19 April 2012
EMA/465846/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Jakavi

International non-proprietary name: **ruxolitinib**

Procedure No. **EMEA/H/C/002464**

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	Jakavi
Applicant:	Novartis Europharm Ltd. Wimblehurst Road Horsham, W Sussex RH12 5AB United Kingdom
Active substance:	ruxolitinib
International Non-proprietary Name/Common Name:	ruxolitinib
Pharmaco-therapeutic group (ATC Code):	Protein kinase inhibitors (L01XE18)
Therapeutic indication:	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.
Pharmaceutical form:	Tablet
Strengths:	5 mg, 15 mg, 20 mg
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package size:	60 tablets

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List of abbreviations

A/G ratio	Albumin to globulin ratio
Abs Retic	Absolute reticulocyte
AlloSCT	Allogeneic hematopoietic stem cell transplant
ALP	Alkaline phosphatase
ATP	Adenosine triphosphate
$AUC_{0-\infty}$	Area under the serum concentration-time curve from time zero to infinity. For extrapolation to infinity Clast / λz is used, where Clast is the estimated concentration at the last sample time point above LOQ from linear regression of the terminal elimination phase
AUC_{0-t}	Area under the serum concentration-time curve from time zero to time t, using the log-linear trapezoidal rule. Concentrations below the LOQ are set to zero and therefore excluded from the calculation. Actual sample collection times are used. Where 0-t is shown as τ this denotes the AUC under a dosing interval
BCS	Biopharmaceutics classification system
BID	Twice daily
CHO	Chinese hamster ovary cells
C_{max}	Maximum serum concentration after a single dose
CNS	Central nervous system
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
FCA	Freund's Complete Adjuvant
FDA	Food and Drug Administration
G	Gestation day
GLP	Good Laboratory Practices
hA1	Human adenosine 1
Hgb	Haemoglobin
HDPE	High-density polyethylene
hERG	Human-ether-a-go-go-related gene
HU	Hydroxyurea
i.v.	Intravenous
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IPSS	International Prognostic Scoring System
JAK	Janus kinase
Kg	Kilogram
LD	Lactation day
LLNA	local lymph node assay
LOQ	Limit of quantification
M:E	Myeloid:erythroid ratio
MF	Myelofibrosis
mg	Milligram
mL	Milliliter
MPN	Myeloproliferative neoplasm
MTD	Maximum tolerated dose
NCE	Normochromatic erythrocytes
NO	Nitric oxyde
NOAEL	No-oberved-adverse-effect-level
NOEL	No-observed-effect-level
PBMC	Peripheral blood mononuclear cell
PBPK	Physiologically based pharmacokinetic
PCE	Polychromatic erythrocytes
PD	Pharmacodynamic
PET-MF	Post-essential thrombocythemia myelofibrosis
PK	Pharmacokinetic
PMF	Primary myelofibrosis
PPV-MF	Post-polycythemia vera myelofibrosis
QD	Once daily
rAIA	rat adjuvant induced arthritis
STAT	Signal transducers and activators of transcription
$T_{1/2}$	Time for plasma concentration to reduce by 50%
TCSA	3,3´,4´,5´-Tetrachlorosalicylanilide

TK	Toxicokinetics
t_{max}	Time to the maximum observed serum concentration
µg	Microgram
µL	Microliter
WBC	White blood count

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd. submitted on 1 June 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Jakavi, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 November 2010.

Jakavi was designated as an orphan medicinal product EU/3/08/572 and EU/3/09/620 on 07 November 2008 and 03 April 2009. Jakavi was designated as an orphan medicinal product in the following indications: treatment of chronic idiopathic myelofibrosis and treatment of myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Jakavi as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website ema.europa.eu/Find medicine/Rare disease designations.

The applicant applied for the following indication:

Jakavi is indicated for treatment of adult patients with myelofibrosis, including primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decision EMEA/000901-PIP01-10 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance ruxolitinib contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 20 November 2008, 18 December 2008, 05 January 2009, 23 April 2009 and 18 March 2011. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

Jakavi (Jakafi) has been given a Marketing Authorisation in the United States on 16 November 2011.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Tomas Salmonson** Co-Rapporteur: **Robert James Hemmings**

- The application was received by the EMA on 1 June 2011.
- The procedure started on 22 June 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 September 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 09 September 2011.
- During the meeting on 20 October 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 October 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 December 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 27 January 2012.
- During the CHMP meeting on 16 February 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 March 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 2 April 2012.
- During the meeting on 19 April 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Jakavi on 19 April 2012.

2. Scientific discussion

2.1. Introduction

Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) that can present as an apparently de novo disorder termed primary MF (PMF) or evolve from other MPNs and can be termed secondary MF, post Polycythaemia Vera MF (PPV-MF) or post Essential Thrombocythaemia MF (PET-MF). The 10-year risk of developing MF is < 4% in ET and 10% in PV. The median age at diagnosis is approximately 65

years. The incidence of PMF has been shown to increase with age and is estimated at 0.4 to 1.4 cases per 100,000 individuals per year in Western countries (Barosi, et al 2011).

MF is characterised by a clonal stem cell proliferation associated with production of elevated levels of several inflammatory and proangiogenic cytokines. Resulting bone marrow stromal reaction includes varying degrees of collagen fibrosis, osteosclerosis and angiogenesis. The altered bone marrow milieu results in release of hematopoietic stem cells into the blood and extramedullary hematopoiesis, particularly hepatomegaly and splenomegaly. MF results in laboratory and physical exam abnormalities including progressive anaemia, leucopenia or leucocytosis, thrombocytopenia or thrombocythaemia, ineffective haematopoiesis and haematopoietic failure, massive splenomegaly and portal hypertension, and progression to leukaemia. Clinically, patients suffer from the consequences of massive splenomegaly including abdominal pain or discomfort and pain under the left costal margin, risk of vascular events (including thrombosis and haemorrhage), severe constitutional symptoms (fevers, night sweats, weight loss), a hypermetabolic state, cachexia and premature death. Causes of death for patients with MF include leukaemic transformation, infections, bleeding, thrombosis, heart failure, liver failure, solid tumours, respiratory failure, and portal hypertension.

The IWG-MRT identified 5 risk factors independently associated with shortened survival in PMF, termed the International Prognostic Scoring System (IPSS): age > 65 years, presence of constitutional symptoms (weight loss, fever, or night sweats), anaemia as determined by haemoglobin (Hgb) < 10 g/dL or evidenced by the need for chronic red blood cell transfusions, leucocytosis (white blood cell [WBC] count > 25 x 109/L), and a circulating peripheral blood blast percentage of ≥ 1%. The IWG-MRT identified 4 risk groups with non-overlapping survival curves based on the absence or presence of 1 or more of these risk factors. The median survival of patients was 135 months in the Low risk group (zero risk factors), 95 months in the Intermediate-1 risk group (one risk factor), 48 months in the Intermediate-2 risk group (two risk factors), and 27 months in the High risk group (≥ 3 risk factors). Analysis of relative survival showed that mortality in all of the patients at 5 and 10 years after diagnosis was 40% and 60% greater, respectively, than the expected mortality in a general population with similar demographic characteristics.

In the EU, hydroxyurea (HU) is approved on a national basis in a few countries (e.g. France, Italy, Sweden and Spain) and is used to control excessive myeloproliferation. Other therapies used to treat MF include danazol, erythropoiesis-stimulating agents, androgens and prednisone, and immunomodulatory agents. Other therapeutic options include splenectomy and splenic irradiation and the potentially curative option of allogeneic stem cell transplant (alloSCT). However, the 1-year transplant-related mortality in patients who undergo alloSCT is 27% (Ditschkowski, et al 2004), and alloSCT is rarely a viable option in patients > 60 years of age.

The impact of fatigue on patients with MF is profound; of 456 MF patients, 84% reported fatigue, without difference according to primary vs. secondary MF (Mesa, et al 2007).

Within the past 5 years, it has been found that approximately 96% of patients with PV, 65% of patients with PMF and 55% of patients with ET have a somatic gain-of-function mutation in the JAK2 resulting in substitution of phenylalanine for valine at position 617 (JAK2V617F) within the pseudokinase domain. JAK2 is one of four Janus kinases. Erythropoietin, thrombopoietin, and granulocyte-macrophage colony stimulating factor have been shown to signal only through receptors which utilize JAK2 homodimers. JAK signalling involves recruitment of signal transducers and activators of transcription (STAT) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

It is also apparent that PMF, as well as ET and rarely even PV, occurs in the absence of the JAK2V617F mutation. However, it appears that the majority of patients with MF have overactivation of the JAK-

STAT pathway, regardless of JAK2V617F status. Increased JAK2 signalling, evidenced by constitutively phosphorylated STAT3, is not strictly dependent on the presence of JAK2V617F mutation. Patients with MF demonstrate high levels of circulating inflammatory cytokines such as interleukin-6 (IL-6), which are likely responsible for the hypercatabolic state and constitutional symptoms, such as weight loss and fatigue, frequently seen in these patients. Many of these pro-inflammatory cytokines use JAK1, which is hyperactivated in the peripheral blood of patients with MF. The association of JAK1 with the very high levels of JAK activating inflammatory cytokines provides a rationale for the alleviation of constitutional symptoms through JAK1 inhibition. Cytokine elevations in MF occur regardless of mutational status or disease subtype.

About the product

Ruxolitinib (INCB018424 phosphate, INC424, ruxolitinib phosphate) is a selective inhibitor of Janus Associated Kinase 1 (JAK1) and JAK2 (IC50 values of 3.3 nM and 2.8 nM, respectively) which mediates the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function. The chemical name is (R)-3-(4-(7H-pyrrolo [2, 3-d] pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate. The molecular formula is C17H21N6O4P and the molecular weight is 404.36.

The compound was originally developed by Incyte Corporation, Wilmington, Delaware, USA. Incyte and Novartis have entered into a joint partnership for the co-development of ruxolitinib in haematology and oncology.

The applicant claimed the approval for the following indication:

Jakavi is indicated for treatment of adult patients with myelofibrosis, including primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

The final indication following CHMP review of this application is:

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.

2.2. Quality aspects

2.2.1. Introduction

The product is presented as immediate release tablets containing 5 mg, 15 mg and 20 mg of ruxolitinib (as ruxolitinib phosphate) as active substance. Other ingredients are lactose monohydrate, microcrystalline cellulose, magnesium stearate, colloidal anhydrous silica, sodium starch glycolate, povidone, hydroxypropyl cellulose

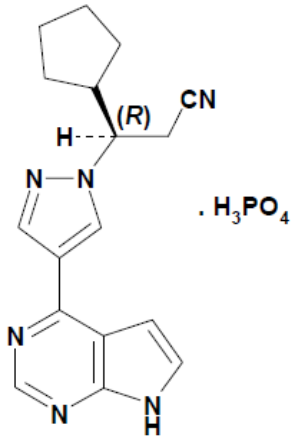
The tablets are packed in High-density polyethylene (HDPE) bottle with induction seal and child-resistant closure.

2.2.2. Active Substance

Ruxolitinib phosphate is a white to almost white, non-hygroscopic powder, highly soluble in water, and the solubility is pH dependant. Ruxolitinib phosphate has the chemical name (R)-3-(4-(7H-Pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate or 1H-Pyrazole-1-propanenitrile, β-cyclopentyl-4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-, (βR)-, phosphate (1:1). Polymorphism has been shown to exist for ruxolitinib phosphate drug substance and only one

anhydrous crystalline form has been used. Anhydrous crystalline form used is the most stable solid form. Ruxolitinib phosphate has one quiral centre in the molecule (R-absolute configuration).

Chemical structure



Manufacture

Ruxolitinib phosphate is chemically synthesised in seven steps. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents, have been presented. The active substance is purified by recrystallisation.

Batch analysis data produced with the proposed synthetic route provided show that the active substance can be manufactured reproducibly.

Specification

The active substance specification includes tests for appearance (visual examination), particle size (laser diffraction) identification of Ruxolitinib (IR, X-ray), impurities (HPLC), residual solvents (GC), water (KF), Heavy metals, sodium (ICP-OES), assay and related substances (HPLC)

The specifications reflect all relevant quality attributes of the active substance. The analytical methods used in the routine controls are suitability described. The validation studies are in accordance with the ICH Guidelines. Impurity limits in the specification are justified by toxicology studies.

Certificates of analysis issued by the active substance manufacturer are provided. The results comply with the specifications, and show good uniformity from batch to batch.

Stability

Four batches of the active substance have been storage under long term ICH conditions (25°C/60% RH) up to 24 months and under accelerated ICH conditions (40°C 75% RH). The primary stability batches are stored in sealed LDPE bags inside HDPE container. This packaging is considered to be equivalent to the proposed commercial packaging of sealed double LDPE bags inside metal containers.

The parameters investigated during stability include parameters such as appearance, identifications by HPLC, water content, assay and impurities.

Photostability data was also provided. One batch was directly exposed to light (1200 and 2400klux). Exposure of the free base to light (1200 and 2400klux) causes a change in the colour of the active substance and showed that the free base is sensitive to light. Therefore it is recommended that ruxolitinib phosphate should be protected from light where possible.

Stability data under stress testing conditions after 1 month storage at 50°C and 60°C, each at <30% RH and at 75% RH, without packaging (open) was also provided.

Other stability data under stress testing conditions: at 80°C under nitrogen, oxygen, and with 2% water in sealed ampoules, in acidic solutions at 50°C and 70°C and basic solutions at 50°C up to one month storage was also provided.

The results justify the retest period proposed by the applicant in the intended packaged.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The properties of the active substance suggested that a tablet manufacturing process based upon wet granulation might be suitable for development of a market formulation.

The excipients selected are standard ingredients in tablet formulations, and are in compliance with internationally accepted pharmacopoeial standards. The compatibility between active substance and excipients was investigated during development. Stability studies on tablets at accelerated conditions of 40°C/75% RH and long term at 25°C/60% RH support the use of all the excipients in the finished product formulation.

During the development the influence of the medium pH and the dissolution behaviour of the tablets were investigated. The results showed that dissolution medium pH has no significant impact on the dissolution due to the high solubility of the substance over the physiological pH range. Dissolution method developed was shown to be discriminatory however not optimal for the higher strength. Therefore unless other dissolution methods are shown to be non-discriminatory, the proposed dissolution method should be replaced. It is recommended to develop and replace the propose method with a more optimal one.

The proposed formulations have also been used for the batches used in the clinical and pre-clinical studies.

All excipients chosen are well-known and comply with the Ph Eur. The specification is considered justified based on batch and stability data and considering relevant guidance's and requirements. The limits for degradation products are acceptable, considering ICH requirements.

The composition is: lactose monohydrate (filler), cellulose microcrystalline (filler), sodium starch glycolate (disintegrant), magnesium stearate (lubricant), stearic acid (lubricant), colloidal silicon dioxide (Glidant), hydroxypropyl cellulose (binder), povidone (binder)

The description and choice of container closure system is in accordance with the EU plastic directive 2002/72/EC and 94/62/EC. The tablets will be packaged in HDPE bottles with HDPE cap with a polypropylene inner closure. The raw materials are stated to comply with Ph. Eur. 3.1.3 "Polyolefines" and Ph. Eur. 3.2.2 "Plastic Containers and Closure for Pharmaceutical use".

The experience with the active substance and the data from the stability studies performed with the tablets shows that the chosen HDPE bottles with HDPE cap with a polypropylene inner closure are considered sufficiently protective, compatible with the finished product and adequate to support the stability and use of the medicinal product.

Adventitious agents

The lactose monohydrate is of animal origin. It is manufactured from milk sourced from healthy animals in the same conditions as milk collected for human consumption. No other ruminant materials, with the exception of calf rennet, are used in the preparation. Regarding the TSE compliance of the

Lactose monohydrate, it is confirmed that the lactose used is in accordance with the Public Statement (EMEA/CPMP/571/02).)

Manufacture of the product

The proposed commercial manufacturing process involves blending, wetting, sieving and tabletting. The manufacturing process of ruxolitinib tablets is robust and consistently yields drug product that meets the predetermined quality characteristics. A summary of the process validation protocol that will be used to validate the commercial process at commercial scale in the commercial site as listed in the dossier is presented in a Process Validation Scheme for the Drug Product.

For each strength, three validation batches will be processed using the same process and the same equipment as the batches intended for marketing.

The batch analysis data show that the product can be manufactured reproducibly according to the agreed finished product specification.

Product specification

The product specifications include tests by validated methods for appearance, identity tests of Ruxolitinib phosphate (HPLC, UV), water (KF), uniformity of dosage units by content uniformity (HPLC), degradations products (HPLC), dissolution (HPLC), enantiomer (HPLC), microbial enumeration test (Ph Eur), and assay (HPLC, 95-105 %).

The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Batch analysis data on twelve batches of 5 mg tablets, one batch of 15 mg tablets and three batches of 20 mg confirm satisfactory uniformity of the product at release.

Stability of the product

Stability data was provided for three batches of finished product at the lowest (5mg) and highest (25mg) strengths. While the 25mg tablet is not part of the current application, as all of the strengths are quantitatively proportional and manufactured by compressing varying amounts of a common final blend, the use of the 5mg and 25mg is considered to have bracketed the 15mg and 20mg tablet strengths. The stability batches are a mixture of pilot and commercial scale batches.

The formulations meet the requirements for bracketing as laid out in ICH Q1D "Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products".

Furthermore, the stability batches are tested to the same finished product specification as that of proposed commercial batches. The stability batches are packed in the proposed HDPE bottle and closure packaging.

Stability data is provided for the proposed product at 25ºC/60%RH and 40ºC/75%RH. Stability testing parameters included: appearance, water content, assay of ruxolitinib, degradation products and dissolution.

Photostability data in line with ICH requirement has been carried out for one batch of 5mg and 25mg tablet. These batches are manufactured at the proposed finished product manufacturing site. No significant difference was observed between tablets exposed to light stress condition and unexposed control samples. Therefore it can be concluded that ruxolitinib tablets are not sensitive to light. The proposed HDPE bottle and closure packaging is considered to provide adequate protection.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The CHMP recommends development and replacement of the current apparatus II paddle method with the apparatus I basket method used for the dissolution testing. Upon finalisation of the development and validation the new method should be introduced via appropriate regulatory procedure. As a consequence, the product specification for dissolution testing should also be revised.

2.3. Non-clinical aspects

2.3.1. Introduction

The goal of the nonclinical studies was to support the registration of ruxolitinib for the proposed indication.

The rat and dog were selected as the rodent and non-rodent species for chronic toxicity testing because both have historically been used in safety evaluations, and ruxolitinib is pharmacologically active in both species. The oral route was chosen because it is the intended route of administration in humans.

Additional nonclinical studies have been conducted to support the development of ruxolitinib phosphate cream as a topical formulation for the treatment of patients with psoriasis. These include repeated dose topical studies of up to 9 months in duration in the minipig, dose range finding topical studies for a 2-year dermal carcinogenicity study in mice, a murine local lymph node assay, acute skin and ocular irritation studies in rabbit, phototoxicity and photoallergy studies in the guinea pig, and an *in vitro* photoclastogenicity study. The results of these studies have not been included in this assessment report since the therapeutic indication for this submission is the oral route only.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Ruxolitinib is a potent ATP competitive inhibitor of JAK1 (IC50 = 3.3 ± 1.2 nM) and JAK2 (IC50 = 2.8 ± 1.2 nM), with modest selectivity against TYK2 (IC50 = 19 ± 3.2 nM) and marked selectivity against

JAK3 (IC50 = 428 ± 243 nM), when assessed at 1 mM ATP concentrations. The results from further testing against a broad panel of 30 kinases using the respective Km concentrations of ATP for each individual kinase support that ruxolitinib is a selective inhibitor of JAKs.

Ruxolitinib inhibited 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 IC50 ranging from 80-320 nM.

The effect of ruxolitinib on the growth of progenitor colonies derived from mononuclear cells from patients with PV was also evaluated in colony-forming assays. Ruxolitinib inhibited erythroid colony formation with an IC50 of 223 nM compared to 407 nM for normal donors. While cells bearing the JAK2V617F mutation were not significantly more sensitive to ruxolitinib compared to cells from healthy volunteers with respect to colony formation in the presence of optimal erythropoietin concentrations, growth factor-independent colony formation, a unique characteristic of PV and other MPNs, was inhibited more potently with an IC50 of 67 nM.

The potency in blocking JAK activity in hematopoietic cells in vivo was established in a whole blood assay that measured STAT3 phosphorylation in response to IL-6 or thrombopoietin (TPO) stimulation. In human whole blood, exogenous ruxolitinib blocked IL-6 or TPO induced STAT3 phosphorylation with IC50 values of 282 nM and 281 nM, respectively. There were no effects on total STAT3 levels. Similar results were obtained using whole blood from dogs (IC50 = 119 nM), rats (IC50 = 95 nM) and rabbits (IC50 = 600 nM).

Treatment of mice with ruxolitinib resulted in a dose-dependent suppression of phosphorylated STAT3 and tumour growth in the cytokine-dependent INA-6 multiple myeloma xenograft model.

Ruxolitinib also inhibited splenomegaly in mice resulting from intravenous inoculation of cells expressing the clinically relevant JAK2V617F mutation. Moreover, genomic PCR analysis of spleen samples to detect JAK2V617F cells showed that the mutant allele burden was significantly decreased by treatment with ruxolitinib (33% decrease, $P < 0.01$). Mice bearing Ba/F3-JAK2V617F cells and treated with ruxolitinib had a significantly improved survival compared to animals treated with vehicle. After 3 weeks of treatment, > 90% of vehicle-treated mice had succumbed to disease while > 90% of ruxolitinib-treated mice survived. Treatment with ruxolitinib also reduced inflammatory cytokine levels (e.g. TNF-α, IL-6) in these mice.

The major metabolites of ruxolitinib were active but demonstrated slightly to significantly weaker activity than the parent compound in both enzyme and cell-based assays (IL-6 induced INA-6 proliferation and IL-6 induced STAT3 phosphorylation).

The results from the various primary pharmacodynamic studies show that ruxolitinib and its major metabolites have inhibitory effects on JAKs at clinically relevant concentration (Cmax at highest clinical dose is 1.48 µM).

Secondary pharmacodynamic studies

The effects of ruxolitinib on inflammatory cytokine-stimulated activation of JAK/STAT signalling and its functional consequences were examined in vitro in human T cells and peripheral blood mononuclear cells (PBMCs). The therapeutic utility of ruxolitinib in inflammatory diseases *in vivo* was evaluated in the rat adjuvant induced arthritis (rAIA) model. The results indicate a potential utility of oral or topical ruxolitinib for treatment of inflammatory conditions.

Safety pharmacology programme

Ruxolitinib did not demonstrate significant cross-reactivity with any of the 50 *in vitro* binding assays and enzyme assays in which it was evaluated but 26% inhibition at 1 µM was noted for the human adenosine 1 receptor (hA1) which prompted determination of an IC50 value for ruxolitinib-mediated inhibition of binding to this adenosine receptor, and the other adenosine family of receptors. The IC50 values for hA1, hA2a and hA2b receptors were 2.1 µM, > 30 µM and 11 µM, respectively.

The IC50 for the inhibitory effect of ruxolitinib on the hERG potassium current was 131.6 µM. The Cmax at the highest proposed therapeutic dose in humans (25 mg bid) is 1.48 µM (0.049 µM unbound) [INCYTE-DMB-10.56.3]. Therefore, the risk of inhibition of hERG in humans given ruxolitinib appears to be low. Additionally, a study to assess the effects of ruxolitinib on heart rate corrected QT intervals in healthy subjects has been undertaken [INCB 18424-138].

In vivo, ruxolitinib was evaluated in CNS and respiratory studies in the rat and in a cardiovascular study in telemeterized conscious dogs. Two findings in safety pharmacology nonclinical assessments were considered to be adverse: decreases in minute volume in female rats given a single oral dose of 150 mg/kg (NOAEL 50mg/kg) in a respiratory assessment of ruxolitinib; and decreases in arterial blood pressure along with increases in heart rate in radiotelemetry-implanted conscious dogs dosed 30 mg/kg (NOAEL 10mg/kg). The mean Cmax in female rats at the NOAEL dose of 50 mg/kg and in dogs at the NOAEL dose of 10 mg/kg are 10.4-fold and 15.7-fold greater, respectively, than the Cmax at the highest proposed therapeutic dose in humans (25 mg bid) associated with a mean Cmax value of 1.48 µM (0.049 µM unbound).

Pharmacodynamic drug interactions

No formal drug interactions studies were carried out.

2.3.3. Pharmacokinetics

The methods of analyses have been adequately validated in compliance with GLP.

