l/h in men, with 39% inter-subject variability in MF patients. Clearance was 12.7 l/h in PV patients, with a 42% inter-subject variability and no relationship was apparent between oral clearance and gender, patient age or race, based on a population pharmacokinetic evaluation in PV patients.

Paediatric population

The safety and effectiveness of Jakavi in paediatric patients have not been established (see section 5.1, “Paediatric population”).

Renal impairment

Renal function was determined using both Modification of Diet in Renal Disease (MDRD) and urinary creatinine. Following a single ruxolitinib dose of 25 mg, the exposure of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites tended to increase with increasing severity of renal impairment, and were most markedly increased in the subjects with severe renal impairment. It is unknown whether the increased metabolite exposure is of safety concern. A dose modification is recommended in patients with severe renal impairment and end-stage renal disease (see section 4.2). Dosing only on dialysis days reduces the metabolite exposure, but also the pharmacodynamic effect, especially on the days between dialysis.

Hepatic impairment

Following a single ruxolitinib dose of 25 mg in patients with varying degrees of hepatic impairment, the mean AUC for ruxolitinib was increased in patients with mild, moderate and severe hepatic impairment by 87%, 28% and 65%, respectively, compared to patients with normal hepatic function. There was no clear relationship between AUC and the degree of hepatic impairment based on Child-Pugh scores. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1 -5.0 hours versus 2.8 hours). A dose reduction of approximately 50% is recommended for patients with hepatic impairment (see section 4.2).

[redacted]

5.3 Preclinical safety data

Ruxolitinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity and reproductive toxicity studies and in a carcinogenicity study. Target organs associated with the pharmacological action of ruxolitinib in repeated dose studies include bone marrow, peripheral blood and lymphoid tissues. Infections generally associated with immunosuppression were noted in dogs. Adverse decreases in blood pressure along with increases in heart rate were noted in a dog telemetry study, and an adverse decrease in minute volume was noted in a respiratory study in rats. The margins (based on unbound C_{max}) at the non-adverse level in the dog and rat studies were 15.7-fold and 10.4-fold greater, respectively, than the maximum human recommended dose of 25 mg twice daily. No effects were noted in an evaluation of the neuropharmacological effects of ruxolitinib.

Ruxolitinib decreased foetal weight and increased post-implantation loss in animal studies. There was no evidence of a teratogenic effect in rats and rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans. No effects were noted on fertility. In a pre- and post-natal development study, a slightly prolonged gestation period, reduced number of implantation sites, and reduced number of pups delivered were observed. In the pups, decreased mean initial body weights and short period of decreased mean body weight gain were observed. In lactating rats, ruxolitinib and/or its metabolites were excreted into the milk with a concentration that was 13-fold higher than the maternal plasma concentration. Ruxolitinib was not mutagenic or clastogenic. Ruxolitinib was not carcinogenic in the Tg.rasH2 transgenic mouse model.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Cellulose, microcrystalline
- Magnesium stearate
- Silica, colloidal anhydrous
- Sodium starch glycolate (Type A)
- Povidone
- Hydroxypropylcellulose
- Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

[redacted]

6.5 Nature and contents of container

PVC/PCTFE/Aluminium blister packs containing 14 or 56 tablets or multipacks containing 168 (3 packs of 56) tablets.

Not all pack sizes or types may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/010-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23.08.2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

[redacted]

14.6.2 Annex II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

[redacted]

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH

Roonstrasse 25

D-90429 Nürnberg

Germany

B. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. Other conditions and requirements of the Marketing Authorisation

- Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 9 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

An updated RMP shall be submitted annually until renewal.

- Obligation to conduct post-authorisation measures

[redacted]

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Follow-up efficacy and safety data from the extension phase of studies INCB 18424-351 and INC424A2352 including data on the time related endpoints (overall survival, progression free survival and leukaemia free survival) should be provided annually.	Annually in October
Post-Authorisation efficacy study to provide long-term efficacy and safety data of ruxolitinib including (late) achievement of response, duration of (various) responses, as well as incidence of AEs including haematological transformation and second malignancies from the study B2301.	Week 80 CSR: June 2015 Final CSR: December 2019

[redacted]

14.6.3 ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

[redacted]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 5 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

14 tablets
56 tablets

[redacted]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[redacted]

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/004 14 tablets

EU/1/12/773/005 56 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 5 mg

[redacted]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 5 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