Ruxolitinib exhibited a high apparent permeability in Caco-2 cell monolayers and the data indicate that ruxolitinib crosses Caco-2 cell monolayers through a passive mechanism and is not a substrate for transporters including P-gp.

Absorption

Ruxolitinib was rapidly absorbed with variable but high oral bioavailability in mice, rats, rabbits and dogs with a similarly short half-life after single and multiple dosing. Tmax values ranged from 0.5 to 2 h; comparably to humans, in whom Tmax was reached within 1 to 3 h after a single oral dose. The terminal elimination half-life was generally short after oral and i.v. dosing, ranging from 0.4 h (rat) to 2.5 h (dog), comparable to that in humans after oral dosing, which was approximately 3 h. In mice and dogs, there were minimal or no gender differences, but there were gender differences in rats with a several-fold difference in oral exposure between male and female rats likely due to more extensive metabolism in male rats compared to females.

Distribution

Blood partitioning results indicate minor to no preferential partitioning of [14C] ruxolitinib -derived radioactivity into blood cells of mice, rats, dogs and humans.

The plasma protein binding of ruxolitinib is species-dependent. The *ex vivo* fraction unbound as determined in plasma from CByB6F1 Hybrid mice, CD-1 mice, hairless mice, rats, rabbits and dogs

given ruxolitinib was 4.9%, 2.7%, 3.0%, 18%, 13% and 9.7%, respectively. The *in vitro* fraction unbound in human plasma was 3.3%.

In Sprague-Dawley (albino) rats, the highest concentrations of drug-derived radioactivity were observed in the tissues and contents of the gastrointestinal tract, urinary bladder, renal cortex, renal medulla, liver, aorta, and adrenal gland. In Long-Evans (pigmented) rats, the highest concentrations of radioactivity were in the tissues and contents of the gastrointestinal tract, followed by urine, bile, uveal tract, liver, renal medulla, renal cortex, skin (pigmented), and kidney. Penetration of ruxolitinib and ruxolitinib-derived radioactivity into central nervous system tissues was limited (less than 10% of plasma concentration). Disappearance of radioactivity was rapid and complete in most tissues in albino and pigmented rats. The ruxolitinib-derived radioactivity from skin and uveal tract showed rather long elimination half-life but was not irreversibly bound to melanin.

The tissue distribution of [14C] ruxolitinib-derived radioactivity was assessed in maternal and fetal tissues of pregnant Sprague-Dawley rats. The results indicate that low amounts of drug-derived radioactivity crossed the placenta and disappeared rapidly from the fetuses, resulting in limited fetal exposure.

Metabolism

Ruxolitinib is metabolised via Phase I and Phase II reactions and a large number of metabolites were identified in all species. The predominant metabolic pathways in mice, rats, dogs, and humans were mono- and dioxygenation and in some cases, subsequent glucuronidation. In general, the metabolite profiles and excretion patterns in humans were similar to those observed in nonclinical species. In humans after a single oral 25 mg dose of [14C] ruxolitinib, parent compound was the predominant entity in circulation, representing 57% of the total radioactivity based on AUC. One metabolite was at an exposure greater than 10% of the total circulating drug-related material (M18 at 17% based on AUC). Other observed ruxolitinib-related components in human plasma were present at exposures less than 10% of total radioactivity, and consisted of mono- and di-hydroxylated and ketone metabolites. Two minor human metabolites in circulation (M38 and M49) were not previously observed in plasma of nonclinical species, but their low circulating exposure in human (less than 3% based on 14C-AUC) is well below the threshold that would raise a safety concern. The animals in the toxicity studies have thus been exposed to the major human metabolites.

Excretion

In rats, excretion of drug-derived radioactivity was rapid after either a single oral or i.v. dose of [14C] ruxolitinib (92% and 87%, respectively, excreted in urine and faeces within 12 h of dosing). Excretion in urine, bile, and faeces of bile duct cannulated rats accounted for approximately 50%, 37% and 12% of the dose, respectively with a total overall recovery of approximately 100% of administered radioactivity within 24h post-dose. Excretion of radioactivity was also rapid in male and female dogs after a single oral dose with 80% to 82% of the dose excreted within 24h of dosing. Excretion in urine and faeces accounted for 34% to 36% and 55% to 58% of the dose, respectively with a total overall recovery of approximately 94% to 96% of administered radioactivity within 96h post-dose. Excretion in urine and faeces of humans after a single oral 25 mg dose of [14C] ruxolitinib accounted approximately for 74% and 22% of the dose, respectively, with a total overall recovery of approximately 96% of administered radioactivity within 144h. Excretion in humans was rapid, with greater than 70% of the radioactivity recovered by 24h post-dose. Unchanged ruxolitinib constituted less than 3% of the radioactivity in mouse, rat, and human excreta, and approximately 15% in dog, also indicative of extensive metabolism, the primary route of elimination.

Excretion to milk was studied in lactating rats. Mean milk: plasma concentration ratios of radioactivity were greater than one at all measurable sampling times with a ratio of 13.4 based on AUCinf, indicating that ruxolitinib-derived radioactivity preferentially partitions into milk.

2.3.4. Toxicology

The Applicant has performed a full program of non-clinical toxicity studies including single and repeat dose toxicity testing, genotoxic and carcinogenicity testing, reproductive and developmental studies and phototoxicity. All pivotal studies were performed according to GLP. The application also contains studies of the topical toxicology of ruxolitinib.

Single dose toxicity

Single dose toxicity studies presented in table 1 were conducted in rats and dogs.

Table 1: Summary of single dose toxicity studies with ruxolitinib

Species (strain)	N° of animal/ sex/ group	Route of administration (vehicle/ formulation)	Dose (mg/kg)	Remarks, including approximate LD_{50} (mg/kg) or maximum tolerated dose (MTD)	Study No.
Rat Crl:CD® (SD)IGS BR non-GLP	6m 6f	Oral, 0.1% Tween 20 in 0.5% methylcellulose	0, 100, 300, 900	Mortality: ≥ 300 mg/kg (f), 900 mg/kg (m). Individual males at 100 mg/kg and surviving females at 300 mg/kg: lethargy and ventral recumbency. NOAEL: 100 mg/kg Lethal dose: f: 300 mg/kg, m: 900 mg/kg	[T06-06-06]
Rat Crl:CD® (SD)IGS BR non-GLP	6m 6f	Oral, 0.5% methylcellulose	0, 50, 100	Well tolerated NOEL: 100 mg/kg	[T06-08-14]
Dog Beagle non-GLP	4m 4f	Oral, 0.5% methylcellulose	5, 10, 20, 40	Emesis noted at 2 hrs post-dose at 40 mg/kg. NOAEL: 40 mg/kg	[T06-09-06]

f = female animals; m = male animals; NOEL=No-observed-effect level; NOAEL=No-observed-adverse-effect level

In single dose toxicity it was concluded that ruxolitinib was well tolerated following single oral doses of up to 100 and 300 mg/kg in female and male rats, respectively and 40 mg/kg in dogs.

Repeat dose toxicity

Table 2: Summary of repeat dose toxicity studies with ruxolitinib.

Study ID	**Species/Sex / Number per group**	**Dose (mg/kg), oral gavage. (NOAEL is underlined)**	**Duration**
[T08-01-13] non-GLP	Mouse (CD-1)/M+F/10	0, 30, 100, <u>300</u>, 600	7 days
[T08-02-07]	Mouse (CD-1)/M+F/10	0, 30, 60/<u>180</u> (15 days), 90	28 days
[T08-05-07]	Tg.rasH2 mice/ 25M+25F/group	0, 50, 100, 175, 250, 350	28 days

[T06-06-12] non-GLP	Rat (Sprague-Dawley)/M+F/6	0, 100, 200 (M); 0, 50, 100 (F)	8 days
[T06-08-03]	Rat (Sprague-Dawley)/M+F/15	0, 15, 50, 100	28 days
[T08-06-02]	Rat (Sprague- Dawley)/F/10	0, 75, 150, 250	13 weeks
[T07-10-06]	Rat (Sprague-Dawley)/M+F/23	0, 5, 15, 30 (M), 60 (F)	6 months
[T06-09-07] non-GLP	Dog (Beagle)/M+F/2	0, 3, 10, 30	10 days
[T06-11-03]	Dog (Beagle)/M+F/6	0, 3, 10, 20	28 days
[T07-10-07]	Dog (Beagle)/M+F/7	0, 0.5, 2.5, 5, 10	6 months
[T08-07-03]	Dog (Beagle)/M+F/7	0, 0.75, 1.5, 3, 6	12 months

Repeat oral dose toxicity studies with ruxolitinib of up to 4 weeks in mice, 6 months in rats, and 12 months in the dog were conducted. The findings observed in all of these species were primarily those expected that are related to the pharmacological mode of action of the drug and included decreases in lymphocytes, eosinophils, reticulocytes, red blood cell, haemoglobin and haematocrit as well as hypocellularity of the bone marrow and lymphoid organs (spleen, thymus, lymph nodes). In the 4-week CByB6F1 mice toxicity study, acute exudative inflammatory changes in nasal cavities at ≥ 175 mg/kg were noted. Increase in nasal exudative inflammation (minimal to moderate in severity) was also noted in the 26-week carcinogenicity study (12-fold exposure margin to highest clinical dose). No such effects have been noted in the clinical studies.

In the 13- week rat study, minimal heart fibrosis was seen in females at ≥ 150 mg/kg (a dose associated with an AUC (91 μM*h) that is 11-fold greater than the AUC at a 25 mg BID clinical dose). The fibrous connective tissue replacing cardiac myocytes was primarily affecting the papillary muscles at the apex of the heart. Absence of bronchus associated lymphoid tissue was also noted in individual animals.

In the 6 month rat study, minimal adrenal cortical atrophy in seven of 15 male rats was noted at the highest dose administered, 60 mg/kg/day. These microscopic changes were not observed at recovery necropsy. The minimal cortical atrophy observed at the end of 6 months treatment, were fully reversed after a 6 week recovery period.

In the 6-month dog study, prostatic hypoplasia/atrophy in male dogs and oestrus/diestrus were noted in one mid- and several high dose dogs but not in control animals. All male dogs with prostatic hypoplasia/atrophy in the 6 month study had normal testes with active spermatogenesis.

Demodectic mange, bacterial pneumonia and viral-induced papillomas were seen in the dogs (see discussion on non-clinical aspects).

The mean unbound AUC values associated with nonclinical NOAEL doses compared to those of the highest therapeutic dose (25 mg twice daily) are 12-fold higher in Tg.rasH2 mice (26-week carcinogenicity study), 16-fold higher in female rats but approximately 2-fold lower in male rats (6 month study), and approximately equivalent in dogs (12 month study). Comparisons for mean Cmax are similar.

Genotoxicity

Table 3: Genotoxicity studies with ruxolitinib

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses[a] (mg/kg)	GLP Compliance	Testing Facility
Reverse gene mutation	Salmonella typhimurium	In vitro	48-72 hours	1.5, 5.0, 15, 50, 150, 500, 1500, 5000 µg/plate	No	BioReliance T06-01-03]
	Salmonella typhimurium/ Escherichia coli	In vitro	48-56 hours	±S9: 33.3, 100, 333, 1000, 2500, 5000 µg/plate	Yes	Covance Laboratories, Inc. T06-08-01
Chromosome aberration	Peripheral human lymphocytes	In vitro	3 hours +S9, 22 hours –S9 with harvest ≈22 hours from treatment start	+S9: 10-95 µg/mL -S9: 10-65 µg/mL	Yes	Covance Laboratories, Inc. T06-08-02
In vivo micronucleus	Rat/CD(SD) IGS BR	Oral gavage	Single dose	0, 62.5, 125, 250	Yes	Covance Laboratories, Inc. T06-10-02

Carcinogenicity

Table 4: Carcinogenicity studies with ruxolitinib

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses[a] (mg/kg)	GLP Compliance	Testing Facility	Study Number
One month dose range finder	Mouse (CByB6F1)	Oral gavage	28-30 days	0, 50, 100, 175, 250, 350	Yes	BioReliance	[T08-05-07]
26-week study	Mouse/Tg.rasH2	Oral gavage	26 weeks	0, 15, 45, 125	Yes	BioReliance	[T09-02-03]

A 26-week oral (gavage) carcinogenicity study conducted in transgenic mice (Tg.rasH2) has been completed. There was no statistically significant increase in the incidence of neoplasms, but exudative inflammation of the nasal cavity in ruxolitinib treated groups was noted.

Reproduction Toxicity

Table 5: Overview of reproductive and developmental toxicity studies with ruxolitinib

Study type/ Study ID / GLP	**Species; Number / group**	**Oral Dose (mg/kg/day)**	**Dosing period**
Male and female fertility/ T09-06-01/GLP	Rat Crl:CD® (SD)/22	0-10-30-60	Males: 28 days prior to mating and for at least 10 weeks overall Females: 14 days prior to mating to Gestation Day 7. Treated males were paired with treated females.

Embryo-fetal development (dose range finding)/T07-10-14/GLP	Rats CRL:CD® (SD)IGS BR time-mated/6F	0-15-30-60- 120	Gestation Day 7-20
Embryo-fetal development /T07-12-04/GLP	Rats CRL:CD® (SD)IGS BR time-mated/25F	0-15-30-60	Gestation Day 7-20
Embryo-fetal development (dose range finding)/T07-10-13/GLP	Rabbit NZW/25F	0-10-25-50- 100	Gestation Day 8-21
Embryo-fetal development /T07-12-05/GLP	Rabbit NZW/20F	0-10-30-60	Gestation Day 8-21
Peripost Natal/T10-02-03/GLP	Rat CRL:CD/100F	0-5-15-30	Gestation Day 6 - Lactation Day 20

Fertility and early embryonic development was evaluated in rats and showed increases in post-implantation loss (NOAEL, 10 mg/kg). In embryo-fetal assessments, an increase in late resorptions (rabbit only) and reduced fetal weights (rats and rabbits) were noted at the highest and maternally toxic dose (NOAEL for the rat and rabbit studies was 30 mg/kg/day).

In rabbits, an increased number of malformations were noted in animals treated with ruxolitinib but not in the control group. Hydrocephaly was noted in one fetus and umbilical hernias were noted in two fetuses from separate litters from dams given 60 mg/kg/day. An unossified pubis was also noted in one fetus at this high dose. Incidental skeletal malformations included fused ribs in one 10 mg/kg/day fetus, fused thoracic centra in two 10 mg/kg/day fetuses from one litter and fused ribs and thoracic centrum in one 30 mg/kg/day fetus.

Toxicokinetic data

Table 6: Toxicokinetic parameters of ruxolitinib in mice, rats and dogs in multiple dose studies of 28 days or longer at the corresponding NOAEL

		Species						
Gender	PK Parameters	TgM[a]	CDM[b]	Rat	Rat	Dog	Dog	Dog
Male	Day	176	27	28	181	28	175	357
	Dose (mg/kg)	125	180	50	30	10	2.5	1.5
	Cmax (µM)	24.4	16.0	1.17	0.445	4.82	3.01	0.630
	Tmax (h)	0.500	0.500	0.50	0.500	1.2	0.64	0.929
	AUC0-24h (µM·h)	67.8	38.9	1.08	0.662	23.0	7.54	2.36
	T1/2 (h)	1.39	1.26	ND	1.11	2.06	1.2	1.89
Female	Day	176	27	28	181	28	175	357
	Dose	125	180	50	60	10	2.5	1.5

		Species						
Gender	PK Parameters	TgM[a]	CDM[b]	Rat	Rat	Dog	Dog	Dog
	Cmax (μM)	13.1	12.6	3.51	6.11	4.51	3.48	0.844
	Tmax (h)	0.500	0.500	0.50	0.500	1.0	0.64	0.786
	AUC0-24h (μM·h)	78.0	38.4	11.1	25.8	16.7	8.10	2.57
	T1/2 (h)	3.91	0.897	2.3	1.40	1.55	1.1	1.50
	References	[T09-02-03]	[T08-02-07]	[T06-08-03]	[T07-10-06]	[T06-11-03]	[T07-10-07]	[T08-07-03]

a: CByB6F1 Hybrid mice (Tg.rasH2 non-transgenic littermates)

b: CD-1 mouse; administered 60 mg/kg from Days 0-12 and 180 mg/kg from Days 13-27

ND: Half-life not determined due to insufficient data points to characterize plasma concentration decay

Table 7: Comparative toxicokinetic data and total systemic exposure of ruxolitinib following oral administration to mice, rats, dogs and myelofibrosis patients

			Systemic (plasma) exposure				
Species	Gender	Dose [a]	Cmax (nM)	Ratio to humanb	AUC (nM·h)	Ratio to human [b]	References
Human	M/F	0.66 [c]	1481		8726		[INCYTE-DMB-10.56.3]
Tg.rasH2 mouse	Male	125	24400	16.5	67800	7.8	[INCYTE-DMB-09.76.2]
	Female	125	13100	8.8	78000	8.9	[INCYTE-DMB-09.76.2]
CD-1 mouse	Male	180	16000	10.8	38900	4.5	[INCYTE-DMB-08.107.1]
	Female	180	12600	8.8	38400	4.4	[INCYTE-DMB-08.107.1]
Rat	Male	30	445	0.3	662	0.1	[INCYTE-DMB-08.105.1]
	Female	60	6110	4.1	25800	3.0	[INCYTE-DMB-08.105.1]
Dog	Male	1.5	630	0.4	2360	0.3	[INCYTE-DMB-09.75.1]
	Female	1.5	844	0.6	2570	0.3	[INCYTE-DMB-09.75.1]

Data presented are for animals after daily repeated oral administration at the end of the dosing for the given studies (Day 176 for CByB6F1 Hybrid mouse, Day 28 for CD-1 mouse, Day 181 for rat and Day 357 for dog). Data for human are extrapolated from dose normalized data obtained in myelofibrosis patients following bid dosing [study INCB 18424-251].

a: Dose in mg/kg/day represents highest therapeutic dose in myelofibrosis patients and NOAEL in animals

b: Ratios of exposure in animals to those in patients based on total AUC values. Ratios based on unbound drug are described in [CTD Section 2.4.5.6]

c: Calculated from total daily dose (50 mg/day) and an approximate mean body weight of 75 kg for myelofibrosis patients in Phase 2 and Phase 3 studies.

The mean unbound AUC values associated with nonclinical NOAEL doses compared to those of the highest therapeutic dose (25 mg twice daily) are 12-fold higher in Tg.rasH2 mice (26-week carcinogenicity study), 16-fold higher in female rats but approximately 2-fold lower in male rats (6 month study), and approximately equivalent in dogs (12 month study). Comparisons for mean Cmax are similar.

Local Tolerance

No local tolerance studies have been conducted since clinical studies with an i.v. formulation were not required to support the proposed indication.

Other toxicity studies

Phototoxicity

No phototoxicity or photoallergy or irritancy studies have been performed via the oral route of administration. In GLP studies with topical administration, at concentrations of up to 10% in the liquid vehicle, dimethylformamide, ruxolitinib was negative for skin sensitization potential in the murine LLNA. Ruxolitinib cream at concentrations of ≤ 1.5% was also tested in a guinea pig model of photoallergy, and was determined to lack both photoallergic and contact hypersensitivity potential. In a phototoxicity assay in male albino hairless guinea pigs, no adverse skin reactions and no evidence of a phototoxic response were observed following dermal treatment of ruxolitinib cream at concentrations of ≤ 1.5% in the presence or absence of solar-simulated ultraviolet radiation. Ruxolitinib was considered photoclastogenic in an *in vitro* assay using CHO cells.

Chromosomal aberration assay in Chinese hamster ovary (CHO) cells in the presence of ultraviolet light. (T08-02-11)

In the chromosomal aberrations assay repeat, replicate cultures of CHO cells were treated with concentrations of 1.79, 5.00, 10.0, 20.0, 28.6, 30.0, 60.0, 80.0, 120, 160, and 200 µg/mL without and with UV exposure. Cultures were harvested 20 hours after the initiation of treatment. Cultures treated with 20.0, 28.6, and 60.0 µg/mL without UV light exposure and 1.79, 20.0, 28.6, 30.0, and 60.0 µg/mL with UV light exposure were analyzed for chromosomal aberrations. Concentrations of ≥ 80 µg/mL were associated with levels of cytotoxicity that made them unevaluable. No significant increase in cells with chromosomal aberrations was observed in the cultures analyzed from the assay without UV light exposure. Significant increases in cells with chromosomal aberrations were observed in the cultures treated with 28.6, 30.0, and 60.0 µg/mL from the assay with UV light exposure.

2.3.5. Ecotoxicity/environmental risk assessment

Table 8: Summary of main study results

Substance (INN/Invented Name): INC424 / INCB018424 (ruxolitinib)			
CAS-number (if available): 1092939-17-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log Kow	Study report: Notox Project 495597)	log Kow = 2.3 – 2.6 (at pH 4), 2.3 – 2.4 (at pH 7), 2.5 – 3.0 (at pH 9).	log Kow < 4.5. Ruxolitinib is therefore not a potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$: Following a bibliographic search, the maximum prevalence in the general population in the European Community is estimated to be 0.25 per 10,000 persons equating to an estimated 12, 645 affected persons in the		PECsurface water = DOSEai * Fpen / WASTEWinhab * DILUTION = 50 mg/inhab/d * 0.000025 / (200 L/d * 10) **PECsurface water = 0.000625 µg/L**	< 0.01 threshold

EU (EuroStat 2008).			
Other concerns (e.g. chemical class)			No

2.3.6. Discussion on non-clinical aspects

The Applicant has conducted an adequate program to elucidate the pharmaco-toxicological properties of ruxolitinib. The mechanism of action through the selective inhibition of JAKs seems clear. Based on the non-clinical pharmacology data there is support for effect in the intended disease for this application.

The detected adverse effects in safety pharmacology studies are not a cause for major concern due to the relatively high exposure margins compared with the highest clinical dose. 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 Cmax) 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.

Based on comparative PK characteristics of ruxolitinib the animal species used for toxicology studies are considered appropriate.

A full program of non-clinical toxicity studies has been conducted in appropriate animal species, including single and repeat dose toxicity testing, genotoxic and carcinogenicity testing, reproductive and developmental studies and phototoxicity. The findings observed in all of these species were primarily those expected that are related to the pharmacological mode of action of the drug and included decreases in lymphocytes, eosinophils, reticulocytes, red blood cell, haemoglobin and haematocrit as well as hypocellularity of the bone marrow and lymphoid organs (spleen, thymus, lymph nodes). Notably, the dose limiting toxicity for ruxolitinib in the clinical setting is thrombocytopenia, which has not been observed in nonclinical toxicology evaluations.

Minimal heart fibrosis was seen in rats. Absence of bronchus associated lymphoid tissue was also noted in individual animals. The absence of heart fibrosis in the dogs and the relatively high exposure to ruxolitinib in the rats compared to the clinical dose indicate a low clinical relevance of this finding.

Reversible minimal adrenal cortical atrophy was noted in rats. Furthermore, as this finding has not been reproduced in the ruxolitinib mouse or dog toxicity studies it is considered of low significance.

Prostatic hypoplasia/atrophy in male dogs and oestrus/diestrus were noted in dogs. Prostate growth and development is partially mediated by prolactin and growth hormone, both of which stimulate gene transcription via the JAK-STAT pathway. Therefore the effects on the prostate are possibly a consequence of the pharmacologic activity of ruxolitinib. All male dogs with prostatic hypoplasia/atrophy had normal testes with active spermatogenesis. The minimal finding is likely due to sexual immaturity in a small proportion of the dogs after 6 months, and the proportions are too low to assess accurately across dose groups. This interpretation is further supported by the data from the 12-month dog study which confirmed no effect.

Demodectic mange, bacterial pneumonia and viral-induced papillomas were seen in the dogs. Ruxolitinib has immunosuppressive effects which is the most probable cause to the increased incidence of infections. The risk for adverse effects occurring in patients due to immunomodulatory effects of ruxolitinib has been noted in the SmPC.

In rats and dogs, the exposure margins at NOAL compared to the highest clinical dose are limited by the exaggerated pharmacological effects of JAK inhibition. The complete toxicity profiles can therefore not be characterised due to these limitations.

Genotoxicity studies in bacterial *in vitro* systems and in mammalian *in vitro* and *in vivo* systems with and without metabolic activation did not reveal any evidence for a mutagenic or clastogenic potential for ruxolitinib. Further, six selected impurities demonstrated no evidence of a potential for mutagenicity in AMES evaluations (data not shown).

A 26-week oral (gavage) carcinogenicity study conducted in transgenic mice (Tg.rasH2) has been completed. The mouse model selected was considered to be acceptable by CHMP in a Scientific Advice (EMEA/CHMP/SAWP/593338/2008. November 20). The Tg.rasH2 mouse model not only responds to a range of weak and strong genotoxic carcinogens but it has also demonstrated some sensitivity to non-genotoxic carcinogens. There was no statistically significant increase in the incidence of neoplasms. Exudative inflammation of the nasal cavity in ruxolitinib treated groups resulted in the nasal cavity being considered to be a target organ for non-neoplastic inflammatory lesions.

A 2-year carcinogenicity study in rats is on-going. Considering that ruxolitinib is not genotoxic, not carcinogenic in the Tg.rasH2 mice, and noting the absence of preneoplastic lesions in repeated dose toxicity studies, and considering the patient population, it is acceptable that the results from the 2-year carcinogenicity study will be submitted post-approval as suggested.

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 rabbits, an increased number of malformations were noted. These malformations were not observed at the highest dose level. The observed malformations are within normal ranges for untreated rabbits. The rabbit study is however inconclusive due to the very low exposure margins obtained compared to the clinical use.

The lack of juvenile toxicity studies is accepted as this application is intended to support an indication in adult patients.

Based on the observed reprotoxic effects, the use of ruxolitinib during pregnancy is not recommended. 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 may be excreted in human milk and because the risk to nursing infants is unknown, ruxolitinib should not be used during breast-feeding.

No phototoxicity or photoallergy or irritancy studies have been performed via the oral route of administration. The topical/dermal tests for sensitization and phototoxicity are considered relevant to assessing the risk of similar reaction following oral drug treatment as the distribution of ruxolitinib and its metabolites to skin is similar following oral administration as after topical application. The studies indicate a low risk of phototoxic or sensitization reactions of ruxolitinib.

No immunotoxicity studies have been conducted, which is acceptable considering the known immunomodulatory effects of ruxolitinib.

Ruxolitinib PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Phase II studies are not required. Therefore ruxolitinib is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The application is considered approvable from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development programme for the proposed indication includes the following studies:
Two pivotal phase III studies and one supportive phase I/II study to assess efficacy and proof of concept in the proposed indication.

- ***Study INC424A2352*** is an open-label, randomised, active-comparator, multicentre study comparing the efficacy and safety of ruxolitinib tablets versus best available therapy (BAT) as selected by the Investigator in 219 patients with PMF, PPV-MF, or PET-MF. This is considered the main study for the purposes of this application in the EU.
- ***Study INCB18424-351*** is a randomised, double-blind, placebo controlled, multicentre study comparing the efficacy and safety of ruxolitinib tablets to a matched placebo in 309 patients with PMF, PPV-MF, or PET-MF. This study is considered as supportive data, as advised by the CHMP.
- The phase I/II trial, ***study INCB18424-251***, is a 2-centre, open-label, dose escalation study in patients with PMF, PPV-MF, or PET-MF which includes a preliminary assessment of efficacy and proof of concept in the claimed indication.

GCP

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 9: Controlled studies INCB 18424-351 and INC424A2352

	Study INCB 18424-351 Start: 24-Aug-2009; Cut-off: 2-Nov-2010	Study INC424A2352 Start: 1-Jul-2009; Cut-off: 4-Jan-2011
Study design	Double-blind, randomized 1:1 (ruxolitinib: placebo), no stratification.	Open-label, randomized 2:1 (ruxolitinib: BAT), IWG-MRT risk stratification.
Primary endpoint at	Week 24	Week 48
Populations	Men/women 18 years or older Diagnosis of MF (PMF, PPV-MF, or PET-MF) Classified as IWG-MRT High risk or Intermediate risk-2 Life expectancy > 6 months. Palpable spleen length ≥ 5 cm below the left costal margin. Naïve to JAK inhibitor therapy. Peripheral blast count < 10%	

	Study INCB 18424-351 Start: 24-Aug-2009; Cut-off: 2-Nov-2010	Study INC424A2352 Start: 1-Jul-2009; Cut-off: 4-Jan-2011
	Resistant or refractory to, intolerant of, or not a candidate for available therapy, and for whom treatment of MF was indicated. Peripheral blood absolute CD34+ count > $20x10^6$L	Not a candidate for stem cell transplantation (especially if no suitable donor was available).
Treatment	If assigned to ruxolitinib, starting dose was based on baseline platelet count: Patients with baseline platelet count > 200,000/µL started at 20 mg b.i.d. Patients with baseline platelet count > 100,000/µL to ≤ 200,000/µL started at 15 mg b.i.d. Dose regimen could be adjusted based on safety and efficacy so that each patient was titrated to their most appropriate dose. Doses were not to exceed 25 mg b.i.d. Patients on placebo or BAT who met protocol-specified criteria for crossover could begin dosing at 5 mg b.i.d. or 10 mg b.i.d. for lower platelet counts	
Criteria for crossover from control to ruxolitinib	Crossover before Week 24 required both symptom worsening and ≥ 25% spleen volume increase from baseline Crossover after Week 24: ≥ 25% spleen volume increase from baseline After the primary data analysis was complete and the study was unblinded, patients in the placebo arm could cross over to ruxolitinib.	Qualifying progression event: ≥ 25% spleen volume increase from on study nadir (including baseline) or splenectomy Patients could crossover at any time if they had a qualifying progression event.
Criteria for continuing treatment with ruxolitinib for patients randomized to ruxolitinib	Before Week 24, patients randomized to ruxolitinib who were unblinded for symptomatic spleen growth had to withdraw from the study. After Week 24, patients randomized to ruxolitinib who were unblinded for spleen growth could remain in the study if the Investigator determined they were receiving benefit. After the primary data analysis was complete and the study was unblinded, patients receiving ruxolitinib could remain in the study if the Investigator determined they were receiving benefit.	If a patient had a qualifying progression event (described above), they could enter the extension phase and remain in the study if the Investigator determined they were receiving benefit.

	Study INCB 18424-351 Start: 24-Aug-2009; Cut-off: 2-Nov-2010	Study INC424A2352 Start: 1-Jul-2009; Cut-off: 4-Jan-2011
Primary efficacy assessment	Number of patients with ≥ 35% spleen volume reduction at Week 24	Number of patients with ≥ 35% spleen volume reduction at Week 48
Secondary efficacy assessments	Duration of response, Overall survival	
	≥ 50% reduction in symptom score, Change in total symptom score (both at Week 24)	Spleen volume reduction response rate (at Week 24), Time to response, PFS, LFS, OS, duration of response, density of fibrosis
Exploratory Assessments	Spleen volume and length by visit, Body weight, JAK2V617F allele burden, ECOG status, transfusion status, plasma PD markers, Pop PK, EORTC QLQ-C30,	
	LFS, density of fibrosis, OS at Week 144, STAT3, Symptoms at Week 24 LOCF	FACT-Lym
Study sites	68 sites in the United States, 6 sites in Canada, and 15 sites in Australia	56 sites in 9 EU countries

The applicant claimed the approval for the following indication:

Jakavi is indicated for treatment of adult patients with myelofibrosis, including primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

The final indication following CHMP review of this application is:

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.

2.4.2. Pharmacokinetics

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

Distribution

The apparent volume of distribution at steady state is 53-65 litres in myelofibrosis 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.

Elimination

Ruxolitinib is mainly metabolized 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 hepatic 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 intestinal CYP3A4, Pgp and BCRP.

Ruxolitinib is mainly eliminated through metabolism. The mean elimination half-life of ruxolitinib is approximately 3 hours. Following a single oral dose of [14C]-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. Oral clearance has been estimated to approximately 19 L/h.

The pharmacokinetics is dose and time linear. Thus, there is little or no accumulation under multiple dose conditions. Ruxolitinib is eliminated through metabolism.

Dose proportionality and time dependencies

Data from single and multiple dose studies in healthy volunteers indicate that ruxolitinib exposure was linear with respect to dose.

No significant change in ruxolitinib pharmacokinetics was detected after continuous administration for up to 10 days when administered once daily (q.d.) and twice daily (b.i.d).

Special populations

The pharmacokinetics of ruxolitinib and metabolites have been studies under single-dose conditions in patients with normal, mild, moderate, severe or end-stage renal function impairment. Renal function was measured using Modification of Diet in Renal Disease (MDRD) as well as U-creatinine. As expected, the (total) exposure of ruxolitinib is not affected by renal impairment (mild to end stage renal disease-ESRD). However, the exposure of several metabolites is increased, in particular that of M11 and M27.

The PD effect is prolonged in patients with ESRD and a reduction of the initial dose is proposed as well as dosing after dialysis, on dialysis days only. Available data in this population suggest that the starting dose for patients with ESRD on haemodialysis is a single dose of 15 mg or 20 mg, to be administered after haemodialysis has been completed and only on the day of haemodialysis. A single dose of 15 mg is for patients with platelet count between 100,000/mm3 and 200,000/mm3 or a single dose of 20 mg for patients with platelet count of >200,000/mm3. Subsequent doses should be administered once daily on haemodialysis days following each dialysis session. Dosing only on dialysis days applying a dialysis frequency of 3 times a week, is estimated to result in low STAT3 inhibitory effect 24-48 hours post dose.

The rationale is to avoid overexposure of the metabolites. There are no human safety data on the higher metabolite exposures and no data on off-target activities which potentially could lead to adverse

effects. With the proposed dosing regimen, the PD effect becomes very low 24-48 (72) hours post dose (See figures 1 and 2 below) and there is a risk of insufficient efficacy. Therefore, if needed based on efficacy, daily dosing could be applied. However, dose titration needs to proceed carefully, monitoring safety and efficacy.

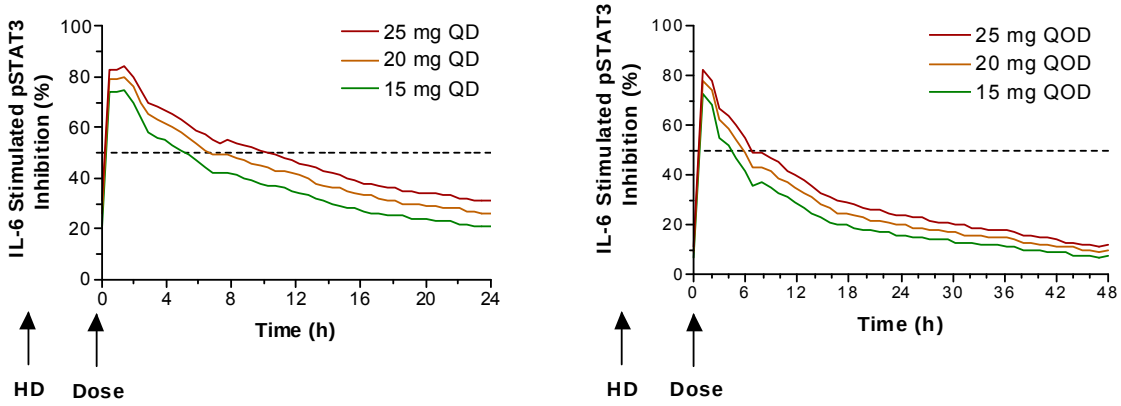


Figure 1: Simulation of steady state pharmacodynamics activity profiles (ruxolitinib plus metabolites, in equivalent ruxolitinib PD) following q.d. (left figure) or q.o.d. (right figure) administration of ruxolitinib in ESRD patients receiving pre-dose hemodialysis (HD)

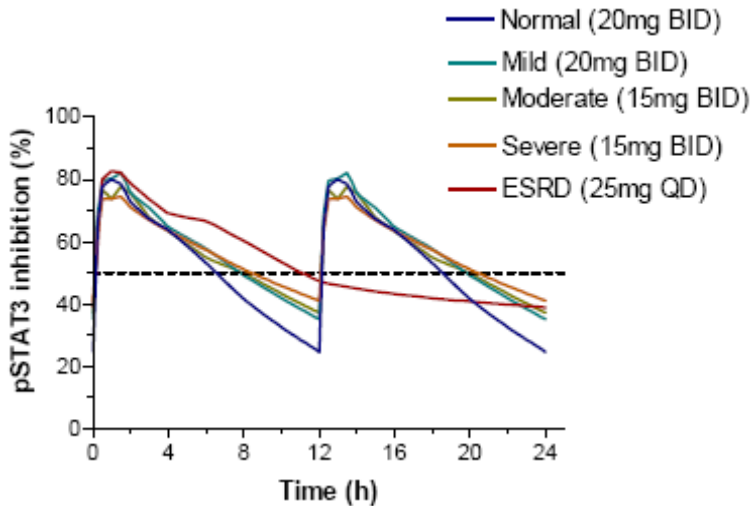


Figure 2: Simulation of steady-state profiles of total PD (ruxolitinib plus metabolites) following multiple-dose administration of INCB018424 in patients with various degrees of renal impairment (ESRD has received pre-dose HD)

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

In healthy subjects, no significant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in myelofibrosis 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.

The table below provides the total number of patients enrolled by age group for the development programme broken down by PK, controlled, and non-controlled trials.

Table 10: Number of patients enrolled by geriatric age group for PK, controlled and non-controlled trials (safety set)

Age Group	PK	Controlled*	Non Controlled	Total*
<65 years	38	199 (119)	137	374 (294)
65 – 74 years	19	223 (135)	96	338 (250)
75 – 84 years	1	96 (44)	31	128 (76)
≥ 85 years	0	7 (3)	2	9 (5)
*Number in parentheses is value if control arms from Study INCB 18424-351 and Study CINC424A2352 are excluded.				

Pharmacokinetic interaction studies

The applicant has performed a number of *in vitro* studies on the effects of ruxolitinib on CYP enzymes and transport proteins. Induction has been investigated *in vitro*. PXR mediated induction has been investigated in a reporter gene assay, where a clear positive signal was observed. There was no induction via CAR and the Ah receptor *in vitro*.

In vivo interaction studies have been performed with ketoconazole and erythromycin, rifampicin and methotrexate.

In healthy subjects co-administration of ruxolitinib (10 mg single dose) with a strong CYP3A4 inhibitor, ketoconazole, resulted in ruxolitinib Cmax 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.

In healthy subjects co-administration of ruxolitinib (10 mg single dose) with erythromycin 500 mg twice daily for four days (mild or moderate CYP3A4 inhibitors) resulted in ruxolitinib Cmax and AUC that were higher by 8% and 27%, respectively, than with ruxolitinib alone.

On the basis of in silico modelling, 50% dose reduction should be considered when using medications which are dual inhibitor of CYP2C9 and CYP3A4 enzymes such as fluconazole

Patients should be closely monitored and the dose titrated based on safety and efficacy when CYP3A4 inducers are administered (such as, but not limited to, avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St.John's wort (Hypericum perforatum))

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 ruxolitinib alone. The exposure of ruxolitinib active metabolites was unchanged.

Population PK and PK/PD

Population PK analysis has been performed for the parent drug. The final model chosen in the population PK analysis was a 2 compartment model with linear absorption. Gender was found to be a statistically significant covariate on CL/F while bodyweight was a covariate for Vc/F. It appears as the individual predictions from the model can be considered reasonably reliable for use in further PKPD analyses. The applicant has performed PK/PD analyses related to both efficacy and safety parameters. The EC_{50}s observed for spleen volume were generally roughly similar to the STAT3 EC_{50}s in healthy

volunteers. Looking at spleen volume the EC_{50} found in patients positive for the JAK2V617F mutation was about half the EC_{50} in patients negative for the mutation.

2.4.3. Pharmacodynamics

Mechanism of action

Ruxolitinib inhibited cytokine-induced STAT3 phosphorylation in whole blood from healthy subjects and myelofibrosis 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 myelofibrosis patients, indicating no accumulation of either parent or active metabolites.

Primary and Secondary pharmacology

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

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.

2.4.4. Discussion on clinical pharmacology

The phase I studies of ruxolitinib have mainly been performed in healthy volunteers. Population PK analysis has been performed in patients. Target effect PD measurements have been performed in many of the PK studies by investigating inhibition of cytokine stimulated STAT3 in healthy volunteers.

With regard to effects on blood pressure and according to a review by the Applicant, JAK1/2 dependent cytokines are not expected to play a major role in blood pressure regulation under normal physiologic conditions but may affect blood pressure under pathophysiologic conditions characterized by increased cytokine expression and enhanced JAK activation. In the case of myelofibrosis, JAK1/2 inhibition might be expected to change blood pressure toward levels observed before the onset or the progression of disease and before levels of circulating cytokines become increased. If the predominant effect of cytokines and increased JAK1/2 signalling is vasodilatory driven by inducing iNOS and excessive nitric oxide (NO) production, then JAK1/2 inhibition would be expected to increase blood pressure, in some cases unmasking previously elevated blood pressure. By contrast, the net effect of chronic cytokine elevation may be to cause vasoconstriction, driven by inhibition of eNOS (causing endothelial dysfunction), angiotensin II-AT1 receptor signalling and effects on vascular reactivity and remodelling. In such cases, JAK1/2 inhibition could result in a decrease in blood pressure toward normal. The effect of JAK1/2 inhibition on blood pressure will be determined by the net balance of its effects on both vasodilatory and vasoconstrictor mechanisms. In conclusion, there are mechanistic relationships between JAK signalling and inhibition, and blood pressure, however not easily predictable in the individual patient.

Ruxolitinib has pharmacologically active metabolites. The contribution of the metabolites to drug efficacy appears quite small. The *in vitro* activity of the metabolites was investigated using spiked whole blood samples. Thus, it may be assumed that the protein binding in the *in vitro* test was the same as *in vivo*. The applicant has simulated, based on systemic exposure and *in vitro* activity STAT3

inhibition, some of the scenarios where this information, and also *ex vivo* PD data was available. The PD response was over predicted in some situations but in general the prediction was reasonable.

Dose proportionality was demonstrated in the single and multiple dose studies.
There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis however based on the available data, a proposed dosing regimen is described in section 2.4.2 – "special populations" and reflected in section 4.2 of the SmPC.

Other dosing regimens may be more suitable from an efficacy perspective. However, due to increased metabolite exposure and lack of knowledge on the potential safety consequences of these exposures, dose modification should be followed by careful monitoring of safety and efficacy in individual patients.

The applicant is recommended to provide simulations on the PD-time course obtained with different dosing regimens, including daily schedules and potentially b.i.d schedules, attempting to obtain PD curves similar to the ones reached in normal renal function. Meanwhile, information regarding daily dosing is proposed in the SmPC if proceeding with careful monitoring of safety.

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 ruxolitinib 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 ruxolitinib and as clinically indicated thereafter once their liver function and blood counts have been stabilised. Ruxolitinib dose can be titrated to reduce the risk of cytopenia (see sections 4.2, 4.4 and 5.2 of the SmPC).

No additional dose adjustments are recommended for elderly patients.

There is no drug interaction study with an oral contraceptive

Available in vitro data gives a weak indication that ruxolitinib may be a mild inducer of PXR regulated enzymes. There is however, no time-dependency in CL observed and the in vitro signal is very weak. Therefore, the SmPC does not contain any induction warnings. However, in order to confirm adequate contraception due to the teratogenicity considerations, the performance of a DDI study with oral contraceptives is included in the RMP (see section 2.7).

Following concomitant use of ruxolitinib and rifampicin (a potent CYP3A4 inducer), the ruxolitinib pharmacodynamic activity was overall 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 Emax. It is possible that in the individual patient, an increase of the ruxolitinib dose is needed when initiating treatment with a strong enzyme inducer (see section 4.5 of the SmPC).

Based on the results of the interaction studies, when administering ruxolitinib with strong CYP3A4 inhibitors the unit dose of ruxolitinib 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 sections 4.2, 4.4 and 4.5).

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

Although ruxolitinib is not a relevant hepatic CYP3A4 inhibitor, it may not be excluded that ruxolitinib inhibits CYP3A4 in the intestine. Increased systemic exposure may be found in drugs which are metabolised by CYP3A4 and particularly in those undergoing extensive intestinal metabolism. Safety

monitoring of the orally administered CYP3A4 metabolised drugs which are extensively metabolised in the intestine is therefore advised when combining with ruxolitinib. The interaction is likely to be minimized if the time between drug co-administrations is kept apart during the absorption phase (e.g. at least 2 hours).

Ruxolitinib may inhibit P-glycoprotein and BCRP in the intestine. This may result in increased systemic exposure of substrates of these transporters such as dabigatran etixilate, cyclosporin, rosuvastatin and potentially digoxin. Therapeutic Drug Monitoring (TDM) or clinical monitoring of the affected drug is advised. The potential inhibition of P-gp and BCRP in the intestine can be minimized when staggered co-administration of dabigatran etixilate, cyclosporin and rosuvastatin with ruxolitinib is employed.

The RMP includes performing a drug interaction study with an oral CYP3A4 substrate such as midazolam. Besides worst case administration times, the study could include an investigation of staggered dosing to support a clear labelling language on how to reduce a possible effect.

The concurrent use of haematopoietic growth factors and ruxolitinib has not been studied. It is not known whether the JAK inhibition by ruxolitinib reduces the efficacy of the haematopoietic growth factors or whether the haematopoietic growth factors affect the efficacy of ruxolitinib as reflected in sections 4.4 and 4.5 of the SmPC.

The concomitant use of cytoreductive therapies and ruxolitinib has not been studied. The safety and efficacy of this co-administration is therefore not known as reflected in sections 4.4 and 4.5 of the SmPC.

2.4.5. Conclusions on clinical pharmacology

The data submitted by the applicant are considered appropriate. However, additional PK studies and simulations are proposed to fill information gaps. The lack of data is reflected in the SmPC.

Simulations supporting an optimized dosing regimen in ESRD are recommended.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- Due to the concerns regarding potential teratogenicity, and a very weak signal on enzyme induction, a study should be performed to confirm lack of interaction with oral contraceptives (see section 2.7 RMP).

- Based on *in vitro* inhibition data and the possible concentrations of ruxolitinib in the enterocyte, it may not be certified that ruxolitinib does not inhibit CYP3A4 *in vivo*, thereby affecting the large number of orally administered CYP3A4 substrates. Therefore an *in vivo* interaction study is needed (see section 2.7 RMP).

2.5. Clinical efficacy

2.5.1. Dose response study

Dose-finding study 18424-251

This was a multicentre, open-label, non-randomised, dose escalation study of INCB018424 in 154 subjects ≥18 years with therapy-requiring PMF, PPV-MF, or PET-MF. An interim report that contains available data for all subjects through 31 December 2009 with an addendum presenting additional survival data through 01 Mar 2011 was included in the application. All analyses were exploratory.

The disease severity system used (Lille (Dupriez) Scoring System) differed from the one used in the Phase 3 studies (IWG criteria; published 2009).

The study was comprised of 3 parts. Part 1 was a dose escalation phase to determine the MTD utilizing a bid regimen; with thrombocytopenia as DLT the 25 mg bid dose was confirmed as the MTD. Part 2 examined 3 alternative dose regimens (qd regimen, low-dose regimen of 10 mg bid, and an induction/maintenance regimen consisting of 25 mg bid/10 mg bid).

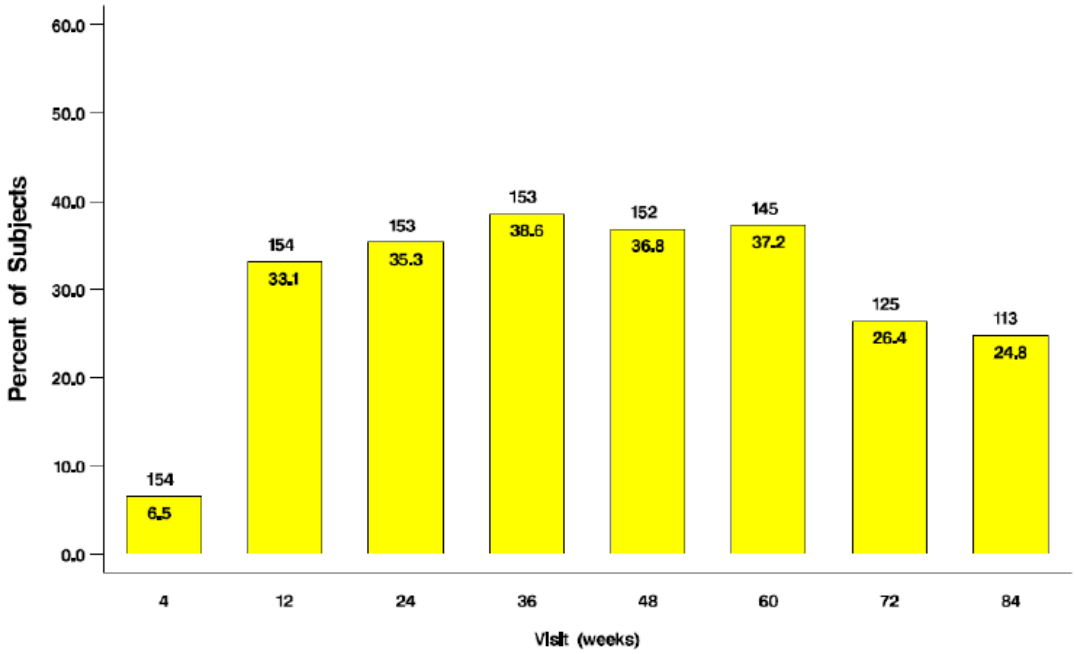
Part 3 examined 3 groups of subjects to further evaluate the safety and efficacy of the selected dose levels, but also to explore dose selection and modification based on platelet count values as doses of 10 mg bid and 25 mg bid differed in efficacy but also in the propensity for thrombocytopenia: Subjects with baseline platelet count >200,000/µL began administration at 15 mg bid; subjects with baseline platelet count ≤200,000/µL began administration at 10 mg bid. For later cohorts, doses were titrated based on efficacy and safety to a maximum of 25 mg bid.