Multipack: 168 (3 packs of 56) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

[redacted]

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[redacted]

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/006 168 tablets (3x56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 5 mg

[redacted]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 5 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

56 tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

[redacted]

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[redacted]

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/006 168 tablets (3x56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 5 mg

[redacted]

MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 5 mg tablets
Ruxolitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday

[redacted]

Wednesday

Thursday

Friday

Saturday

Sunday

[redacted]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 10 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

14 tablets
56 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

[redacted]

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[redacted]

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/014 14 tablets

EU/1/12/773/015 56 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 10 mg

[redacted]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 10 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

Multipack: 168 (3 packs of 56) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

[redacted]

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[redacted]

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/016 168 tablets (3x56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 10 mg

[redacted]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 10 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

56 tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

[redacted]

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[redacted]

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR

United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/016 168 tablets (3x56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 10 mg

[redacted]

MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 10 mg tablets
Ruxolitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday

[redacted]

Tuesday

Wednesday

Thursday

Friday

Saturday

Sunday

[redacted]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 15 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 15 mg ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

14 tablets
56 tablets

[redacted]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[redacted]

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/007 14 tablets

EU/1/12/773/008 56 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 15 mg

[redacted]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 15 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 15 mg ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

Multipack: 168 (3 packs of 56) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

[redacted]

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[redacted]

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/009 168 tablets (3x56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 15 mg

[redacted]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 15 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 15 mg ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

56 tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

[redacted]

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[redacted]

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/009 168 tablets (3x56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 15 mg

[redacted]

MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 15 mg tablets
Ruxolitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday

[redacted]

Wednesday

Thursday

Friday

Saturday

Sunday

[redacted]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 20 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

14 tablets
56 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

[redacted]

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[redacted]

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/010 14 tablets

EU/1/12/773/011 56 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 20 mg

[redacted]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 20 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

Multipack: 168 (3 packs of 56) tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

[redacted]

Oral use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[redacted]

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/012 168 tablets (3x56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 20 mg

[redacted]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 20 mg tablets
Ruxolitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg ruxolitinib (as phosphate).

3. LIST OF EXCIPIENTS

Contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

56 tablets. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

[redacted]

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[redacted]

Novartis Europharm Limited

Frimley Business Park

Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/773/012 168 tablets (3x56)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Jakavi 20 mg

[redacted]

MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Jakavi 20 mg tablets
Ruxolitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday

[redacted]

Wednesday

Thursday

Friday

Saturday

Sunday

[redacted]

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Jakavi 5 mg tablets

Jakavi 10 mg tablets

Jakavi 15 mg tablets

Jakavi 20 mg tablets

ruxolitinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Jakavi is and what it is used for

Jakavi contains the active substance ruxolitinib.

Jakavi is used to treat adult patients with an enlarged spleen or with symptoms related to myelofibrosis, a rare form of blood cancer.

[redacted]

Jakavi is also used to treat patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

How Jakavi works

Enlargement of the spleen is one of the characteristics of myelofibrosis. Myelofibrosis is a disorder of the bone marrow, in which the marrow is replaced by scar tissue. The abnormal marrow can no longer produce enough normal blood cells and as a result the spleen becomes significantly enlarged. By blocking the action of certain enzymes (called Janus Associated Kinases), Jakavi can reduce the size of the spleen in patients with myelofibros is and relieve symptoms such as fever, night sweats, bone pain and weight loss in patients with myelofibrosis. Jakavi can help reduce the risk of serious blood or vascular complications.

Polycythaemia vera is a disorder of the bone marrow, in which the mar row produce too many red blood cells. The blood becomes thicker as a result of the increased red blood cells. Jakavi can relieve the symptoms, reduce spleen size and the volume of red blood cells produced in patients with polycythaemia vera by selectively blocking enzymes called Janus Associated Kinases (JAK1 and JAK2), thus potentially reducing the risk of serious blood or vascular complications.

If you have any questions about how Jakavi works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take Jakavi

Follow all the doctor's instructions carefully. They may differ from the general information contained in this leaflet.

Do not take Jakavi

- if you are allergic to ruxolitinib or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant or breast-feeding.

If either of the above applies to you, tell your doctor who will then decide whether you should start treatment with Jakavi.