Table 11: Spleen Size Reduction and Incidence of Thrombocypenia at different Doses

Parameter	25 mg BID	15 mg BID	10 mg BID
N as of October 10, 2008	47	20	25
Proportion achieving at least 50% reduction in spleen size[a] (subjects with palpable spleen at baseline)	56% (22 of 39)	31% (5 of 16)	35% (8 of 23)
Proportion with Grade 3 thrombocytopenia	23.4%	0%	4.0%
Proportion with Grade 4 thrombocytopenia	6.4%	0%	0%

a Only subjects with a palpable spleen at Baseline and at least 1 month of spleen size data are included in the spleen reduction analysis.

Efficacy



The number on the top of each box is the number of subjects used as the denominator, and the number inside the box is the percent of subjects

Figure 3: Proportion of Subjects with Clinical Improvement (ITT Subjects)

At Week 12, 33.1% of subjects were assessed as showing clinical improvement, and no subject had progressive disease or had relapsed. In general, the proportion of subjects who were assessed as showing clinical improvement increased through Week 36 and stayed at this level until Week 60.

At Week 24 (6 months of treatment), 43.8% of subjects had a ≥ 50% reduction from Baseline in spleen length. At Week 72 (approx 1.5 years of treatment), 23.6% of subjects had a ≥ 50% reduction from Baseline in spleen palpation length.

Patients who initiated dosing at 15 mg bid and had subsequent optimization of treatment showed the highest consistent response rate over time. Dosing at the MTD of 25 mg bid resulted in 27.5% grade 3-4 anaemia and 36.1% grade 3-4 thrombocytopenia with approximately 50% of patients requiring dose reductions.

Table 12: Proportion of Subjects Achieving ≥ 50% Reduction from Baseline in Spleen Palpation Length by Visit Based on Initial Treatment (ITT)

	Total[a]	10 mg bid	15 mg bid	25 mg bid	50 mg bid	All qd
Week 4, n/N (%)	52/138 (37.7)	9/27 (33.3)	13/34 (38.2)	16/37 (43.2)	3/4 (75.0)	11/36 (30.6)
Week 8	55/138 (39.9)	8/27 (29.6)	17/34 (50.0)	16/37 (43.2)	3/4 (75.0)	11/36 (30.6)
Week 12	60/138 (43.5)	9/27 (33.3)	16/34 (47.1)	20/37 (54.1)	3/4 (75.0)	12/36 (33.3)
Week 24	60/137 (43.8)	9/26 (34.6)	18/34 (52.9)	18/37 (48.6)	2/4 (50.0)	13/36 (36.1)
Week 36	55/137 (40.1)	8/26 (30.8)	16/34 (47.1)	16/37 (43.2)	2/4 (50.0)	13/36 (36.1)
Week 48	50/136 (36.8)	6/26 (23.1)	18/33 (54.5)	15/37 (40.5)	1/4 (25.0)	10/36 (27.8)
Week 60	45/129 (34.9)	5/25 (20.0)	14/27 (51.9)	16/37 (43.2)	1/4 (25.0)	9/36 (25.0)
Week 72	26/110 (23.6)	3/24 (12.5)	0/9	14/37 (37.8)	1/4 (25.0)	8/36 (22.2)

Based on average dose, subjects receiving >10-≤15 mg or >15-≤20 mg bid had larger median percent changes from baseline compared with subjects receiving >5-≤10 mg bid.

The starting dose regimen selected for the phase III studies was 15 and 20 mg bid for patients with baseline platelet counts 100,000 – 200,000 and >200,000, respectively. Preliminary evidence of efficacy was obtained.

2.5.2. Main studies

INC B424A2-352: A randomised study of the JAK inhibitor INC424 tablets compared to best available therapy in subjects with primary myelofibrosis (PMF), post-polycythemia veramyelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF)

INCB 18424-351: A randomised, double-blind, placebo-controlled study of the JAK inhibitor INCB018424 tablets administered orally to subjects with primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF), or post-essential thrombocythemia-myelofibrosis (PET-MF)

Methods

Study Participants

Study 352:

219 subjects were randomised in 2:1 ratio, with 146 subjects receiving ruxolitinib and 73 patients receiving best available therapy as determined by the investigator.

Key inclusion criteria

1. Subjects 18 years of age or older.

2. Subjects must have received the diagnosis of PMF, PPV-MF or PET-MF, according to the 2008 WHO criteria, regardless of JAK2 mutation status.

3. Subjects with MF requiring therapy must be classified as high risk (3 or more prognostic factors) OR Intermediate risk level 2 (2 or more prognostic factors). The prognostic factors, defined by the International Working Group are: • Age > 65 years • Presence of constitutional symptoms (weight loss, fever, night sweats) • Marked anaemia (Hemoglobin < 10g/dL)* • Leukocytosis (history of WBC > 25 x109/L) • Circulating blasts ≥ 1%. * For the purpose of evaluating risk factors, subjects receiving regular transfusions of packed red blood cells were considered to have hemoglobin < 10 g/dL.

4. Subjects with peripheral blood blast count of < 10%.

5. ECOG performance status of 0, 1, 2 or 3.

6. Subjects with a palpable spleen measuring 5 cm or greater from the costal margin to the point of greatest splenic protrusion.

7. Subjects with a stable therapeutic regimen for at least 2 weeks before screening and no less than 4 weeks prior to baseline.

Key exclusion criteria

1. Subjects with a life expectancy of less than 6 months.

2. Females who are pregnant or are currently breastfeeding.

3. Subjects with inadequate bone marrow reserve as demonstrated by: a) Absolute neutrophil count (ANC) ≤ 1000/μL. b) Platelet count < 100,000/μL without the assistance of growth factors, thrombopoietic factors or platelet transfusions.

4. Subjects with any history of platelet count < 50,000/μL or ANC < 500/μL except during treatment for a myeloproliferative disorder or treatment with cytotoxic therapy for any other reason.

5. Direct bilirubin > 2.0 x upper limit of normal (ULN). Alanine aminotransferase (ALT) > 2.5x institutional ULN. Creatinine > 2.0 mg/dL.

6. Subjects with clinically significant bacterial, fungal, parasitic or viral infection which require therapy

7. Subjects currently without the option of stem cell transplantation, either because they were not a candidate, or because a suitable donor was not available.

8. Subjects with cardiac disease which in the Investigator's opinion could jeopardize the safety of the subject or the compliance with the protocol.

9. Subjects for whom the dose or dose regimen of any therapy used to treat MF was modified at any time from 2 weeks prior to the start of screening through the beginning of baseline evaluations.

10. Subjects who had splenic irradiation within 12 months prior to Screening.

11. Subjects undergoing treatment with hematopoietic growth factor receptor agonists (i.e. Epo, G-CSF, romiplostim, eltrombopag) at any time within 2 weeks prior to Screening or 4 weeks prior to baseline.

Study 351

309 subjects were randomised to receive either ruxolitinib or placebo. 155 subjects received ruxolitinib and 154 patients received placebo.

Key inclusion criteria

1. 18 through 85 years of age.

2. Life expectancy of at least 6 months.

3. Diagnosed with PMF, PPV-MF or PET-MF, according to the 2008 WHO criteria irrespective of JAK2 mutation status.

4. Subjects with myelofibrosis requiring therapy must be classified as high risk (3 or more prognostic factors) OR intermediate risk level 2 (2 or more prognostic factors) if they have also been diagnosed with PMF, PPV-MF, or PET-MF at least 24 months prior to study entry.
5. ECOG performance status of 0, 1, 2 or 3.
6. Must have palpable spleen measuring 10 cm or greater below the costal margin.
7. Have adequate bone marrow reserve as demonstrated by: ANC > 1000/μL and platelet count > 100,000/μL without the assistance of growth factors, thrombopoietic factors or platelet transfusions. Subjects may not have received growth factors for at least one month prior to receiving the first dose of study medication.
8. Total bilirubin ≤ 2.0 mg/dL; Alanine aminotransferase (ALT) ≤ 2.5x institutional ULN; Creatinine ≤ 2.0 mg/dL.

Key exclusion criteria

1. Females who are pregnant or are currently breastfeeding.
2. Subjects with clinically significant bacterial or viral infection which require therapy
3. Subjects with NYHA Class III or IV impairments.
4. Treatment within the last 12 weeks prior to Screening with androgens to treat any MF symptoms.
5. Subjects with a known history of platelet counts < 50,000/μL or ANC < 500/μL except during treatment with cytotoxic therapy or irradiation.
6. Subjects who have had splenic irradiation within 3 months prior to Screening.
7. Subjects with cardiac disease which in the Investigator's opinion may jeopardize the safety of the subject or the compliance with the protocol.

Treatments

In the ruxolitinib arm, starting dosages of 15 mg and 20 mg bid were selected, with starting dose based on baseline platelet count; 100,000 – 200,000 and >200,000, respectively. Doses were permitted to be increased by 5 mg bid after 4 weeks of therapy in patients who met all of the following conditions: a) Inadequate efficacy was demonstrated by palpable spleen length below the costal margin that had been reduced by < 40% at the Week 4 visit relative to baseline. In 352, after Week 4, dose increases in ruxolitinib were allowed during the Randomized Treatment Phase only for those subjects who exhibited an increase in palpable spleen size; b) Platelet count at the Week 4 blood draw was > 150,000/μL and platelet count had never been below 150,000/μL at a prior laboratory evaluation while receiving ruxolitinib; and c) ANC levels remained at or above 1000/μL since enrolment in the study.

Table 13: Dose Reductions in Ruxolitinib or Matching Placebo Tablets for Safety for Subjects With Platelet Count Declines

Platelet Count at Time of Decline (in thousands)	Dose at the Time of Platelet Decline				
	25 mg bid	20 mg bid	15 mg bid	10 mg bid	5 mg bid
	Dose that MUST be Instituted				
≥ 125 K/μL	No dose reduction required				
100 to < 125 K/μL	**20 mg bid**	20 mg bid	15 mg bid	10 mg bid	5 mg bid
75 to < 100 K/μL	**10 mg bid**	**10 mg bid**	10 mg bid	10 mg bid	5 mg bid
50 to < 75 K/μL	**5 mg bid**	**5 mg bid**	**5 mg bid**	**5 mg bid**	5 mg bid
< 50 K/μL	MUST STOP ADMINISTRATION				

Study 352

In the control arm, BAT (oral or parenteral therapies) was commercially available and was administered according to manufacturer's instructions and Investigator discretion.

Reference therapy: Best-available therapy (BAT), which included the following medications:

- Hydroxycarbamide, anagrelide (anti-neoplastic agents)
- Prednisone, methylprednisone, prednisolone (glucocorticoids)
- Epoetin alfa, an anti-anaemic preparation
- Thalidomide, lenalidomide (Immunosuppresants)
- Mercaptopurine, thioguanine (purine analogs)
- Danazol, an anti-gonadotropins or similar agent
- Pegasys and Interferon-α (Interferons)
- Melphalan (nitrogen mustard analog)
- Acetylsalicyclic acid (platelet aggregation inhibitor)
- Colchicine, a preparation with no effect on uric acid metabolism

BAT also included the option of no treatment. BAT (oral or parenteral therapy) was commercially available and administered according to manufacturer's instructions and Investigator discretion. No experimental drugs were permitted during the study. It was recommended that control-group subjects who could not maintain platelet counts ≥ 50,000/μL and/or neutrophils ≥ 500/μL; or experienced another Grade 4 toxicity during the Randomised Treatment Phase were to either decrease the dose of BAT or switch to an alternative treatment approach.

Study 351

Placebo was used in the control arm.

Objectives

Study 352

Primary Objective: To compare the efficacy, safety, and tolerability of ruxolitinib given twice daily compared to best available therapy (BAT) in subjects with PMF, PPV-MF, or PET-MF.

Secondary Objective: To evaluate the population pharmacokinetics of ruxolitinib.

Study 351

Primary Objectives: To evaluate the efficacy, safety, and tolerability of ruxolitinib given twice daily compared with placebo, in subjects with PMF, PPV-MF, or PET-MF.

Secondary Objectives: To evaluate the effect of ruxolitinib on the subject reports of MF symptoms, and to evaluate the population pharmacokinetics of ruxolitinib.

Outcomes/endpoints

Efficacy:

Endpoints	Study INCB 18424-351	Study INC424A2352
Primary endpoint	Spleen volume response rate at Week 24	Spleen volume response rate at Week 48
Secondary endpoints in both trials	Duration of response Overall survival	
Exploratory endpoints in both trials	Spleen volume and length by visit Body weight JAK2V617F allele burden Eastern Cooperative Oncology Group (ECOG) status Transfusion dependence Plasma pharmacodynamic markers Population pharmacokinetics European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-30 (EORTC QLQ-C30)	
Secondary endpoints unique to 1 trial	Symptom response rate Symptoms at Week 24	Spleen volume response rate at Week 24 Time to response Progression free survival Leukemia free survival Bone marrow histomorphology
Exploratory endpoints unique to 1 trial	Leukemia free survival Bone marrow histomorphology Overall survival at Week 144 STAT3 Symptoms at Week 24-last observation carried forward CD34+ cell count > 200,000/µL	Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) Time to definitive deterioration for ECOG and patient-reported outcome (PRO)

Safety:

Safety and tolerability was assessed by: monitoring the frequency, duration and severity of adverse events (AEs), performing physical exams, and evaluating changes in vital signs and electrocardiograms (ECGs) as well as serum chemistry and haematology results.

Pharmacokinetics:

The concentrations from this study were analysed separately and were used as external validation dataset for the population pharmacokinetic model generated from pooled data from Studies INCB18424-251, INCB018424-351, and CINC424A2352.

Biomarkers:

JAK2V617F allele burden was determined for all subjects enrolled in the study.

Quality of life:

QoL was assessed in subjects using the EORTC QLQ-C30 questionnaire and FACT-lym questionnaire. Both of these instruments are self-administered questionnaires used for cancer subjects in clinical studies and contain functional subscales (physical, role, emotional, cognitive, and social).

Sample size

Study 352:

The sample size of this study was originally calculated based on the primary efficacy variable, the proportion of subjects achieving 35% reduction in spleen volume from baseline at Week 48. Assuming at least 35% of the active subjects would achieve a 35% reduction from baseline to Week 48, and that rate for the control subjects would be no more than 10%, a sample size of 150 subjects (100 in active

and 50 in control) would provide at least 90% power to detect a treatment difference in the primary endpoint at a 2-sided alpha level of 0.05 using the Chi-square test.

This study planned to enrol approximately 150 subjects. The protocol defined that the study would be closed to screening when at least 130 subjects had been enrolled, with 130 plus half of the subjects remaining in screening totalling at least 150 subjects. However, a significant increase in screening activity resulted in a total randomization level that was higher than anticipated. As a result, the total enrolment for the study was 219 subjects.

Study 351:

In order to provide a large safety database and adequate power for secondary efficacy variables, 240 subjects were planned to be randomized using a 1:1 ratio of ruxolitinib to placebo.

The primary efficacy endpoint of this study is the proportion of subjects achieving >35% reduction in spleen volume from Baseline to Week 24. It was assumed that at least 30% of the active subjects would achieve a >35% reduction from baseline to Week 24, and that rate for the placebo subjects would be no more than 10%. Under this assumption, a sample size of 240 subjects (120 per group) would provide a 97% power to detect a treatment difference in the primary endpoint at two-sided alpha level of 0.05 using the chi-square test.

This study planned to enrol approximately 240 subjects. Based on the study's screen fail rate, it was projected that it would be necessary to screen approximately 330 subjects to enrol 240. An estimate of the last day for screening was produced, targeting a total of 330 subjects screened to achieve 240 subjects enrolled. However, the screening rate increased considerably from that expected, resulting in a total of 476 patients being screened. As a result, the total enrolment for the study was 309 patients.

Randomisation

There was a block randomization with a block size of six, stratified by prognostic category of Intermediate (2 risk factors) or High risk (3 or more risk factors). The randomization list was created by StatWorks under Incyte responsibility using a validated SAS® program. This program generated the final randomization list. This list was provided to the IVRS provider (Clarix) to be used for patient randomization in one of the two treatment arms (Ruxolitinib or best available therapy).

Blinding (masking)

Study: 352

This was an open-label study.

The primary endpoint for this study was based on the change in splenic volume by independent central review of MRI or CT scans; these results were not provided to Investigators unless the subject reached an endpoint of 25% increase in spleen volume relative to the on-study nadir (including baseline). Images were read and measured by an external radiologist (an independent central reviewer) who was blinded to treatment assignment.

Study: 351

Subjects, Investigators, and the Sponsor remained blinded to the initial treatment assignment until the database was frozen and the primary data analysis was complete. Individual subject unblinding occurred if the subject had worsening symptomatic or asymptomatic spleen growth and qualified for early crossover or needed to be unblinded for safety reasons.

Statistical methods

Study: 352

The primary analysis for this study was conducted when all enrolled subjects completed Week 48 or were withdrawn from the study. Efficacy and safety results for the primary analysis were based on the Randomized Treatment Phase up to the time the last randomized subject had completed the Week 48 visit. For subjects who were eligible to enter the Extension Phase due to disease progression, the data captured were reported in the listings and flagged as having been collected in the Extension Phase (exceptions were LFS and OS, which were analyzed regardless of phase).

The primary efficacy endpoint was the proportion of subjects in the FAS who achieved ≥ 35% reduction in spleen volume from baseline at Week 48. Subjects without an evaluable spleen volume assessment at baseline were excluded from the primary analysis. The key secondary efficacy endpoint was defined as the proportion of subjects achieving a ≥ 35% reduction in spleen volume from baseline at Week 24. Other secondary efficacy endpoints were the duration of maintenance of a ≥ 35% reduction from baseline in spleen volume, the time to achieve a first ≥ 35% reduction in spleen volume from baseline, PFS, LFS, OS, and bone marrow histomorphology. In addition, supportive efficacy analyses included those on the PP set and on subgroups.

Confidence intervals (CIs) for response rate were calculated as exact binomial CIs. The two proportions were compared using the Cochran-Mantel-Haenszel (CMH) test stratified by prognostic category (Intermediate-2 or High). In the event that the proportion of one group was less than 4%, the exact CMH test was used instead.

Subjects experiencing a protocol-defined progression qualifying event prior to the Week 48 visit were considered as failures regardless of the spleen volume.

Missing values were not imputed. A subject was required to have a baseline spleen volume measurement to be included in the primary efficacy analysis. A subject with a missing Week 48 spleen volume measurement was considered as not having achieved the ≥ 35% reduction.

The primary efficacy endpoint was analysed using the PP set and on all subjects in the FAS considering subjects without baseline spleen volume measurement as failures.

The primary efficacy endpoint was also analysed using a logistic regression model with baseline spleen volume and treatment as the model effects and adjusted to baseline prognostic category. The odds ratio with a 95% CI of achieving ≥ 35% reduction in spleen volume was presented.

Another logistic regression model was fitted with baseline spleen volume, gender (male or female), MF type (PMF, PPV-MF or PET-MF), baseline prognostic category (Intermediate-2 or High), previous HU use, platelet count and treatment (active or control) as the model effects. This analysis produced the odds ratio with 95% CI of active vs. control after adjusting for the covariates.

The percent change from baseline at Week 48 was analyzed in an analysis of covariance (ANCOVA) model with baseline and treatment as the model effects for a between-group comparison.

Study 351

The proportion of subjects achieving ≥35% reduction in spleen volume from Baseline to Week 24 was calculated by treatment group. The two proportions were to be compared using the Chi-squared test. Per the SAP, the Chi Square test was replaced by Fisher's Exact test because of the low proportion of responders in one group.

This analysis was also conducted in the per-protocol population.

No imputation for missing data was performed. Subjects with missing Baseline values were excluded from analyses where a change from Baseline was calculated or when the Baseline was used as a covariate. A subject with a missing Week 24 spleen volume were considered as having not achieved the >35% reduction.

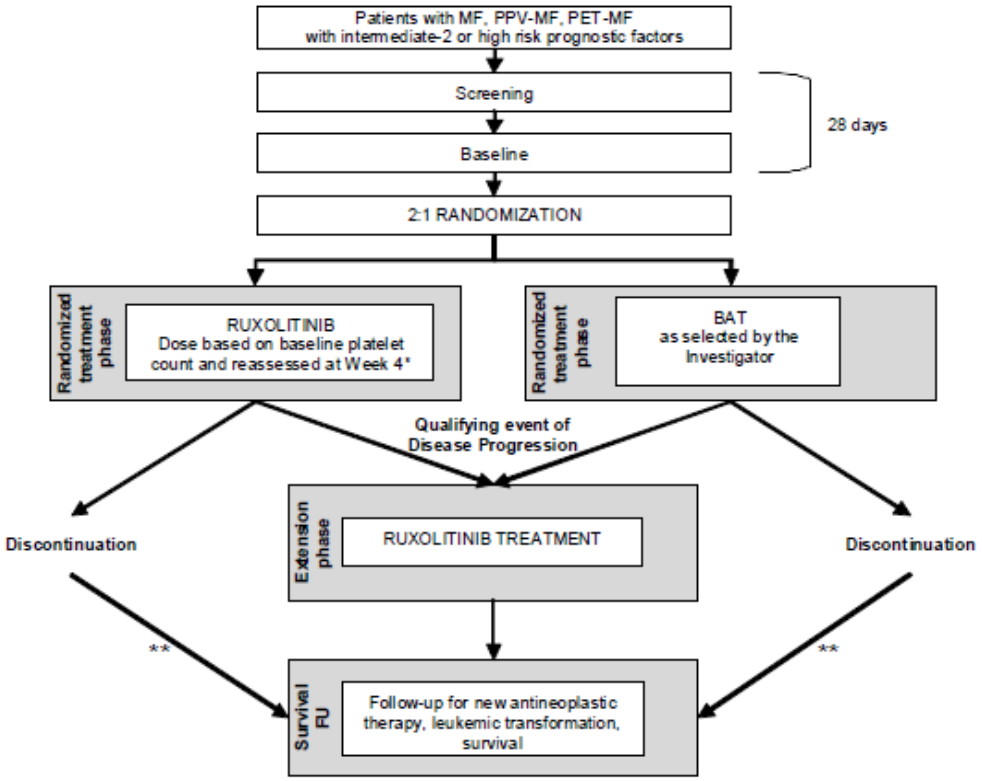
The primary efficacy endpoint was also analyzed using a logistic regression model with Baseline spleen volume, sex (male or female), MF disease sub-type (PMF, PPV-MF or PET-MF), hydroxyurea usage in the 3 months prior to entering the study, and treatment (active or control) as the model effects. This analysis produced the p-value of treatment effect and the odds ratio with 95% confidence interval of active versus control after adjusting for the covariates.

The percent change from Baseline to Week 24 was analyzed using both parametric and non-parametric methods. The Wilcoxon Rank-Sum test was used for a between-group comparison in the median percent change from Baseline, and a linear model with Baseline and treatment as the model effects were used for a between-group comparison in the mean percent change from Baseline.

Results

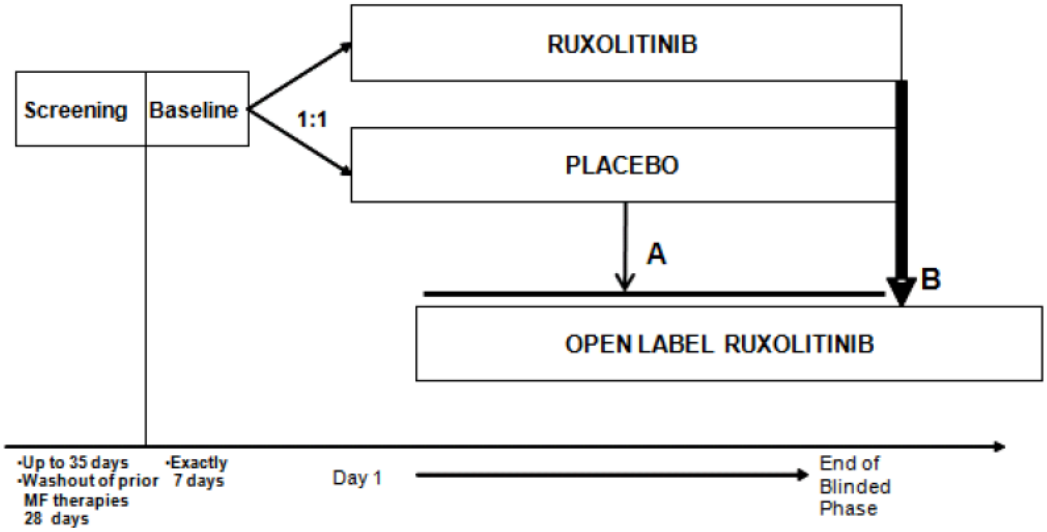
Participant flow

Design of Study INC424A2352



* Dose was reassessed throughout for safety and at specific time points for both safety and efficacy with potential dose adjustments; see Study INC424A2352 Protocol – Section 5.3.
** Implemented with Protocol Amendment 3.
A qualifying disease progression event (25% increase in spleen volume from on-study nadir or splenectomy) permits participation in the Extension Phase.

Design of Study INCB 18424-351



Recruitment

Study 352:

Study initiation date: 01-Jul-2009 (first subject first visit). Data cut-off date: 04-Jan-2011 (last subject last visit). The Randomized Treatment and Extension Phases are ongoing; the maximum duration of treatment at the end of the trial will not exceed 171 weeks for any subject consisting of an enrolment period of 27 weeks + 48 weeks before primary analysis + 96 weeks after LSLV for the primary endpoint. After Protocol Amendment 3, subjects who consented were followed for OS, LFS, and new anti-neoplastic therapy until the study was concluded. Survival information will be collected until the LSLV of the Extension Phase.

Study 351:

Study initiation date: 24-Aug-2009. Data cut-off date: 02-Nov-2010. The study is ongoing. Subjects receiving benefit could continue treatment until the later of marketing approval or when the last randomized subject remaining in the study had completed Week 144 (36 months).

Conduct of the study

Study 352:

The study protocol was amended five times. Important changes were:

- The duration of study treatment for the Randomized Treatment and Extension Phases was clarified
- Removal of the protocol-planned interim analysis at the time of the New Drug Application filing to the Food and Drug Administration
- Modification of the current definition of duration of response
- Classified secondary efficacy endpoints as "key" and "other".
- Permitted all BAT subjects to receive ruxolitinib and move to the Extension Phase of the study after demonstration of superiority for the primary or key secondary endpoints and provided ruxolitinib continued to show an acceptable safety profile
- Required subjects to discontinue from the Extension Phase if an increase in spleen volume of at least 25% was observed as compared to: Baseline spleen volume, if they were randomized to ruxolitinib or, Spleen volume at crossover if they were randomized to BAT
- Elimination of the requirement for a maximum dose of ruxolitinib to be 5 mg bid less than the dose which caused a platelet count reduction < 100,000/µL

This study planned to enrol approximately 150 subjects. However total randomization level were higher than anticipated. The Sponsor did not feel it was ethical to prohibit screened subjects who met all inclusion/exclusion criteria for randomization to the study. As a result, the total enrolment for the study was 219 subjects.

Protocol deviations

Overall, major protocol deviations were reported in a total of 17 subjects (7.8%).

The predominant protocol deviations in the ruxolitinib treatment arm were: • Use of prohibited concomitant medications (HU, interferon, thalidomide, busulfan, lenalidomide, or anagrelide) (6 subjects) • Unconfirmed diagnosis of PMF, PPV-MF, PET-MF (5 subjects).

The most common protocol deviations in the BAT treatment arm were: • Crossover of BAT subjects into the ruxolitinib treatment arm without meeting the protocol definition of disease progression (6 subjects) • Change in therapy after baseline MRI and before start of study drug (1 subject) • Subjects without a palpable spleen volume ≥5 cm (1 subject)

Study 351:

The original protocol was amended 3 times but the study was initiated and all patients enrolled under the last amendment. The study was analysed per protocol.

The meta-analysis of overall survival originally noted in the SAP was not conducted. This was agreed to by the FDA at the pre-NDA meeting.

Protocol deviations

Fourteen subjects were excluded from the per-protocol population because of violations of inclusion/exclusion criteria (8 subjects in the ruxolitinib group and 6 subjects in the placebo group).

Minor deviations in prior MF therapy wash-out duration or deviations with respect to prior treated malignancy within 5 years were noted in 7 subjects.

Baseline data

Table 14: Baseline demographic characteristics in Studies INCB 351 and 352 (full analysis set)

	Study INCB 18424-351		Study INC424A2352	
	Ruxolitinib	Placebo	Ruxolitinib	BAT
Variable	N = 155	N = 154	N = 146	N = 73
Age (years)				
Mean (STD)	66.7 (8.8)	68.7 (8.7)	65.1 (9.7)	65.2 (10.3)
Median	66.0	70.0	67.0	66.0
Range	43.0, 91.0	40.0, 86.0	35.0, 83.0	35.0, 85.0
≤ 65 years	70 (45.2)	52 (33.8)	69 (47.3)	36 (49.3)
> 65 years	85 (54.8)	102 (66.2)	77 (52.7)	37 (50.7)
Gender – n (%)				
Male	79 (51.0)	88 (57.1)*	83 (56.8)	42 (57.5)
Female	76 (49.0)	65 (42.2)*	63 (43.2)	31 (42.5)

Differences include age, with a higher proportion of patients > 65 years of age in the placebo arm (66.2%) than in the ruxolitinib arm (54.8%) in Study INCB 18424-351.

Table 15: Baseline disease characteristics in Studies 351 and 352 (full analysis set)

	Study INCB 18424-351		Study INC424A2352	
	Ruxolitinib	Placebo	Ruxolitinib	BAT
Variable	**N = 155**	**N = 154**	**N = 146**	**N = 73**
Disease subtype – n (%)				
PMF	70 (45.2)	84 (54.5)	77 (52.7)	39 (53.4)
PPV-MF	50 (32.3)	47 (30.5)	48 (32.9)	20 (27.4)
PET-MF	35 (22.6)	22 (14.3)	21 (14.4)	14 (19.2)
Missing	0	1 (0.6)	0	0
Fibrosis grade at baseline – n (%)				
0	2 (1.3)	1 (0.6)	3 (2.1)	2 (2.7)
1	14 (9.0)	18 (11.7)	21 (14.4)	3 (4.1)
2	63 (40.6)	51 (33.1)	55 (37.7)	27 (37.0)
3	65 (41.9)	71 (46.1)	59 (40.4)	34 (46.6)
Missing	11 (7.1)	13 (8.4)	7 (9.6)	6 (8.2)
Spleen volume, cm^3	**n=155**	**n=153**	**n=144**	**n=72**
Mean (STD)	2745.7 (1247.0)	2797.6 (1388.5)	2662.1 (1351.3)	2631.1 (1405.3)
Median	2597.7	2566.3	2407.6	2317.9
Range	478.1, 7461.8	521.0, 8880.7	451.3, 7765.6	728.5, 7701.1
Palpable spleen length below costal margin, cm	**n=155**	**n=153**	**n=146**	**n=72**
Mean (STD)	16.1 (5.7)	16.4 (6.3)	14.9 (6.5)	15.8 (6.7)
Median	16.0	16.0	14.0	15.0
Range	0.0, 33.0	5.0, 34.0	5.0, 30.0	5.0, 37.0
< 10 cm	32 (20.6)	27 (17.5)	47 (32.2)	17 (23.3)
≥ 10 cm	123 (79.4)	126 (81.8)	99 (67.8)	55 (75.3)
ECOG Performance Status – n (%)				
0	47 (31.1)	38 (25.5)	58 (39.7)	26 (35.6)
1	87 (57.6)	82 (55.0)	77 (52.7)	37 (50.7)
2	14 (9.3)	25 (16.8)	10 (6.8)	9 (12.3)
3	3 (2.0)	4 (2.7)	1 (0.7)	1 (1.4)
Missing	4 (2.6)	5 (3.2)	0	0
IWG risk category – n (%)				
High	90 (58.1)	99 (64.3)	72 (49.3)	36 (49.3)
Intermediate-2	64 (41.3)	54 (35.1)	74 (50.7)	37 (50.7)
Less than Intermediate-2 or Unknown	1 (0.6)	1 (0.6)	0	0
JAK2 mutation at Screening – n (%)				
Positive	113 (72.9)	123 (79.9)	110 (75.3)	49 (67.1)
Negative	40 (25.8)	27 (17.5)	35 (24.0)	20 (27.4)
Unknown	2 (1.3)	4 (2.6)	1 (0.7)	4 (5.5)
Previous hydroxyurea use [a] – n (%)				
Yes	104 (67.1)	87 (56.5)	110 (75.3)	50 (68.5)
Previous splenic radiotherapy– n (%)				
Yes	1 (0.6)	0	0	4 (5.5)

In Study 351, the mean duration since initial diagnosis was 4.8 years. In this study, patients were not stratified by baseline disease characteristics.

In Study 352, the mean duration since initial diagnosis was 31.1 months and 33.2 months in the ruxolitinib and BAT arms, respectively. In this study, patients were stratified by baseline IWG-MRT risk category.

The populations in Studies 351 and 352 differed with regard to their previous treatment for MF. (Patients in Study 351 had to be resistant or refractory to, intolerant of, or not candidates for available therapy for MF. In Study 352, patients could not be candidates for stem cell transplantation, did not need to have failed previous therapies, could have been candidates for available therapy, or could have no adequate therapeutic options. For patients in Study 352 with no adequate therapeutic options, BAT could include no pharmacologic therapy).

Numbers analysed

Table 16: Disposition of patients in Studies INCB 18424-351 and INC424A2352 (Safety set)

	Study INCB 18424-351		Study INC424A2352		Total
	ruxolitinib	Placebo	ruxolitinib	BAT	ruxolitinib
Patient disposition	**N=155**	**N=151**	**N=146**	**N=73**	**N=301**
Reason	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Ongoing in randomized treatment phase [1]	135 (87.1)	78 (51.7)	91 (62.3)	31 (42.5)	226 (75.1)
Discontinued randomized treatment phase	20 (12.9)	73 (48.3)	55 (37.7)	42 (57.5)	75 (24.9)
Crossed over to ruxolitinib [2]		36 (23.8)		18 (24.7)	
Continued in Extension [3]	0		29 (19.9)		29 (9.6)
Death [4]	0	0	0	0	0
Adverse event(s)	16 (10.3)	14 (9.3)	12 (8.2)	4 (5.5)	28 (9.3)
Consent withdrawn	1 (0.6)	7 (4.6)	2 (1.4)	9 (12.3)	3 (1.0)
Protocol deviation	0	0	2 (1.4)	0	2 (0.7)
Disease progression	3 (1.9)	13 (8.6)	1 (0.7)	3 (4.1)	4 (1.3)
Non-compliance with study medication	0	0	2 (1.4)	0	2 (0.7)
Non-compliance with study procedures	0	0	0	1 (1.4)	0
Other	0	3 (2.0)	7 (4.8)	7 (9.6)	7 (2.3)

[1] Receiving randomized treatment
[2] Crossed over to ruxolitinib after protocol-defined disease progression on Placebo/BAT to qualify for cross-over
[3] Treatment with ruxolitinib after disease progression event qualifying for entering extension phase
[4] Includes only those patients for whom death was reported as the primary reason for discontinuation of therapy. Death was not recorded an adverse event of Common Terminology Criteria for Adverse Events (CTCAE) Grade 5, but all deaths were recorded with an adverse event term or terms listed as the cause of death.

Outcomes and estimation

Primary endpoint

Table 17: Percentage of patients with at least 35% reduction in spleen volume from baseline to Week 24 in Study 351, to Weeks 24 and 48 in Study 352

	Study INCB 18424-351		Study INC424A2352			
	Week 24		Week 48		Week 24	
	Ruxolitinib	Placebo	Ruxolitinib	BAT	Ruxolitinib	BAT
	N=155	N=154	N=144	N=72	N=144	N=72
Patients with ≥35% spleen volume reduction at	65 (41.9)	1 (0.7)	41 (28.5)	0	46 (31.9)	0
95% CI	(34.1, 50.1)	(0.0, 3.6)	(21.3, 36.6)	(0.0, 5.0)	(24.4, 40.2)	(0.0, 5.0)
p-value [1]	< 0.0001		< 0.0001		< 0.0001	

The table includes patients with non-missing baseline MRI measurement of spleen volume only.
[1] In Study INC424A2352, p-value was calculated using the exact Cochran-Mantel-Haenszel (CMH) test because the proportion of patients in the BAT arm with ≥ 35% reduction in spleen volume from baseline was < 4%. In Study INCB 18424-351, p-value was calculated using Fisher's exact test

An analysis of data at week 24 in the 352 study, a secondary endpoint, showed that 46 patients (31.9%) of patients in the ruxolitinib arm reached the cut-off at that time point. Considering the longer median duration of the disease and a situation with lack of alternative therapy for patients in the ruxolitinib arm in the 351 study, a higher response rate as compared to the patients in the 352 study is unexpected.

For patients who remained on study, the median percent reduction from baseline in spleen volume in both ruxolitinib arms was approximately 30%, was reached at Week 12 and was maintained throughout the study. The control arms had a median relative increase from baseline in spleen volume throughout the study.

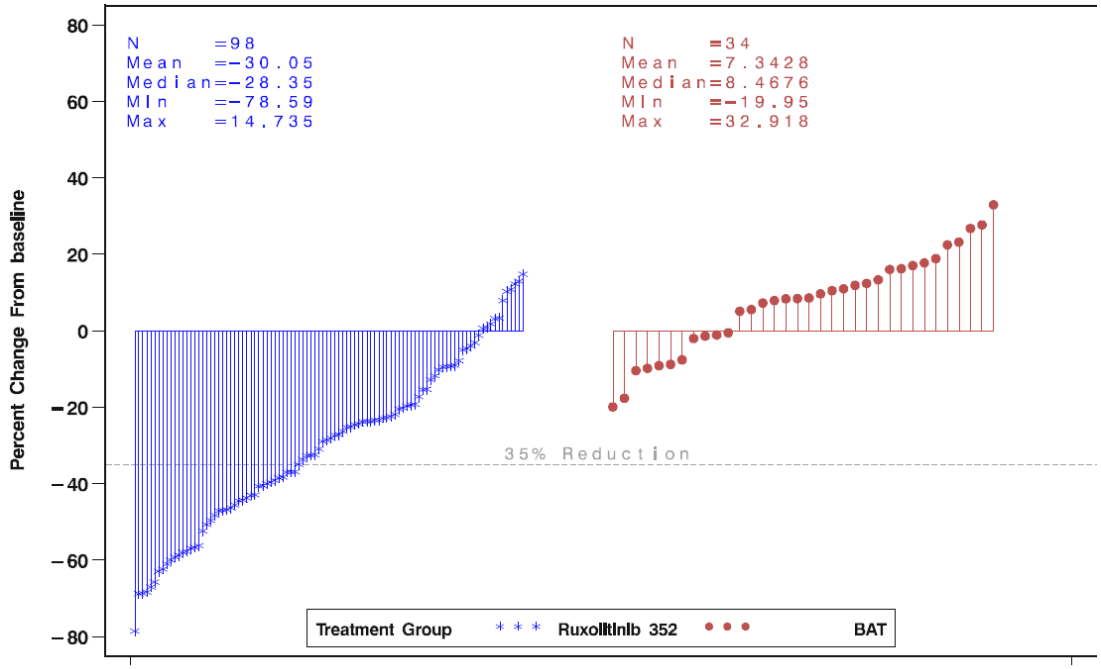


Figure 4: Waterfall plot of percent change from baseline in spleen volume at Week 48 in Study 352

The waterfall analyses confirm the efficacy and show that the majority of, albeit not all, patients in the ruxolitinib arms achieved some level of spleen volume reduction, which was not the case in neither the placebo arm nor the BAT arm. It is also clear from the study 351 data that patients may achieve spleen volume reductions spontaneously.

Secondary endpoints

- Duration of response

Updated duration of response using method 1 (the primary analysis method specified in Study 351) and method 2 (the primary analysis method specified in Study 352) is shown below.

Table 18: Duration of response in studies INCB 18424-351 (data cutoff 01 March 2011) and CINC424A2352 (data cutoff 01 June 2011) FAS

Statistics	INCB 18424-351 Ruxolitinib	CINC424A2352 Ruxolitinib
Method 1 (loss of response is date of < 35% reduction from baseline)	**N=80**	**N=70**
Number (%) of Observed Events	25 (31.3)	24 (34.3)
Number (%) of Censored Events	55 (68.8)	46 (65.7)
Median (95% CI)	N/A	N/A
Probability of response duration > 12 weeks (95% CI)	0.91 (0.81,0.95)	0.82 (0.71,0.90)
Probability of response duration > 24 weeks (95% CI)	0.75 (0.63,0.84)	0.72 (0.59,0.81)
Probability of response duration > 36 weeks (95% CI)	0.66 (0.53,0.76)	0.64 (0.51,0.75)
Probability of response duration > 48 weeks (95% CI)	0.58 (0.41,0.71)	0.62 (0.48,0.73)
Method 2 (loss of response is date of < 35% reduction from baseline that is also ≥ 25% increase from nadir)	**N=84**	**N=70**
Number (%) of Observed Events	16 (19.0)	17 (24.3)
Number (%) of Censored Events	68 (81.0)	53 (75.7)
Median (95% CI)	48.29 (46.71 - N/A)	N/A
Probability of response duration > 12 weeks (95% CI)	0.99 (0.91,1.00)	0.93 (0.83,0.97)
Probability of response duration > 24 weeks (95% CI)	0.91 (0.82,0.96)	0.88 (0.77,0.94)
Probability of response duration > 36 weeks (95% CI)	0.79 (0.65,0.88)	0.79 (0.66,0.87)
Probability of response duration > 48 weeks (95% CI)	0.66 (0.47,0.80)	0.74 (0.61,0.84)

With Method 1, the median duration of response has not been reached for any of the studies.

With Method 2 (loss of response is the date of observation of < 35% reduction from baseline that was also ≥ 25% increase from nadir), the updated median duration of maintenance of ≥ 35% reduction of spleen volume on Study 351 is 48 weeks. The updated median duration of maintenance of response in study 352 has not been reached.

- Time to first at least 35% reduction in spleen volume from baseline in Study INC424A2352

Table 19: Time to first at least 35% reduction in spleen volume from baseline in Study INC424A2352

Time to first ≥ 35% reduction	Ruxolitinib N= 69	BAT N= 1
Median (95% CI), weeks	12.29 (12.14, 14.43)	15.43 (NA, NA)
Minimum, weeks	11.00	15.43
Maximum, weeks	49.14	15.43
Kaplan-Meier estimates of time to first 35% reduction (95% CI)		
12 Weeks	0.23 (0.14, 0.34)	0 (NA, NA)
24 Weeks	0.67 (0.54, 0.76)	1.00 (NA, NA)
36 Weeks	0.87 (0.76, 0.93)	1.00 (NA, NA)
48 Weeks	0.97 (0.89, 0.99)	1.00 (NA, NA)

The median time to response coincides with the first MRI assessment at Week 12.

- Progression free survival in Study INC424A2352

Progression was defined as increase of spleen volume of at least 25% compared with on-study nadir, splenectomy, splenic irradiation, leukemic transformation, or death. The most common progression event was increase in spleen volume of at least 25% from nadir, seen in 40 patients (27.4%) on ruxolitinib and 13 patients (17.8%) on BAT.

Updated PFS in the 352 study is shown below.

Table 20: Progression free survival in study CINC424A2352 (data cutoff 01 June 2011) (FAS)

	Ruxolitinib	BAT	Log-rank p-value	HR* (95% CI)
	N= 146	N= 73		
No. of events - n (%)	56 (38.4)	25 (34.2)	0.411	0.81 (0.51,1.30)
No. censored - n (%)	90 (61.6)	48 (65.8)		
Median (95% CI), weeks	N/A	72.3 (59.3, N/A)		
Kaplan-Meier estimates (95% CI) at				
24 weeks	0.97 (0.92,0.99)	0.88 (0.77,0.94)		
48 weeks	0.76 (0.67,0.82)	0.73 (0.60,0.83)		

*HR of ruxolitinib over BAT; HR < 1 denotes benefit to ruxolitinib arm, while HR > 1 denotes benefit to BAT arm.

There was no statistically significant difference between treatment arms in the updated PFS analysis.

Data are not mature and cross over to ruxolitinib is likely to confound further follow-up.

- Overall survival, leukaemia-free survival, and progression-free survival (the latter analysed in study 352 only)

Updated OS data are shown below.

Table 21: Overall survival in studies INCB 18424-351 (data cutoff 01 March 2011) and CINC424A2352 (data cutoff 01 June 2011) (FAS)

	INCB 18424-351		CINC424A2352	
	Ruxolitinib	Placebo	Ruxolitinib	BAT
Statistics	N = 155	N = 154	N = 146	N = 73
Survival status – n (%) [1]				
Number of events	13 (8.4)	24 (15.6)	13 (8.9)	5 (6.8)
Number censored	142 (91.6)	130 (84.4)	133 (91.1)	68 (93.2)
Length (weeks) of survival [2]				
Median (95% CI)	NA	NA	NA	NA
Probability of survival [3]				
by 48 weeks (95% CI)	0.93 (0.87, 0.96)	0.85 (0.77, 0.90)	0.96 (0.91, 0.98)	0.94 (0.86, 0.98)
Hazard Ratio[5]	0.499		1.13	
95% CI of hazard ratio	(0.254, 0.98)		(0.40, 3.17)	
p-value (log-rank test) [4]	0.0395		0.819	

[1]All data were included in this summary.

[2]Time-to-event quartiles were estimated by using the Kaplan-Meier method. Confidence interval was calculated by using the Brookmeyer and Crowley method

[3] Probability was estimated by using the Kaplan-Meier method. Confidence interval was calculated by using the pointwise log-log transformation

[4] For Study CINC424A2352, baseline risk level was used as a factor in obtaining both hazard ratio estimate and logrank test p-value

[5] HR of ruxolitinib over control.

Source: [Appendix 1 -Table 67-1.1], [Appendix 1 -Table 14.2-2.8]

The currently available overall survival results from both studies, with a data cut-off date of 01/03/2011, shows a nominal improvement in overall survival in patients treated with ruxolitinib in the study 351, but no difference in the study 352. Further analyses of the study 352 data with a cut-off date of 01/06/2011 shows a nominal improvement in overall survival in patients treated with ruxolitinib, compared to the control treatment. None of these results reached formal statistical significance due to the low number of events in the treatment and control arms in both studies. Further follow-up data is likely to be confounded due to the crossover of patients treated in the control arms to the ruxolitinib arms.

Updated data on LFS and OS are quite similar because the number of events is identical (all events were deaths) with the differences between the two statistical analyses mostly related to the times at which patients are censored. There were no cases of leukaemia reported in the clinical database of study 352, although two cases of patients on BAT who discontinued were described as having leukocytosis and peripheral blood blasts above 20%.

- Change in density of fibrosis in studies INCB 18424-351 and INC424A2352 as measured by the investigators

This was a secondary endpoint in study 352 and an exploratory endpoint in study 351.

Improvement as well as worsening of bone marrow fibrosis was seen among the relatively few ruxolitinib-treated patients with both baseline and follow-up investigator-assessed bone marrow specimens. Conclusions cannot be made on this important issue with the present material and further vigilance is indicated.

- Symptom response rates in Study INCB 18424-351

Symptoms of MF were assessed using a symptom diary, MSAF v2.0. The total symptom score for baseline and on-study time periods was calculated based on the 6 symptom scores of night sweats, itching, abdominal discomfort, pain under ribs on left, feeling of fullness (early satiety), and muscle/bone pain.