Warnings and precautions

Talk to your doctor or pharmacist before taking Jakavi

- if you have any infections. It may be necessary to treat your infection before starting Jakavi. It is important that you tell your doctor if you have ever had tuberculosis or if you have been in close contact with someone who has or has had tuberculosis. Your doctor may perform tests to see if you have tuberculosis. It is important that you tell your doctor if you have ever had hepatitis B.
- if you have any kidney problems. Your doctor may need to prescribe a different dose of Jakavi.
- if you have or have ever had any liver problems. Your doctor may need to prescribe a different dose of Jakavi.
- if you are taking other medicines (see section "Other medicines and Jakavi").

[redacted]

- if you have ever had tuberculosis.
- if you have ever had skin cancer.

Talk to your doctor or pharmacist during your treatment with Jakavi

- if you experience unexpected bruising and/or bleeding, unusual tiredness, shortness of breath during exercise or at rest, unusually pale skin, or frequent infections (these are signs of blood disorders).
- if you experience fever, chills or other symptoms of infections.
- if you experience chronic coughing with blood-tinged sputum, fever, night sweats and weight loss (these can be signs of tuberculosis).
- if you have any of the following symptoms or if anyone close to you notices that you have any of these symptoms: confusion or difficulty thinking, loss of balance or difficulty walking, clumsiness, difficulty speaking, decreased strength or weakness on one side of your body, blurred and/or loss of vision. These may be signs of a serious brain infection and your doctor may suggest further testing and follow-up.
- if you develop painful skin rash with blisters (these are signs of shingles).
- if you notice skin changes. This may require further observation, as certain types of skin cancer (non-melanoma) have been reported.

Blood tests

Before you start treatment with Jakavi, your doctor will perform blood tests to determine the best starting dose for you. You will need to have further blood tests during treatment so that your doctor can monitor the amount of blood cells (white cells, red cells and platelets) in your body and assess how you are responding to the treatment and whether Jakavi is having an unwanted effect on these cells. Your doctor may need to adjust the dose or stop treatment.

Stopping Jakavi

When you stop taking Jakavi, the myelofibrosis symptoms may come back. Your doctor may want to gradually reduce the amount of Jakavi taken each day, before stopping it completely.

Children and adolescents

Do not give this medicine to children or adolescents aged below 18 years because the use of Jakavi in children has not been studied.

Other medicines and Jakavi

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

It is particularly important that you mention any of the following medicines containing any of the following active substances, as your doctor may need to adjust the Jakavi dose for you.

The following may increase the risk of side effects with Jakavi:

- Some medicines used to treat infections. These include medicines used to treat fungal diseases (such as ketoconazole, itraconazole, posaconazole, fluconazole and voriconazole), medicines used to treat certain types of bacterial infections (antibiotics such as clarithromycin, telithromycin, ciprofloxacin, or erythromycin), medicines totreat viral infections, including HIV infection/AIDS (such as apranevir, atazanavir, indinavir,

[redacted]

lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir), medicines to treat hepatitis C (boceprevir, telaprevir).

- Nefazodone, a medicine to treat depression.
- Mibefradil or diltiazem, medicines to treat hypertension and chronic angina pectoris.
- Cimetidine, a medicine to treat heartburn.

The following may reduce the effectiveness of Jakavi:

- Avasimibe, a medicine to treat heart disease.
- Phenytoin, carbamazepine or phenobarbital and other anti-epileptics used to stop seizures or fits.
- Rifabutin or rifampicin, medicines used to treat tuberculosis (TB).
- St. John's wort (*Hypericum perforatum*), a herbal product used to treat depression.

While you are taking Jakavi you should never start a new medicine without checking first with the doctor who prescribed Jakavi. This includes prescription medicines, non-prescription medicines and herbal or alternative medicines.

Pregnancy and breast-feeding

Do not take Jakavi during pregnancy. Talk to your doctor about how to take appropriate measures to avoid becoming pregnant during your treatment with Jakavi.

Do not breast-feed while taking Jakavi. Tell your doctor if you are breast-feeding.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

If you experience dizziness after taking Jakavi, do not drive or use machines.

Jakavi contains lactose

Jakavi contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Jakavi

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The dose of Jakavi depends on the patient's blood cell count. Your doctor will measure the amount of blood cells in your body and find the best dose for you, particularly if you have liver or kidney problems.

- The recommended starting dose in myelofibrosis is 15 mg twice daily or 20 mg twice daily, depending on your blood cell count.
- The recommended starting dose in polycythaemia vera is 10 mg twice daily, depending on your blood cell count.
- The maximum dose is 25 mg twice daily.