  - The proportion of patients who achieved a ≥ 50% improvement from baseline in the Week 24 total symptom score was a secondary endpoint; a statistically significantly larger proportion of patients in the ruxolitinib arm achieved a ≥ 50% improvement from baseline in Week 24 total symptom score compared with the placebo arm (45.9% and 5.3%, respectively, $p < 0.0001$ from Chi-Square test). The median time to 50% reduction in total symptom score was less than 4 weeks among patients achieving this level of improvement.
  - The change from baseline in the Week 24 total score was also a secondary endpoint; a median improvement of 6.9 in the ruxolitinib arm and a median worsening of 2.0 in the placebo arm ($p < 0.0001$ from the Wilcoxon Rank-Sum test) was seen. This represents a mean and median percent improvement from baseline of 46.1% and 56.2% in the ruxolitinib arm and a mean and median percent worsening of 41.8% and 14.6% in the placebo arm, respectively.
  - Results per JAK2 mutational group: Percent of subjects achieving greater than or equal to 50% reduction in total symptom score (TSS) from baseline to week 24, median percent improvement from baseline at week 24 in TSS, and median time to first greater than or equal to 50% improvement from baseline in TSS were all in favour of the JAK2 positive group; 52.3% vs 28.2% in the JAK2 negative group, 65.1% vs 29.4%, and 4.0 vs 6.6 weeks (here a high number of censored patients is noted in the mutation negative group), respectively.

The symptom score instrument is stated to have been validated for patients with MF and MPN, but the validation process is not entirely clear.

Using the EORTC QLQ-C30 instrument, at week 24 the ruxolitinib group showed significant improvement in the global health status and functional subscales compared with the placebo group, with the exception of cognitive functioning. For each of the subscales, the ruxolitinib group had an improvement from baseline, whereas the placebo group had a worsening from baseline. In the 351 study, the mean change for the global health status/quality of life score was +12.3 and -3.4

(p<0.0001) for Jakavi and placebo, respectively. However, The EORTC QLQ-C30 instrument has not been validated in MF patients.

Assessment of symptom and QoL data obtained in the 352 study is inherently difficult as the study was open-designed. In the 351 study, the situation is complicated by the potential problem of maintaining the blind when typical active-drug side effects are commonly seen, such as thrombocytopenia.

However, the credibility of the positive effects observed in these parameters is supported by pharmacodynamic data showing decreased levels of pSTAT3 and inflammation markers in peripheral blood during treatment with active drug.

Ancillary analyses

Exploratory endpoints

- JAK2V617F allele burden in Studies INCB 18424-351 and INC424A2352

Ruxolitinib seems to slightly – modestly decrease the JAK2V617F allele burden in the treated population; -10.9% at week 24 (n=101) and -21.5% at week 48 (n=13) in the 351 study, and -9.3% (n=76) at week 24 and -9.5% (n=60) at week 48 in the 352 study.

Subgroup analyses

The results of the subgroup analyses indicate a better response to ruxolitinib in patients starting at 20 mg BID vs 15 mg BID, and in patients carrying the V617F mutation.

Subgroup analyses in the 351 study are shown below.

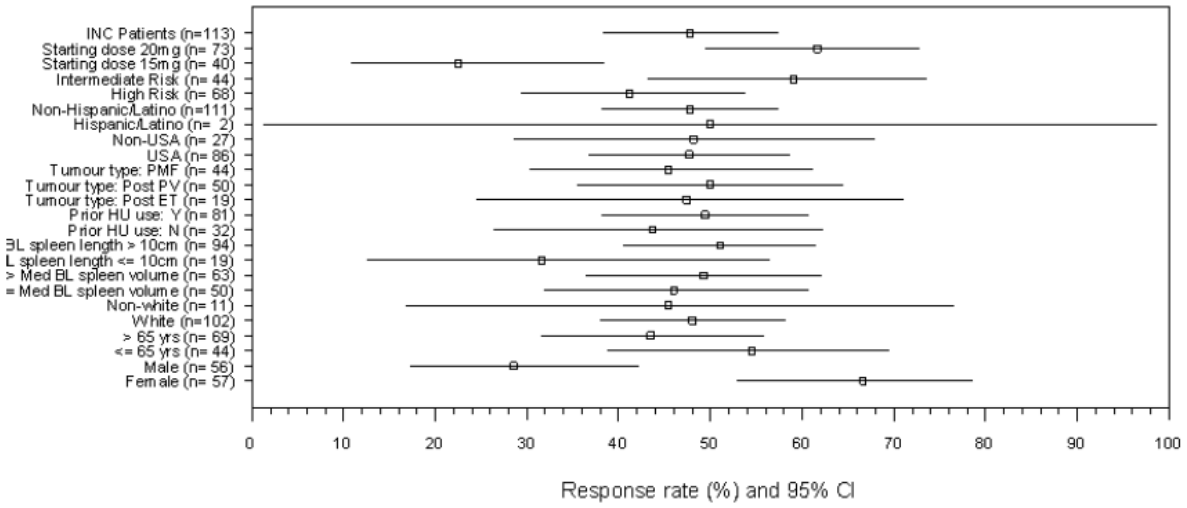


Figure 5: Proportion of patients in each subgroup with at least a 35% reduction from baseline in spleen volume at week 24 in study INCB 18424-351 with positive JAK2 mutation (patients randomised to ruxolitinib in FAS)

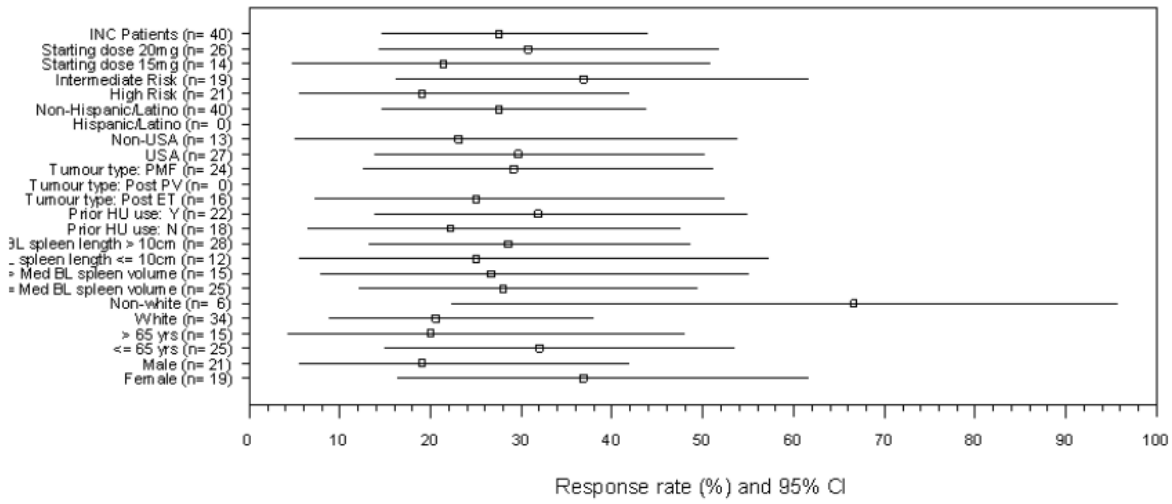


Figure 6: Proportion of patients in each subgroup with at least a 35% reduction from baseline in spleen volume at week 24 in study INCB 18424-351 with negative JAK2 mutation (patients randomised to ruxolitinib in FAS)

Response in terms of spleen volume reduction in relation to JAK2 mutation status is shown below.

Table 22: Percentage of patients with ≥35% reduction from baseline in spleen volume by JAK mutation status (safety set)

	INCB 18424-351				INC424A2352			
	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			

In the subgroup analyses of the study 351, but not in the study 352, a relatively distinct higher response rate is seen for females over males at week 24 in the ruxolitinib arm.

The result of the primary efficacy analysis is supported by the subgroup analyses.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23. Summary of efficacy for trial INCB 18424-351, COMFORT-I

Title: A randomized, double-blind, placebo-controlled study of the JAK inhibitor INCB018424 tablets administered orally to subjects with primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF), or post-essential thrombocythemia-myelofibrosis (PET-MF) Abbreviated title: Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment, COMFORT-I			
Study identifier	Protocol number: INCB 18424-351 EudraCT number: 2009-018068-82		
Design	A Phase III, double-blind, randomized and placebo controlled study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Treatment for 24 weeks Not applicable Subjects receiving benefit could continue treatment until the later of marketing approval or when the last randomized subject remaining in the study completed Week 144 (36 months)
Hypothesis	Superiority		
Treatments groups	Ruxolitinib		Treatment: Starting dose dependent upon the subjects baseline platelet count • >200,000/μL 20 mg BID • 100,000/μL to 200,000/μL 15 mg BID The dose was adjusted based on efficacy and safety to a maximum of 25 mg BID Number randomized: 155
	Placebo		Treatment: Matching placebo tablet BID Number randomized: 154
Endpoints and definitions	Primary endpoint	≥35% spleen volume reduction	Proportion of subjects achieving a ≥35% reduction from Baseline in spleen volume at Week 24, as measured by MRI (or CT)
	Secondary endpoint	Maintenance of spleen volume reduction	Duration of maintenance of a ≥35% reduction from Baseline in spleen volume among the subjects initially randomized to the ruxolitinib treatment group, as measured by MRI (or CT)
	Secondary endpoint	≥50% reduction in total symptom score	Proportion of subjects who had a ≥50% reduction from Baseline in Week 24 total symptom score, as measured by the modified MFSAF v2.0 diary
	Secondary endpoint	Change in total symptom score	Change from Baseline in Week 24 total symptom score, as measured by the modified MFSAF v2.0 diary
	Secondary endpoint	OS	Overall survival
Database lock	2 November 2010 (cut-off date)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The intent-to-treat (ITT) population included all subjects randomized in the study. Treatment groups for this population were defined according to the treatment assignment at randomization.		

Descriptive statistics and estimate variability			**Ruxolitinib**	**Placebo**
	Primary endpoint: **≥35% spleen volume reduction**	Number of subjects	155	153*
		Number of responders	65 (41.9%)	1 (0.7%)
		P-value (Fisher Exact)	<0.0001	
	Secondary endpoint: **Maintenance of spleen volume reduction****	Number of subjects	71	
		Number of events	19 (26.8%)	
		Number of censored	52 (73.2%)	
	Secondary endpoint: **≥50% reduction in total symptom score**	Number of subjects	155	154
		Number of evaluable	148 (95.5%)	152 (98.7)
		Number of subjects achieving a ≥50%	68 (45.9%)	8 (5.3%)
		P-value (Chi Square)	<0.0001	
	Secondary endpoint: **Change in total symptom score**	Number of subjects	155	154
		Number of evaluable	131	105
		Baseline score	18.0 ± 10.9	16.5 ± 11.5
		Week 24 score	9.4 ± 9.7	19.7 ± 13.7
		Change in score	-8.6 ± 10.0	3.2 ± 9.4
		P-value (Wilcoxon Rank Sum)	<0.0001	
	Secondary endpoint: **OS*****	Number of subjects	155	154
		Number of events	10 (6.5)	14 (9.1)
		Number censored	145 (93.5%)	140 (90.9)
		Log-rank P-value	0.3268	
		Hazard Ratio	0.668	
Notes	* One patient was not included in the analysis due to a missing baseline spleen volume value. ** This study was not designed to rigorously assess the time to response, as the first MRI spleen assessment was not performed until Week 12. *** This study was not designed or powered for a robust analysis of overall survival, and in fact, the number of events in each treatment group was too low for a meaningful statistical comparison.			

Table 24: Summary of efficacy for trial CINC424A2352, COMFORT-II

Title: A randomized study of the JAK inhibitor INC424 tablets compared to best available therapy in subjects with primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF), or post-essential thrombocythemia-myelofibrosis (PET-MF) Abbreviated title: COntrolled Myelofibrosis Study With Oral JAK Inhibitor Treatment, COMFORT-II		
Study identifier	Protocol number: CINC424A2352 (formerly INCB 18424-352) EudraCT number: 2009-009858-24	
Design	A Phase III, open label and randomized study	
	Duration of Main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment for 48 weeks Not applicable Subjects receiving benefit could continue treatment until the later of marketing approval or when the last randomized subject remaining in the study completed Week 144 (36 months) of therapy or withdrawn from the study

Hypothesis	Superiority		
Treatments groups	Ruxolitinib		Treatment: Starting dose dependent upon the subjects baseline platelet count • >200,000/µL 20 mg BID • 100,000/µL to 200,000/µL 15 mg BID The dose was adjusted based on efficacy and safety to a maximum of 25 mg BID Number randomized: 146 subjects
	Best Available Therapy (BAT)		Treatment: BAT (oral or parenteral therapy) was commercially available and administered according to manufacturer's instructions and Investigator discretion, this also included the option of no treatment. Number randomized: 73 subjects
Endpoints and definitions	Primary endpoint	≥35% spleen volume reduction at week 48	Proportion of subjects achieving a ≥35% reduction from Baseline in spleen volume at Week 48, as measured by MRI (or CT)
	Key secondary endpoint	≥35% spleen volume reduction at week 24	Proportion of subjects achieving a ≥35% reduction from Baseline in spleen volume at Week 24, as measured by MRI (or CT)
	Other secondary endpoints	Maintenance of spleen volume reduction	Duration of maintenance of spleen volume reduction (DoMSR) ≥35% from Baseline
		Time to achieve first spleen volume reduction	Time to achieve a first ≥35% reduction in spleen volume from Baseline
		PFS	Progression free survival
		LFS	Leukemia-free survival
		OS	Overall survival
		Change in bone marrow histomorph-ology[#]	Change in bone marrow histomorphology, noted as fibrosis density and was tabulated by fibrosis grade at Baseline and post-Baseline (number of subjects and subject percentages)
Database lock	4 January 2011 (cut-off date)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (FAS) Following the intent-to-treat principle, subject data were analyzed according to the treatment to which they were assigned at randomization.			
Descriptive statistics and estimate variability			**Ruxolitinib**	**BAT**
	Primary endpoint: **≥35% spleen volume reduction at**	Number of subjects	144	72*
		Number of responders	41 (28.5%)	0
		95% CI	21.3, 36.6	0.0, 5.0

	week 48	P-value (CMH Test)	<0.0001	
	Key secondary endpoint: **≥35% spleen volume reduction at week 24**	Number of subjects	144	72*
		Number of responders	46 (31.9%)	0
		95% CI	24.4, 40.2	0.0, 5.0
		P-value (CMH Test)	<0.0001	
	Other secondary endpoint: **Maintenance of spleen volume reduction****	Number of subjects	69	
		Number of events	14 (20.3%)	
		Number of censored	55 (79.7%)	
		Median weeks	N/A	
		Kaplan-Meier estimates (95% CI) 12 weeks 24 weeks 36 weeks 48 weeks	 0.92 (0.82, 0.97) 0.87 (0.76, 0.93) 0.77 (0.63, 0.87) 0.52 (0.18, 0.78)	
	Other secondary endpoint: **Time to achieve first spleen volume reduction**	Number of subjects	69	1
		Median weeks (95 % CI)	12.29 (12.14, 14.43)	15.43 (N/A)
		Minimum, weeks	11.00	15.43
		Maximum, weeks	49.14	15.43
		Kaplan-Meier estimates (95% CI) 12 weeks 24 weeks 36 weeks 48 weeks	 0.23 (0.14, 0.34) 0.67 (0.54, 0.76) 0.87 (0.76, 0.93) 0.97 (0.89, 0.99)	
	Other secondary endpoint: **PFS*****	Number of subjects	146	73
		Number of events	44 (30.1%)	19 (26.0%)
		Number censored	102 (69.9%)	54 (74.0%)
		Log-rank P-value	0.46	
		Hazard Ratio (95% CI)	0.81 (0.47, 1.39)	
	Other secondary endpoint: **LFS*****	Number of subjects	146	73
		Number of events	6 (4.1%)	4 (5.5%)
		Number censored	140 (95.9%)	69 (94.5%)
		Log-rank P-value	0.51	
		Hazard Ratio (95% CI)	0.65 (0.18, 2.31)	
	Other secondary endpoint: **OS*****	Number of subjects	146	73
		Number of events	6 (4.1%)	4 (5.5%)
		Number censored	140 (95.9%)	69 (94.5%)
		Log-rank P-value	0.58	
		Hazard Ratio (95% CI)	0.70 (0.20, 2.49)	

Notes	*	One subject was not included in the analysis due to a missing baseline MRI measurement of spleen volume.
	**	Duration of response was defined where the start date was the first spleen volume measurement that was ≥35% reduction from baseline, and the end date was defined as the first scan that was no longer equal to a 35% reduction **and** that was a >25% increase over nadir.
	***	The study was not powered to detect any statistically significant differences in these secondary time-to-event endpoints.
	#	Eleven subjects (7.5%) in the ruxolitinib treatment arm improved in baseline fibrosis grade as compared to 2 subjects (2.7%) in the BAT arm; more ruxolitinib-treated subjects were reported with a worsening in fibrosis density than BAT-treated subjects (11.0% vs. 4.1%, respectively). However, it is difficult to make assessments as to whether or not fibrosis scores improve, worsen, or remain relatively stable over this period of time. Therefore, the shift table of data has not been presented here, within the 'results & analysis' section.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The results of two pivotal studies, 351 performed in US, Canada, and Australia and 352 performed in EU, are submitted together with results of the supportive dose-finding study 251. The 351 study was double-blinded placebo-controlled while the 352 study was open and controlled by investigator's best choice of available therapy. Cross-over was allowed in both studies. The studies recruited from different patient populations in that subjects eligible for the 351 protocol were to be without available treatment options while this was not the case in the 352 study. The principal primary endpoint, the proportion of subjects achieving a ≥35% reduction from baseline in spleen volume by independent review, was shared by both studies but analysed after 24 weeks in 351 and after 48 weeks in 352; the primary endpoint of the 351 study corresponded to a secondary endpoint of the 352 study. Other secondary endpoints included duration of response, overall survival, symptom evaluation (exploratory in 352), and leukaemia-free survival (exploratory in 351).

Thus, the design of the 352 study adheres to the scientific advice given by CHMP. The 351 study would have been difficult to continue for a longer period of time with maintained blinding and the different designs of the pivotal studies are considered additive and acceptable. However, due to the partly different patient populations enrolled, direct comparison of ruxolitinib-related outcomes between the studies is hampered. The patient population in both studies are representative of the target population.

Both pivotal studies recruited more patients than pre-planned. No protocol amendments or violations are identified that would substantially impact on the efficacy analyses and conclusions. Hence, the studies are considered to have been generally well-conducted.

Efficacy data and additional analyses

For the primary efficacy variable, superiority of the ruxolitinib arm over comparator was shown with high statistical significance ($p<0.0001$) in both pivotal studies; in study 351, 65 (41.9%) and 1 (0.7%) subjects reached this endpoint at week 24 in the ruxolitinib and placebo arm, respectively; in study 352, 41 (28.5%) and 0 patients reached this endpoint at week 48 in the ruxolitinib and BAT arm, respectively. The consistency of these results is supported by secondary and additional response analyses.

The median duration of response was 48 weeks in the 351 study but still not reached in the 352 study. Thus, further information is expected to become available.

The subgroup analyses of the primary endpoint in both pivotal studies indicate that patients harbouring the JAK2V617F mutation have a higher response rate than patients lacking the mutation. A higher response rate was also seen in patients treated with a starting dose of 20 mg bid as compared to 15 mg bid.

The subgroup analyses of the 351 study, but not of the 352 study, also indicate a relatively distinct higher response rate for females over males at week 24 in the ruxolitinib arm.

Assessment of symptom and QoL data obtained in the 352 study is inherently difficult as the study was open-designed. In the 351 study, the situation is complicated by the potential problem of maintaining the blind when typical active-drug side effects are commonly seen, such as thrombocytopenia. However, the credibility of the positive effects observed in these parameters is supported by pharmacodynamic data showing decreased levels of pSTAT3 and inflammation markers in peripheral blood during treatment with active drug.

Currently available updated overall survival data shows, although not statistically significant, an improvement in overall survival with the use of ruxolitinib over placebo/best available therapy; and no difference in progression free survival between ruxolitinib and best available therapy. However, data are immature and solid conclusions on overall survival, progression-free survival, and leukaemia-free survival are currently not allowed.

Improvement as well as worsening of bone marrow fibrosis was seen among the relatively few ruxolitinib-treated patients with both baseline and follow-up investigator-assessed bone marrow specimens. Conclusions cannot be made on this important issue with the available data and further vigilance is indicated. This will be further characterised with the provision of annual updates of the extension phases of studies INCB 18424-351 and INC424A2352 (see obligation to complete post-authorisation measures) and in the non Interventional Ruxolitinib in Myelofibrosis - Long term Safety Study CINC424AIC01T (see RMP).

2.5.4. Conclusions on the clinical efficacy

The application is supported by two well-conducted controlled studies. Superiority of ruxolitinib over placebo and best available therapy in terms of ≥35% reduction of spleen volume from baseline is shown with high statistical significance. Significant improvements in symptom score and QoL were noted in the 351 study. Superior results in terms of spleen volume reduction as well as symptom relief were achieved in the JAK2 mutation positive group. Bone marrow fibrosis is to be included in the RMP. Updates regarding duration of response, PFS, LFS and OS would further contribute to the benefit-risk balance and are considered as a condition to be included in Annex II of the marketing authorisation.

2.6. Clinical safety

Patient exposure

Table 25: Summary of safety studies – enrolment, dose and exposure

Study	Study type	Population	Patients treated	Initial Dose	Median exposure (range) (months)
INCB 18424-251	Phase 1/2 open-label	PMF, PPV-MF PET-MF	154 total		
			117	Ruxolitinib 10, 15, 25, 50 mg bid	14.8 (1.2 – 30.2)
			37	Ruxolitinib 25, 50, 100, 200 mg qd	19.6 (0.5 – 23.1)
INCB 18424-351	Phase 3 double-blind, randomized	PMF, PPV-MF, PET-MF	306 total		
			155[1]	Ruxolitinib 15-20 mg bid	7.8 (2.6-13.6)
			151	Placebo	7.1 (1.1-13.4)
			36[2]	Ruxolitinib 10-20 mg bid	
INC424A2352	Phase 3 open-label, randomized	PMF, PPV-MF, PET-MF	219 total		
			146[1]	Ruxolitinib 15-20 mg bid	11.8 (0.5 – 17.3)
			73	Best Available Therapy	10.4 (0 – 15.4)
			18[3]	Ruxolitinib 5-20 mg bid	
INCB 18424-254	Phase 2 open-label	metastatic, androgen-independent prostate cancer	22	Ruxolitinib 25 mg bid	2.0 (0.8 – 5.8)
INCB 18424-255	Phase 2 open-label	relapsed or refractory multiple myeloma	13[4]	Ruxolitinib 25 mg bid + dexamethasone 40 mg	4.6 (0 – 24.8)
INCB 18424-256	Phase 2 open-label	hydroxyurea-refractory patients with PV or ET	73	Ruxolitinib 10, 25 mg bid 50 mg qd	16.0 (4.8 – 21.7)
Total number of patients treated			**787**		
Total number of patients treated with ruxolitinib			**617**		
INCB 18424-138	4-way cross over thorough QT study	Healthy volunteers	50	Ruxolitinib 25 mg Ruxolitinib 200 mg Placebo Moxifloxacin 400 mg	Single dose

[1] Patients randomized to and treated with ruxolitinib
[2] Patients receiving ruxolitinib after cross-over from placebo could begin ruxolitinib at 10 mg b.i.d according to their platelet count
[3] Patients receiving ruxolitinib after cross-over from BAT could begin ruxolitinib at 5 mg b.i.d according to their platelet count
[4] All patients started treatment with ruxolitinib, 7 out of 13 patients received both treatments at a later time-point

Source: Table 1-1, Summary of Clinical Safety and Clinical Overview

Summary of exposure data:

In the **Phase 3 population**, overall exposure to ruxolitinib was 238.7 patient years. A majority of patients (55.8%) were treated for at least 9 months. The median duration of exposure to ruxolitinib was 9.6 months (range: 0.49-17.25).

In the **MF population**, overall exposure to ruxolitinib was 448.8 patient years. In total, 291 (57.2%) patients were treated for at least 9 months. The median duration of exposure to ruxolitinib was 10.5 months (range: 0.03-30.19).

In the **All cancer population**, overall exposure to ruxolitinib was 552.8 patient years. In total 360 (58.4%) patients were treated for at least 9 months. The median duration of exposure to ruxolitinib was 10.8 months (range: 0.03-30.19).

The overall median dose intensity was 30 mg/day in all three Safety populations.