[redacted]

Your doctor will always tell you exactly how many Jakavi tablets to take.

During the treatment your doctor may recommend a lower or higher dose to you if the results of blood tests show that this is necessary, if you have problems with your liver or kidneys, or if you also need treatment with certain other medicines.

If you receive dialysis, take either one single dose or two separate doses of Jakavi only on dialysis days, after the dialysis has been completed. Your doctor will tell you if you should take one or two doses and how many tablets to take for each dose.

You should take Jakavi every day at the same time, either with or without food.

You should continue taking Jakavi for as long as your doctor tells you to. This is a long-term treatment.

Your doctor will regularly monitor your condition to make sure that the treatment is having the desired effect.

If you have questions about how long to take Jakavi, talk to your doctor or pharmacist.

If you experience certain side effects (e.g. blood disorders), your doctor might need to change the amount of Jakavi you have to take or tell you to stop taking Jakavi for a while.

If you take more Jakavi than you should

If you accidentally take more Jakavi than your doctor prescribed, contact your doctor or pharmacist immediately.

If you forget to take Jakavi

If you forgot to take Jakavi simply take your next dose at the scheduled time. Do not tak e a double dose to make up for a forgotten dose.

If you stop taking Jakavi

If you interrupt your treatment with Jakavi your myelofibrosis-related symptoms may come back. Therefore, you should not stop taking Jakavi without discussing it with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most of the side effects of Jakavi are mild to moderate and will generally disappear after a few days to a few weeks of treatment.

Tell your doctor immediately if you experience any of the following side effects. Some are very common (may affect more than 1 in 10 people), some are common (may affect up to 1 in 10 people):

- any sign of bleeding in the brain, such as sudden altered level of consciousness, persistent headache, numbness, tingling, weakness or paralysis (common)
- any sign of bleeding in the stomach or intestine, such as passing black or bloodstained stools, or vomiting blood (common)
- unexpected bruising and/or bleeding, unusual tiredness, shortness of breath during exercise or at rest, unusually pale skin, or frequent infections (possible symptoms of blood disorders) (very common)

[redacted]

- painful skin rash with blisters (possible symptoms of shingles (*herpes zoster*)) (common)
- fever, chills or other symptoms of infections (very common)
- low level of red blood cells (*anaemia*), low level of white blood cells (*neutropenia*) or low level of platelets (*thrombocytopenia*) (very common)

Other side effects with Jakavi

Very common:
- high level of cholesterol or fat in the blood (*hypertriglyceridaemia*)
- abnormal liver function test results
- dizziness
- headache
- urinary tract infections
- weight gain

Common:
- frequently passing wind (*flatulence*)
- constipation
- high blood pressure (*hypertension*), which may also be the cause of dizziness and headaches

Uncommon:
- tuberculosis

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Jakavi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or blister after "EXP".

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

[redacted]

6. Contents of the pack and other information

What Jakavi contains

- The active substance of Jakavi is ruxolitinib.
- Each 5 mg Jakavi tablet contains 5 mg of ruxolitinib.
- Each 10 mg Jakavi tablet contains 10 mg of ruxolitinib.
- Each 15 mg Jakavi tablet contains 15 mg of ruxolitinib.
- Each 20 mg Jakavi tablet contains 20 mg of ruxolitinib.
- The other ingredients are: microcrystalline cellulose, magnesium stearate, colloidal anhydrous silica, sodium starch glycolate, povidone, hydroxypropylcellulose, lactose monohydrate.

What Jakavi looks like and contents of the pack

Jakavi 5 mg tablets are white to almost white round tablets with “NVR” debossed on one side and “L5” debossed on the other side.

Jakavi 10 mg tablets are white to almost white round tablets with “NVR” debossed on one side and “L10” debossed on the other side.

Jakavi 15 mg tablets are white to almost white oval tablets with “NVR” debossed on one side and “L15” debossed on the other side.

Jakavi 20 mg tablets are white to almost white elongated tablets with “NVR” debossed on one side and “L20” debossed on the other side.

Jakavi tablets are supplied in blister packs containing 14 or 56 tablets or multipacks containing 168 (3 packs of 56) tablets

Not all packs may be marketed in your country.

Marketing Authorisation Holder

Novartis Europharm Limited

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Manufacturer

Novartis Pharma GmbH

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

[redacted]