The median duration of exposure in all three pooled safety populations was around 10 months. In the phase 1-2 Study 251 longer duration of exposure was seen, but the relevance of the safety data from this study is difficult to assess due to the different dosing regimens and higher doses.

In the combined pivotal studies, 75% of the patients in the ruxolitinib arms were still receiving the randomised treatment at data cut-off, indicating that a significantly longer duration of exposure can be expected than that for which safety data is currently available. This is considered an important lack of long-term safety data, which is particularly important since this is First-in-class substance, which involves central parts of the immune and haematopoietic systems in ways not yet fully elucidated.

Dose reductions/interruptions

The most frequently reported AEs requiring dose reduction or interruption in ruxolitinib-treated patients were thrombocytopenia (34.9%), platelet count decreased (7.6%) and anaemia (5.3%). All other AEs requiring dose reduction or interruption occurred with a frequency of 1% or less in ruxolitinib-treated patients. These haematological AEs are a direct consequence of the JAK1 and JAK2 inhibition and AEs appear manageable with dose adjustments and/or transfusions.

Adverse events

Table 26: Percentage of patients with adverse drug reactions in clinical studies*

Adverse drug reaction	Ruxolitinib – myelofibrosis patients N=301*		
	All CTCAE grades[c] (%)	CTCAE grade 3/4[c] (%)	Frequency category
Infections and infestations			
Urinary tract infections[a,d]	12.3	1.0	Very common
Herpes zoster[a,d]	4.3	0.3	Common
Blood and lymphatic system disorders[b,d]			
Anaemia	82.4	42.5	Very common
Thrombocytopenia	69.8	11.3	Very common
Neutropenia	15.6	6.6	Very common
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)	32.6	4.7	Very common
Intracranial bleeding	1.0	1.0	Common
Gastrointestinal bleeding	5.0	1.3	Common
Bruising	21.3	0.3	Very common
Other bleeding (including epistaxis, post-procedural haemorrhage and hematuria	13.3	2.3	Very Common
Metabolism and nutrition disorders			
Weight gain[a]	10.0	1.3	Very common
Hypercholesterolaemia[b]	16.6	0	Very common
Nervous system disorders			
Dizziness[a]	15.0	0.3	Very common
Headache[a]	13.9	0.5	Very common
Gastrointestinal disorders			
Flatulence[a]	2.9	0	Common
Hepatobiliary disorders			
Raised alanine aminotransferase[b]	26.9	1.3	Very common
Raised aspartate aminotransferase[b]	19.3	0	Very common

[*] Myelofibrosis patients randomised to and treated with ruxolitinib from the phase 3 pivotal COMFORT-I and COMFORT-II studies

[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.

The most frequently reported adverse drug reactions were thrombocytopenia and anaemia which are dose dependent and a direct result of ruxolitinib's mechanism of action, JAK inhibition.

In the phase 3 clinical studies, 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/mm3 was 14 days. Platelet transfusions were administered to 4.7% of patients receiving ruxolitinib and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving ruxolitinib and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm3 to 200,000/mm3 before starting ruxolitinib had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm3 (64.2% versus 38.5%).

In phase 3 clinical studies, 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 ruxolitinib 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 ruxolitinib -treated patients and 37.7% of placebo-treated 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 ruxolitinib arm and 41.1% in the best available therapy arm.

Similarly, erythropenia/anaemia caused dose reduction in 5%, but hardly any discontinuations.

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

Increased frequencies of infection AEs may also be directly related to the JAK inhibition by inhibiting/hampering the cytokine signalling of the immune response. Infections were overall more common in the ruxolitinib arms compared with controls in the pivotal studies, with AE frequencies in the SOC group Infections and infestations were 38.1 vs. 41.7% in the ruxolitinib and placebo arms of study 351, respectively; and 63.7 vs. 42.5% in the ruxolitinib and BAT arms of Study 352, respectively. The pooled frequency of the ruxolitinib arms was 50.5%. It appears that while infection AEs overall occur more often in the ruxolitinib arms, Grade 3-4 infections occur at similar frequencies as in the placebo and best available therapy arms.

When all infections in the urinary tract system were grouped together, a prominent difference between treatment arms was seen, but no relevant difference between ruxolitinib and control arms was seen with regard to SAEs or grade 3-4 "UTI grouped terms". No discontinuation due to an UTI grouped term occurred in the ruxolitinib arms.

One case of tuberculosis occurred in a ruxolitinib treated patient in Study 352. With prolonged follow-up, up to September 2011, a total of three reports of tuberculosis during ruxolitinib treatment have been received from the two pivotal trials. No reports have been received for patients treated with comparator.

The frequency of Herpes zoster (shingles) was higher in the ruxolitinib arms (3.3%) compared with the control arms (0.4%, pooled) of the pivotal studies. The frequency of SAE (0.3%) and Grade 3 (also 0.3%) events was low. Sequelae in the form of Grade 1-2 post herpetic neuralgia was also seen in 0.3% (1 patient) in the pivotal studies.

Bleeding and bruising may at least in some cases be a consequence of the haematological side effects (thrombocytopenia).

In the phase 3 pivotal studies 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 hematuria) were reported in 13.3% of patients treated with Jakavi and 10.3% treated with reference treatments.

GI AEs were all of similar frequency as in the placebo arm, but considerably higher than in the BAT arm.

Weight gain was seen clearly more often in the ruxolitinib arms compared with the control arms of the pivotal studies; 9.0% vs. 1.3% in the placebo arm of Study 351; and 11.0% vs. 1.4% in the BAT arm of Study 352. Grade 3-4 events were seen in similar frequencies, however 0.7% vs. 0.7% in Study 351, and 2.1% vs.0% in Study 352. One SAE was seen in the ruxolitinib arm of Study 352 (see discussion of clinical safety).

Serious adverse event and deaths

The overall frequency of SAEs was essentially similar across treatment arms in the pivotal studies, around 30%. Apart from anaemia and pneumonia at about 4% each, all other SAEs in the ruxolitinib arms occurred at the 1 % level or lower.

A non-trivial proportion of deaths were due to infections in both the ruxolitinib arm and the placebo arm of Study 351. Additional deaths due to infection are seen after cross-over to ruxolitinib in both pivotal studies, and in the supportive studies (see discussion on clinical safety).

There were three cases of bleeding with fatal outcome in the ruxolitinib arms of the pooled pivotal studies, compared with one in the control arms. The three events were subdural haemorrhage occurring in association with a platelet count of 70K/mm^3; post-operative retroperitoneal bleeding while on ASA; and cerebral haemorrhage in a setting of progressive metastatic squamous cell carcinoma with portal vein thrombosis and disseminated intravascular coagulation and thrombocytopenia. In the first case, the thrombocytopenia was considered related to ruxolitinib treatment and thereby contributory to the subdural haematoma. In the latter two cases the bleeding events were considered unrelated to ruxolitinib treatment.

Laboratory findings

Haematology

Decreased laboratory values were seen more often in the ruxolitinib arms than the comparator arms in the pivotal studies for haemoglobin, leukocytes, neutrophils, and platelets. This included relatively large differences also in grade 3 and 4 abnormal values for these parameters, particularly for haemoglobin and platelets. However, no difference was seen with regard to lymphocytes.

Table 27: Newly occurring or worsening hematologic abnormalities in Phase 3 patients (Safety set)

		Study INCB 18424-351				Study INC424A2352				Total	
		ruxolitinib		Placebo		ruxolitinib		BAT		ruxolitinib	
		N=155		N=151		N=146		N=73		N=301	
Test	Worsened from baseline to	n at risk	n (%)	n at risk	n (%)	n at risk	n (%)	n at risk	n (%)	n at risk	n (%)
Hemoglobin	Any grade	155	127 (81.9)	150	63 (41.7)	146	119 (81.5)	69	37 (49.3)	301	246 (81.7)
	Grade 1	41	11 (7.1)	36	13 (8.6)	43	17 (11.6)	12	7 (8.2)	84	28 (9.3)
	Grade 2	99	50 (32.3)	90	27 (17.9)	93	46 (31.5)	39	15 (20.5)	192	96 (31.9)
	Grade 3	148	49 (31.6)	143	19 (12.6)	135	44 (30.1)	59	8 (11.0)	283	93 (30.9)
	Grade 4	155	17 (11.0)	150	4 (2.6)	146	12 (8.2)	69	7 (9.6)	301	29 (9.6)
Leukocytes	Any grade	155	32 (20.6)	151	12 (7.9)	146	27 (18.5)	69	9 (12.3)	301	59 (19.6)
	Grade 1	141	13 (8.4)	148	5 (3.3)	136	16 (11.0)	63	1 (1.4)	277	29 (9.6)
	Grade 2	151	12 (7.7)	150	4 (2.6)	137	6 (4.1)	66	7 (9.6)	288	18 (6.0)
	Grade 3	153	7 (4.5)	151	2 (1.3)	146	4 (2.7)	69	0	299	11 (3.7)
	Grade 4	155	0	151	1 (0.7)	146	1 (0.7)	69	1 (1.4)	301	1 (0.3)
Lymphocytes	Any grade	155	64 (41.3)	150	62 (41.1)	142	67 (45.9)	69	38 (52.1)	297	131 (44.1)
	Grade 1	132	7 (4.5)	132	7 (4.6)	111	7 (4.8)	53	3 (4.1)	243	14 (4.7)
	Grade 2	137	35 (22.6)	136	24 (15.9)	112	31 (21.2)	55	13 (17.8)	249	66 (21.9)
	Grade 3	151	17 (11.0)	149	28 (18.5)	139	25 (17.1)	64	18 (24.7)	290	42 (14.0)
	Grade 4	155	5 (3.2)	150	3 (2.0)	142	4 (2.7)	69	4 (5.5)	297	9 (3.0)
Neutrophils	Any grade	155	28 (18.1)	151	6 (4.0)	146	18 (12.3)	69	6 (8.2)	301	46 (15.3)
	Grade 1	151	8 (5.2)	150	2 (1.3)	141	4 (2.7)	65	3 (4.1)	292	12 (4.0)
	Grade 2	153	10 (6.5)	150	1 (0.7)	143	5 (3.4)	68	2 (2.7)	296	15 (5.0)
	Grade 3	154	7 (4.5)	151	1 (0.7)	146	5 (3.4)	69	0	300	12 (4.0)
	Grade 4	155	3 (1.9)	151	2 (1.3)	146	4 (2.7)	69	1 (1.4)	301	7 (2.3)
Platelets	Any grade	155	106 (68.4)	151	29 (19.2)	146	97 (66.4)	69	19 (26.0)	301	203 (67.4)
	Grade 1	135	52 (33.5)	131	20 (13.2)	134	44 (30.1)	62	10 (13.7)	269	96 (31.9)
	Grade 2	155	34 (21.9)	151	7 (4.6)	146	41 (28.1)	69	4 (5.5)	301	75 (24.9)
	Grade 3	155	14 (9.0)	151	2 (1.3)	146	9 (6.2)	69	3 (4.1)	301	23 (7.6)
	Grade 4	155	6 (3.9)	151	0	146	3 (2.1)	69	2 (2.7)	301	9 (3.0)

Total = number of patients who had missing or less than grade x at baseline and with at least one post-baseline value for the parameter.
n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline. Patients are counted only for the worst grade observed post-baseline.
'New' means 'grade 0' at baseline and '≥ grade 1' after baseline
Baseline is defined as the last non-missing value prior to the first dose.

The risk of developing grade 3 or 4 decreased haemoglobin in the pivotal studies increased significantly with the baseline grade of haemoglobin, from 30-35% in patients with baseline anaemia of grade 1 to nearly 80% in those with grade 2. Similarly the risk of developing a grade 3 or 4 decreased platelet count increased with the baseline grade of platelets, from 10 and 7% in patients with baseline thrombocytes of grade 0, to 35 and 17% in those with grade 1, in Study 351 and 352,respectively.

The need for blood transfusions is a measurable consequence of anaemia. This was higher in the ruxolitinib arms compared with the comparator arms, approximately 50-60% vs. 40%. This difference is, however, lower than the difference between arms in decreased haemoglobin values, where a 30-40% difference were seen for any grade, and 20% differences were seen for grade 3 values. No relevant difference in the frequency of platelet transfusions were seen between treatment arms in the pivotal studies. A review of the time course of anaemia and transfusion need showed that after an

initial decrease, the levels of haemoglobin gradually increased to a level close to the level observed in the control arms by week 36 to week 48. Consistent with these observations, the transfusion needs, after an initial increase, decreased over time in both phase III trials. There was no evidence that the reductions in spleen size were correlated with improvements of anaemia.

Clinical chemistry

Adverse albumin changes were less common in ruxolitinib compared with the comparator arms of the pivotal studies, possibly as an effect by ruxolitinib on the B-symptoms /constitutional symptoms (weight loss). Bilirubin changes were essentially equal between study arms, including grade 3 values. No important differences between arms were seen in creatinine values, where no grade ≥3 values were noted in the ruxolitinib arms. Abnormal gamma-GT values were more frequent in the ruxolitinib arms overall, but not for grade 3 values. Grade 1 ALT changes were clearly more common in the ruxolitinib arms, but grade 2-3 changes only occurred at the 1 % level. Abnormal ALP values overall were less common in the ruxolitinib arms than in the comparator arms, and grade 2-3 values occurred at similar frequencies. Grade 1 AST changes were clearly higher in the ruxolitinib arms, but grade 2 values were essentially equal.

In conclusion, a clearly higher frequency of grade 1 liver transaminase values was the only important difference in clinical chemistry values between study arms in the two pivotal studies. No cases fulfilling Hy's law for drug induced liver injury were seen.

Vital signs

Vital signs were comparable between treatment groups. The only relevant change in any of the parameters includes an increase > 25% compared with baseline in systolic blood pressure in the ruxolitinib arms.

In the phase 3 pivotal clinical studies 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 study 351 the mean increase from baseline in systolic BP was 0-2 mmHg on ruxolitinib versus a decrease of 2-5 mmHg in the placebo arm. In study 352 mean values showed little difference between the ruxolitinib-treated and the control-treated patients.

In the pivotal studies, Cardiac failure SAEs (including congestive) occurred at around 1% in the pooled ruxolitinib arms, similar to the combined control arms. Cerebral haemorrhage SAEs occurred in 2 patients in Study 352 (0.7% in combined ruxolitinib arms) and in no other treatment arms. Tachycardia AEs were more frequent in the control arms. Cardiac murmur was somewhat more common in the ruxolitinib arms (5.6% in pooled arms), but the Applicant noted that these events were often associated with concomitant anaemia. QT

A thorough QT Study [INCB 18424-138] was carried out in accordance with ICHE14 guidance. The study met the requirements for a negative QT study. In the pivotal studies, the frequencies of QT prolongation were the same as in the control arms or less. QT does not appear to be a problem with ruxolitinib.

Withdrawal effects

Following interruption or discontinuation of Jakavi, symptoms of myelofibrosis 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.

Safety in special populations

Age

When analyzed by age category, ≤ 65 years old and > 65 years old, the number of patients who experienced AEs was generally similar, although specific SOCs and preferred terms were higher in the > 65 years old age group, such as Blood and lymphatic system disorders (69.1% vs. 54.0%, mainly anaemia and thrombocytopenia), Cardiac disorders (23.5% vs. 12.9%, no single preferred term predominating), Infections and infestations (55.6% vs. 43.9%, with largest differences seen in cystitis and pneumonia), Vascular disorders(24.1% vs. 11.5%, largest difference seen in haematoma). Similarly, SAEs were more frequent in the > 65 years old category (39.5% vs. 16.5%), with a similar pattern as seen for AEs.

Gender

When analyzed by gender, the number of patients who experienced AEs was generally similar, although specific SOCs and preferred terms were unbalanced. It is not unexpected that female patients experienced anaemia (43.2% vs. 29.0%), UTI (11.5% vs. 3.1%), and cystitis (7.2% vs. 0%) in greater frequency than males, since this reflects the background epidemiology. The more frequent weight increased (13.7% vs. 3.1%) could be related to the better efficacy outcomes in females.

The more frequent hepatobiliary disorders in males compared with females (7.4% vs. 2.9%) could be a reflection of background epidemiology, indicated by a similar difference in the placebo arm of Study 351. The difference in anorexia (6.2% in men vs. 1.4% in women) might also reflect the background epidemiology, indicated by similar findings in the BAT arm of Study 352. There is no obvious explanation for the difference in frequency of Herpes zoster (4.9% in men vs. 1.4% in women), but it could be a chance finding due to small numbers.

Race

Since the vast majority of the patients were Caucasian - 89% of ruxolitinib treated patients in Study 351; and 81% in Study 352 (with the remaining 19% as missing) - it is not possible to have a meaningful interpretation of the results for this subgroup analysis.

Baseline platelet count and Baseline palpated spleen length

Analyses by baseline platelet count category (< 200 K and ≥200 K) which was a trigger for different starting doses of 15 mg b.i.d. and 20 mg b.i.d. respectively, and baseline palpated spleen length > 10 cm compared with ≥10 cm did not reveal any important differences, other than those that reflect the underlying difference in degrees of disease and splenic size.

Pregnancy

Two cases of pregnancy after female exposure have been reported; one of the pregnancies occurred after exposure to topical ruxolitinib in a psoriasis study and was ongoing at the time of the report with no complications reported; the other was followed by elective termination of pregnancy on day 460 of treatment with systemic ruxolitinib without further details available.

Immunological events

There were no signs of hypersensitivity reactions from ruxolitinib.

Safety related to drug-drug interactions and other interactions

Pharmacokinetic interaction

Potent CYP3A4 inhibitors such as ketoconazole give rise to an approximate doubling of ruxolitinib exposure. CYP2C9 inhibitors are also likely to give rise to increased exposure. A PBPK simulation on the exposure after treatment with fluconazole, which is a mild to moderate dual CYP3A4 and 2C9 inhibitor, predicted a 3-fold increase in ruxolitinib. Thus, a dose reduction of approximately 50% is appropriate.

In vitro data indicate that ruxolitinib may inhibit intestinal CYP3A4 and intestinal Pgp as well as BCRP. The interactions are thoroughly covered in sections 4.2, 4.4 and 5.2 of the SmPC. There is no drug interaction study with an oral contraceptive. Such a study should be done as a post-authorisation measure due to the considerations of teratogenicity (see section 2.7 RMP).

Possible pharmacodynamic interaction

There is also a theoretical potential pharmacodynamic interaction with haematopoietic growth factor drugs, since it has been shown that the receptors of G-CSF,GM-CSF, erythropoietin and thrombopoietin all signal through the JAK/STAT system, including (JAK1 and) JAK2 (Numata 2005, Perugini 2010, Choi 2011, Okonko 2011, Won 2009). Furthermore, enhanced cell-surface expression following JAK over-expression has also been reported for a number of cytokine receptors, including the thrombopoietin and erythropoietin receptors (Meenhuis 2009, and references therein). It is unclear what the implications of these findings could be for the management of cytopenias during ruxolitinib therapy. It is therefore unknown if there a risk that patients with neutropenia who are using ruxolitinib would be unresponsive to G-CSF or GM-CSF therapy. The Applicant has addressed this in the RMP and SmPC.

Drug-disease interactions

Hepatic impairment

An increase in the exposure and half-life of ruxolitinib was observed in patients with 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 and indicating no clear relationship to the degree of hepatic impairment based on Child-Pugh scores. 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.

Renal impairment

Following a single ruxolitinib dose of 25 mg, the pharmacokinetics were 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 end-stage renal disease requiring haemodialysis (see Fig. 7 below, Cohort 1 are patients with normal function, 5 and 6 are ESRD patients with pre-dose and post-dose dialysis, respectively.).

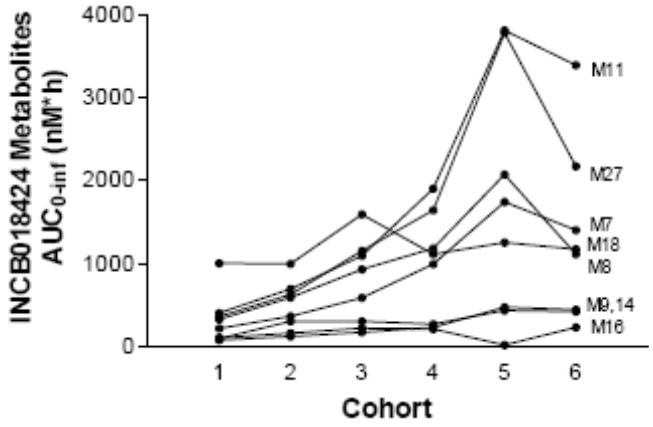


Figure 7: Comparison of geometric mean AUC0-inf values of individual ruxolitinib metabolites

The starting dose of ruxolitinib should be reduced in patients with severe renal impairment. For patients with end-stage renal disease on haemodialysis the starting dose should be based on platelet counts. Subsequent doses (single administration) should be administered on haemodialysis days following each dialysis session. Additional dose modifications should be made with careful monitoring of safety and efficacy. The applicant is recommended to provide PD simulations post-approval to try to optimize the dosing regimen in ESRD.

Discontinuation due to adverse events

The frequency of discontinuations due to AEs were essentially equal across the treatment arms of the two pivotal studies, respectively; 11% in both arms of Study 351 and 8% in both arms of Study 352. With few exceptions, each PT for discontinuation occurred in single patients (i.e. below the 1% frequency), and therefore no important trends can be seen between the ruxolitinib and the control arms. Thrombocytopenia and anaemia constitute the main causes for dose reduction or interruption (approximately 35 and 5 % respectively)

2.6.1. Discussion on clinical safety

The maximum ruxolitinib exposure in any safety study was 24.8 months; maximum exposures in the two pivotal phase-III studies were 13.6 and 17.3 months, respectively. The median duration of exposure in all three pooled safety populations (Phase 3 population, MF population, and All cancer population) was around 10 months. In the phase 1-2 Study 251 longer duration of exposure was seen, but the relevance of the safety data from this study is difficult to assess due to the different dosing regimens and higher doses. In the combined pivotal studies, 75% of the patients in the ruxolitinib arms were still receiving the randomised treatment at data cut-off, indicating that a significantly longer duration of exposure can be expected than that for which safety data is currently available. This is considered an important lack of long-term safety data, which is particularly important since this is a First-in-class substance, which involves central parts of the immune and haematopoietic systems in ways not yet fully elucidated.

The most frequently reported adverse drug reactions were thrombocytopenia and anaemia which are dose dependent and a direct result of ruxolitinib's mechanism of action, JAK inhibition.

Increased frequencies of infection AEs may also be directly related to the JAK inhibition by inhibiting/hampering the cytokine signalling of the immune response. Infections were overall more common in the ruxolitinib arms compared with controls in the pivotal studies. It appears that while infection AEs overall occur more often in the ruxolitinib arms, Grade 3-4 infections occurred at similar

frequencies as in the placebo and best available therapy arms. The longer observation time in the ruxolitinib arms could to some degree explain the higher frequency of infections seen compared with the control arms, which is supported by the much lower frequency in the cross-over group (from BAT), and possibly also by the higher frequency in Study 252 with longer duration of exposure, although higher doses were used in that study.

There is an indication that UTIs may be particularly overrepresented in the ruxolitinib treated patients, the cause for this is unknown and merits further monitoring (see section 2.7 RMP). Cases of Tuberculosis have been observed with ruxolitinib. This may represent opportunistic infections that in theory could be related to ruxolitinib's JAK inhibiting mechanism involving central parts of the immune system. Close monitoring of severe and opportunistic infections will be performed post marketing in a disease registry study. Patients should therefore be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Ruxolitinib 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

The frequency of Herpes zoster (shingles) was higher in the ruxolitinib arms compared with the control arms of the pivotal studies. Herpes zoster is quite commonly seen in patients with haematological malignancies, and based on these figures herpes zoster does not appear to be an important clinical problem with ruxolitinib treatment. However, in the phase 2 Study 251, higher frequencies were seen. If this is primarily due the longer duration of exposure, rather than the higher doses used in this study (or the combination), it could in fact be a larger problem than indicated by the pivotal studies. Physicians should educate patients about early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible.

Treatment with ruxolitinib 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/mm3 or absolute neutrophil count less than 500/mm3. It has been observed that patients with low platelet counts (<200,000/mm3) 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 ruxolitinib. However, platelet transfusions may be required as clinically indicated.

Patients developing anaemia may require blood transfusions. Dose modifications 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 ruxolitinib-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 ruxolitinib.

Complete blood counts should be monitored as clinically indicated and dose adjusted as required.

There is an increased risk of bleeding and bruising with ruxolitinib therapy. The mechanism for the bleeding events is not fully elucidated, although grade 4 thrombocytopenia is associated with an increased incidence of bleeding, as expected. The MF disease in itself has been associated with

impaired platelet function. Other theoretically possible mechanisms may include vascular/endothelial changes, possibly aggravated by ruxolitinib.

According to pharmacokinetic studies, patients with hepatic and renal impairment will have an increased AUC of ruxolitinib due to the decreased metabolism and decreased elimination, respectively. Cytopenias were somewhat more frequent in ruxolitinib treated patients with hepatic or renal impairment compared to patients without these organ impairments. However, patients with raised transaminases did not have a higher frequency of cytopenias compared to the overall patient population.

Apart from the known pharmacokinetic interaction with potent CYP3A4 inhibitors, there is also a potential pharmacodynamic interaction with haematopoietic growth factor drugs, such as G-CSF and erythropoietin, which could be a potential important safety problem if it means that cytopenic patients will be unresponsive to treatment with the needed growth factor in question. This is now addressed in the RMP and SmPC.

Concerning splenic infarction, these AEs often occur as a result of the disease (as evident by the higher frequencies in the placebo arm). A theoretical concern might be that they could occur at discontinuation of ruxolitinib due to sudden massive increase in splenomegaly. One of the three ruxolitinib treated cases occurred after discontinuation. It is possible that stopped ruxolitinib treatment may have aggravated the already ongoing progressing splenomegaly in this patient; however, it is not unlikely that the event would have occurred anyway. While a return of MF symptoms is seen shortly after ruxolitinib discontinuation as a reflection of the discontinued JAK inhibition and consequently increased cytokine signalling, no exceeding of median symptom score following discontinuation compared with median baseline was seen. There is therefore no evidence present of re-bound phenomena to excess levels. Unless abrupt discontinuation is required, gradual tapering of the dose of Jakavi may be considered, although the utility of the tapering is unproven.

Weight gain was seen clearly more often in the ruxolitinib arms compared with the control arms of the pivotal studies. However, 50% of patients with weight gain had normal renal function and albumin, and did not have oedema, fluid retention or any other co-reported AEs as explanatory factors for their weight increase, suggesting that in around 50% of patients with weight increases this may have been a positive treatment effect.

Many of the AEs occurred considerably more frequently in the phase 1/2 Study 251 compared with the pivotal phase 3 studies (not shown). This could in part be explained by the clearly longer duration of exposure in this study (particularly the q.d-arm), but also on the higher doses given in this study (again particularly in the q.d. arm). The relevance of the data from Study 251 is therefore uncertain. The assessment is therefore focused on the pivotal studies.

A non-trivial proportion of deaths were due to infections in both the ruxolitinib arm and the placebo arm of Study 351. Additional deaths due to infection are seen after cross-over to ruxolitinib in both pivotal studies, and in the supportive studies. While a number of these causes of deaths were assessed as not related to study drug by investigators, it is not excluded that the JAK inhibition could have played some role in the course of the infection, due to its inhibiting effects on cytokine signalling.

There were three cases of bleeding with fatal outcome in the ruxolitinib arms of the pooled pivotal studies, compared with one in the control arms. In the first case, the thrombocytopenia was considered related to ruxolitinib treatment and thereby contributory to the subdural haematoma. In the latter two cases the bleeding events were considered unrelated to ruxolitinib treatment. Considering the epidemiology of bleeding in ruxolitinib unexposed PMF (See RMP), and the disease characteristics and other circumstances of these patients, the contribution of ruxolitinib to the bleeding events is uncertain. The effect of ruxolitinib on the platelet count may not be the main mechanism for

bleeding in these observed cases with fatal outcome. Data from ongoing and future trials may clarify this issue.

The practical significance of the more frequent increased systolic blood pressure in the ruxolitinib arms is not clear. Generally, hypertension is associated with an increased risk of stroke and myocardial infarction, and has been identified as a leading cause of cardiovascular death. Pharmacologically, there are mechanistic relationships between JAK signalling and inhibition, and blood pressure, however not easily predictable in the individual patient. Increased systolic blood pressure has been included as an important potential risk in the RMP and as an adverse drug reaction in the SmPC.

There are no data from the use of ruxolitinib in pregnant women. 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 during the treatment with ruxolitinib. In case pregnancy should occur during treatment with ruxolitinib, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the foetus.

Ruxolitinib must also not be used during breast-feeding 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. There are no human data on the effect of ruxolitinib on fertility

Ruxolitinib has no or negligible sedating effect. However, patients who experience dizziness after the intake of Jakavi should refrain from driving or using machines.
The effect (positive or negative) of ruxolitinib therapy on the development of bone-marrow fibrosis is currently unknown, and requires further investigation.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

While nearly 60% of the patients in the phase III trials had dose reductions and nearly 30% had dose interruptions, there was a low discontinuation rate due to adverse events.

Cytopenias are expected by ruxolitinib's JAK inhibiting mechanism of action. These appear manageable by dose modifications and transfusions, and are well covered in the SmPC.

Bleeding and infections could also to some degree be expected by the mechanism of action (bleeding as a consequence of thrombocytopenia), but this requires further investigation and monitoring. An effort to elucidate the full mechanisms for bleeding is desirable. The long-term consequences with regard to severe and opportunistic infections will be addressed in a disease registry study.

The vast majority of non-hematologic adverse events were mild to moderate in severity and occurred at a low frequency.

In conclusion, long-term safety requires further investigation and follow-up of the pivotal trials and in the disease registry study. This should include monitoring of mortality rates and causes of death. Being a first in class-compound, no lessons can be learned by class effects of similar compounds (see section 2.7 RMP).

2.7. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The applicant submitted a risk management plan

Table 28: Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities (routine and additional)**
Important identified risks		
Myelosuppression	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Safety and tolerability will be assessed in a Non Interventional Ruxolitinib in Myelofibrosis - Long term Safety Study (CINC424AIC01T). Ongoing study to evaluate the safety of ruxolitinib in MF patients with a baseline platelet count <100000/mm^3 (study INC424A2201). Extension phases of studies INCB 18424-351 and INC424A2352	SPC Section 4.2 (Posology and method of administration): Instructions for lab monitoring, starting dose and dose modifications Section 4.4: Warning, precaution for lab monitoring, dose reduction and treatment discontinuation, and description of risk factors and nature of risk. Section 4.8 (Undesirable effects) The ADRs of anaemia, thrombocytopenia and neutropenia are listed as very common and described. Section 4.9 (Overdose) Description of nature of the risk and supportive therapy is described.
Infections (including TB, UTI and herpes zoster)	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Safety and tolerability will be assessed in a Non Interventional Ruxolitinib in Myelofibrosis - Long term Safety Study (CINC424AIC01T). Ongoing study to evaluate the safety of ruxolitinib in MF patients with a baseline platelet count <100000/mm^3 (study INC424A2201). Extension phases of studies INCB 18424-351 and INC424A2352	SPC Section 4.4 (Special warnings and precautions for use): Precaution for monitoring, treatment, and description of risk factors and nature of risk. Section 4.8: The ADRs of urinary tract infection, (very common) herpes (common) and tuberculosis (frequency less than 1.0%) are described.
Use in patients with hepatic impairment	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Ongoing study to evaluate the safety of ruxolitinib in MF patients with a baseline platelet count <100000/mm3 (Study	SPC Section 4.2 (Posology and method of administration): Instructions for lab monitoring, starting dose and dose modifications Section 4.4 (Special warnings and precautions for use): Instructions for lab monitoring,

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities (routine and additional)
	INC424A2201). Extension phases of studies INCB 18424-351 and INC424A2352	and dose modifications
Use in patients with moderate or severe renal failure or end stage renal failure requiring hemodialysis	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Ongoing study to evaluate the safety of ruxolitinib in MF patients with a baseline platelet count <100000/mm3 (study INC424A2201). Extension phases of studies INCB 18424-351 and INC424A2352	SPC Section 4.2 (Posology and method of administration): Instructions for lab monitoring, starting dose and dose modifications Section 4.4 (Special warnings and precautions for use): Instructions for lab monitoring, and dose modifications
Elevated transaminases	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Ongoing study to evaluate the safety of ruxolitinib in MF patients with a baseline platelet count <100000/mm3 (study INC424A2201). Extension phases of studies INCB 18424-351 and INC424A2352	SPC Section 4.8 (Undesirable effects) The ADRs of raised alanine aminotransferase are listed as very common.
Bleeding (Hemorrhage)	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Safety and tolerability will be assessed in a Non Interventional Ruxolitinib in Myelofibrosis - Long term Safety Study (CINC424AIC01T). Ongoing study to evaluate the safety of ruxolitinib in MF patients with a baseline platelet count <100000/mm^3 (study INC424A2201). Extension phases of studies INCB 18424-351 and INC424A2352	Section 4.8 (Undesirable effects): The ADRs of bleeding events, bruising, intracranial bleeding, gastrointestinal bleeding and other bleeding events are listed and described with frequencies.
Important potential risks		
AEs after discontinuation of ruxolitinib (with return of MF symptoms)	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Safety and tolerability will be assessed in a Non Interventional Ruxolitinib in Myelofibrosis - Long term Safety Study (CINC424AIC01T). Ongoing study to evaluate the safety of ruxolitinib in MF patients with a baseline platelet count <100000/mm3 (study INC424A2201). Extension phases of studies INCB 18424-351 and INC424A2352	Section 4.4 Special warnings and precautions for use. Withdrawal effects Gradual tapering of the dose of ruxolitinib may be considered. Section 4.8 (Undesirable effects): The recurrence of myelofibrosis symptoms is described.
Increased systolic blood pressure	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities**	Section 4.8 (Undesirable effects) The ADR of increased systolic blood pressure is described.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities (routine and additional)
	Extension phases of studies INCB 18424-351 and INC424A2352	
Developmental toxicity	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Additional data concerning the outcome of pregnancies will be collected in the Non Interventional Ruxolitinib in Myelofibrosis - Long term Safety Study (CINC424AIC01T).	SPC Section 4.1 (Indications) Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Pregnancy and lactation Section 4.6 (Fertility, pregnancy and lactation) There are no data from the use of ruxolitinib in pregnant women.
Important identified interaction		
Overexposure with concomitant strong CYP3A4 inhibitors or fluconazole	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Ongoing study to evaluate the safety of ruxolitinib in MF patients with a baseline platelet count <100000/mm3 (study INC424A2201). Extension phases of studies INCB 18424-351 and INC424A2352	SPC Section 4.2 (Posology and method of administration) Starting dose and frequent monitoring of hematological parameters Section 4.4 (Special warnings and precautions for use) Instructions for lab monitoring, starting dose and dose modifications Section 4.5 Interactions with other medicinal products and other forms of interaction. Interactions resulting in dose reduction
Use with CYP3A4 inducers such as rifampicin	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Ongoing study to evaluate the safety of ruxolitinib in MF patients with a baseline platelet count <100000/mm3 (study INC424A2201). Extension phases of studies INCB 18424-351 and INC424A2352	SPC Section 4.5 (Interaction with other medicinal products and other forms of interaction): Information on interaction and instructions for lab monitoring, dose modifications
Important potential interactions		
Pharmacodynamic interaction between ruxolitinib and hematopoietic growth factors or combination with cytoreductive therapies	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Safety and tolerability will be assessed in a Non Interventional Ruxolitinib in Myelofibrosis - Long term Safety Study (CINC424AIC01T).	SPC Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction): The concurrent use of haematopoietic growth factors and Jakavi has not been studied.
Use with orally administered CYP3A4 substrates	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** An interaction study with a CYP3A4 probe drug sensitive to intestinal inhibition, such as oral midazolam will be conducted.	Section 4.5 (Interactions with other medicinal products and other forms of interaction)
Important missing information		
Safety in MF patients with a platelet count below 100,000 at	Routine pharmacovigilance including cumulative analysis in	Section 4.2 (Posology and method of administration):

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities (routine and additional)
baseline	the PSUR/DSUR. **Additional Activities** Ongoing study to evaluate the safety of ruxolitinib in MF patients with a baseline platelet count <100000/mm^3 (study INC424A2201).	Instructions for lab monitoring, starting dose and dose modifications Section 4.4 (Special warnings and precautions for use): Treatment should be discontinued in patients with platelet count less than 50,000/mm^3
Safety in MF patients with an ANC <500/µL	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR.	SPC Section 4.2 (Posology and method of administration): Instructions for lab monitoring, starting dose and dose modifications. Section 4.4 (Special warnings and precautions for use): Treatment should be discontinued in patients with ANC less than 500 mm^3.
Safety in non-Caucasian patients	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR.	Currently available data do not support the need for risk minimization.
Safety in pediatric patients	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Ruxolitinib Drug Utilization Study will provide information about the possible extent of any off-label use in children	Considering the mechanism of action of ruxolitinib it is possible that it might be used off-label in children. Prescribers are discouraged from prescribing ruxolitinib to children through the current labeling: Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 4.6 (Fertility, pregnancy and lactation)
Risks in off-label use	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Ruxolitinib Drug Utilization Study	Prescribers are discouraged from prescribing ruxolitinib off-label through the current labeling: Section 4.1 (Therapeutic indications)
Long-term safety data, including secondary malignancies	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Long term safety and tolerability will be assessed in a Non Interventional Ruxolitinib in Myelofibrosis - Long term Safety Study (CINC424AIC01T). Extension phases of studies INCB 18424-351 and INC424A2352	The safety profile of ruxolitinib is described in Section 4.8. Currently available data do not support the need for additional risk minimization.
Safety in patients with disease severity different from those in CTs	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR.	Section 4.1 (Therapeutic indications)
Safety in elderly patients over 75 years of age	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Additional data will be collected in the Non Interventional Ruxolitinib in Myelofibrosis - Long term Safety Study (CINC424AIC01T). Extension phases of studies INCB	Section 4.2 (Posology and method of administration): Information on dosing in elderly patients is mentioned. Currently available data do not support the need for additional risk minimization.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities (routine and additional)
	18424-351 and INC424A2352	
Safety in sub-populations with genetic polymorphisms	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR.	Currently available data do not support the need for risk minimization.
Effect on bone marrow fibrosis	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Additional data will be collected in the Non Interventional Ruxolitinib in Myelofibrosis - Long term Safety Study (CINC424AIC01T). Extension phases of studies INCB 18424-351 and INC424A2352	Currently available data do not support the need for risk minimization.
Interaction with oral contraceptives	Routine pharmacovigilance including cumulative analysis in the PSUR/DSUR. **Additional Activities** Additional data will be collected in the Non Interventional Ruxolitinib in Myelofibrosis - Long term Safety Study (CINC424AIC01T). A drug interaction study will be conducted with oral contraceptives.	Section 4.5 (Interactions with other medicinal products and other forms of interaction)

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
To set up Study CINC424AIC01T- Post Authorization Safety Study- Non interventional ruxolitinib in Myelofibrosis, Long-term Safety study which will recruit patients with myelofibrosis, exposed or unexposed to ruxolitinib	- Annual updates reported in PSURs - Final study report submitted in February 2019
To set up a Drug Utilization study in the EU	- Annual study updates reported in PSURs - Final Study report submitted 6 years after launch in major EU markets
To perform a drug interaction study with an oral contraceptive	Final study report submitted in April 2015
To perform a drug interaction study with a CYP3A4 probe drug sensitive to intestinal inhibition, such as oral midazolam.	Final Study report submitted in September 2014

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

This application is based on two pivotal studies, with support from a phase I/II dose-finding study: The double-blind placebo-controlled 351 study (n=309) and the open 352 study (n=219) that was controlled by investigator's best choice of available therapy. Both studies are considered well-conducted.

The primary efficacy endpoint of the pivotal studies was the proportion of patients achieving ≥35% reduction in spleen volume from baseline, analysed at 24 weeks in protocol 351 and at 48 weeks in protocol 352; in study 351, 65 subjects (41.9%; 95% CI 34.1-50.1) reached this endpoint in the ruxolitinib arm and 1 subject (0.7%; 95% CI 0.0-3.6) in the placebo arm, ($p<0.0001$); in study 352, 41 subjects (28.5%; 95% CI 21.3-36.6) reached this endpoint in the ruxolitinib arm and no subject (0%; 95% CI 0.0-0.5) in the BAT arm, ($p<0.0001$). An analysis of data at week 24 (secondary endpoint) in the study 352 showed that 46 patients (31.9%) in the ruxolitinib arm reached the cut-off at that time point. Thus, although the response rate for unknown reasons differs somewhat between the studies, it is concluded that approximately one third of patients reach the pre-specified level of spleen volume reduction. Comparison of these MRI/CT-achieved data with palpation data reveals that they roughly correspond to a spleen size reduction of 50%, which is considered clinically relevant. Waterfall analyses confirm the efficacy and show that the majority of, albeit not all, patients in the ruxolitinib arms achieved *some* level of spleen volume reduction, which was not the case in either the placebo arm or the BAT arm.

Subgroup analyses of the primary endpoint in both pivotal studies indicate that patients harbouring the JAK2V617F mutation have a higher response rate than patients lacking the mutation; 47.8% vs 27.5% in the 351 study, and 32.7% vs 14.3% in the 352 study, respectively.

Duration of response was a secondary endpoint in both studies. In the 351 study, the median duration of response was 48 weeks. However, as the median was not reached in the 352 study, duration of response remains to be described.

The analyses of effect of ruxolitinib on MF-related symptoms and QoL are most reliable for the 351 protocol as the study was placebo-controlled. Using the modified MF symptom assessment instrument, a ≥50% improvement from baseline in total symptom score at week 24 was seen for 45.9% of subjects in the ruxolitinib arm and 5.3% in the placebo arm, ($p<0.0001$), supported by an improvement in mean/median change from baseline in total symptom score for the ruxolitinib arm while a mean/median worsening was noted in the placebo arm, ($p<0.0001$). Using the EORTC QLQ-C30 instrument, although not specifically validated in MF, statistically significant improvements at week 24 in the ruxolitinib arm over the placebo arm were noted in global health status and the majority of functional subscales. In analogy with the outcome seen for spleen volume per mutational group, superior results are achieved in the JAK2 mutation positive group also for symptom relief: Percent of subjects achieving greater than or equal to 50% reduction in TSS from baseline to week 24, median

percent improvement from baseline at week 24 in TSS, and median time to first greater than or equal to 50% improvement from baseline in TSS were all in favour of the JAK2 positive group; 52.3% vs 28.2% in the JAK2 negative group, 65.1% vs 29.4%, and 4.0 vs 6.6 weeks, respectively.

Currently available updated overall survival data shows, although formally not statistically significant, a nominal improvement in overall survival with the use of ruxolitinib over placebo/best available therapy and no difference in progression free survival between ruxolitinib and best available therapy.

Elevation of pSTAT3 and inflammation markers (e.g. IL-6, TNF-α, and CRP) were noted at baseline and decreased following treatment with ruxolitinib, supporting the stated mechanism of action also *in vivo*.

Uncertainty in the knowledge about the beneficial effects.

The results of progression-free survival, overall survival and leukaemia-free survival are immature and need further follow-up in order to confirm the long term benefit of ruxolitinib in the CHMP endorsed indication. This is reflected as an annex II condition.

Risks

Unfavourable effects

Cytopenias were the most frequent AEs in the pivotal studies and are expected by the mechanism of action. Thrombocytopenia and anaemia constitute the main causes for dose reduction or interruption. A very significantly increased risk (nearly 80%) of grade 3-4 haemoglobin levels in patients starting at grade 2, compared with grade 1 (35%) was seen. As a consequence of cytopenias an increased need for blood transfusions were seen; approximately 50-60% vs. 40% in the ruxolitinib arms compared with the controls. No relevant difference in the frequency of platelet transfusions were seen between treatment arms in the pivotal studies (around 5% in both).

There is an increased risk of bleeding and bruising with ruxolitinib therapy. Grade 3-4 AEs and SAEs frequencies were similar to the control arms. Bruising events was the main driver of the difference in bleeding events between study arms, but an increase in bleeding events other than bruising was also seen (19,3 vs. 15,2% in the ruxolitinib vs. control arms pooled data, respectively), this is mentioned in section 4.8 of the SmPC.

Infections were overall more common in the ruxolitinib arms compared with controls in the pivotal studies, although grade 3-4 and SAEs did not generally appear significantly more frequent. In the prolonged follow-up a total of 3 cases of tuberculosis have been observed in the ruxolitinib arms of the pivotal trials, while no reports have been received from comparator arms. This finding is an observandum as it could represent an opportunistic infection.

Weight gain was reported as an AE in 10.0% of the ruxolitinib treated patients in the pivotal studies and in 1.3% in the pooled control arms. However, 50% of patients with weight gain had normal renal function and albumin, and did not have oedema, fluid retention or any other co-reported AEs as explanatory factors for their weight increase, suggesting that in around 50% of patients with weight increases this may have been a positive treatment effect.

Grade 1 raised liver transaminases were frequently seen in the ruxolitinib treated patients, but no increase compared with controls were seen in grade 2 values. Grade 3 values were only seen for ALT, in the ruxolitinib arm at the 1% level. Increases in transaminases were not associated with an increased risk of cytopenias.

There is a known pharmacokinetic interaction with potent CYP3A4 inhibitors, and also it may not be excluded that ruxolitinib inhibits intestinal CYP3A4, Pgp and BCRP. There is no drug interaction study with an oral contraceptive. The risk is handled in the SmPC including clear dose reduction instructions. In addition, the applicant will conduct a DDI study with oral contraceptives as reflected in section 2.7 (RMP). Generally, only minor differences in safety according to mutational status were noted.

Uncertainty in the knowledge about the unfavourable effects

The median duration of exposure in all three pooled safety populations was around 10 months. In the combined pivotal studies, 75% of the patients in the ruxolitinib arms were still receiving the randomised treatment at data cut-off, indicating that a significantly longer duration of exposure can be expected than that for which safety data is currently available. This is considered an important lack of long-term safety data, which is particularly important since this it is a First-in-class substance, which involves central parts of the immune and haematopoietic systems in ways not yet fully elucidated. This is reflected in the RMP as important missing information and data will be provided by a long term Safety Study (CINC424AIC01T) included in the RMP and the extension phases of pivotal trials INCB 18424-351 and INC424A2352 included in annex II as conditions to the marketing authorisation.

Thus, the frequency and type of infections in long-term use is a concern due to the mechanism of action. There is an indication that infections in the urinary tract may be particularly overrepresented in the ruxolitinib treated patients, the cause for this is unknown and merits further investigation and monitoring. This information has been reflected in sections 4.4 and 4.8 of the SmPC. Further data will be provided by the long term Safety Study (CINC424AIC01T) and the extension phases of studies INCB 18424-351 and INC424A2352.

The mechanism for the bleeding events is not clear, and although at least a proportion of events theoretically would be explained by thrombocytopenia this did not appear to be the case with the 3 fatal cases of bleeding in the pivotal trials. Information regarding bleeding is included in the section 4.8 of the SmPC and further data will be provided by the long term Safety Study (CINC424AIC01T) and the extension phases of studies INCB 18424-351 and INC424A2352.

Although theoretical discussions and non-clinical data indicate a favourable effect of ruxolitinib on bone marrow fibrosis, available clinical data do not allow any conclusions to be made. Knowledge about adverse as well as beneficial long-term effects of ruxolitinib on this hallmark feature of the disease is considered to be of important value and further vigilance is indicated. The long term Safety Study (CINC424AIC01T) and the extension phases of studies INCB 18424-351 and INC424A2352 will provide important information.

There is a theoretical possibility of a pharmacodynamic interaction with haematopoietic growth factor drugs, such as G-CSF and erythropoietin, which needs further investigation and could be a potential important safety problem if it means that cytopenic patients will be unresponsive to treatment with the needed growth factor in question. This potential interaction is included in the SmPC sections 4.4. and 4.5.

It is possible that MF patients requiring cytoreductive therapy might in clinical practice be offered symptom reducing ruxolitinib in combination with cytoreductive therapy, such as Hydroxyurea (HU). Combination therapy does not appear to have been studied and the safety of such combination therapy is unknown. This lack of data regarding combination therapy is addressed in sections 4.4. and 4.5 of the SmPC.

Further PK drug interactions are requested and will be provided post authorisation as reflected in section 2.7 (RMP).

Benefit-risk balance

Importance of favourable and unfavourable effects

In addition to cytopenias and cytemias, constitutional symptoms and symptoms related to splenomegaly due to extramedullary hematopoiesis are prominent features of the morbidity seen in MF patients. The current therapeutic arsenal is limited, with hydroxyurea probably being the most widely used drug in the indication of MF in the EU (nationally approved), not well-characterised in the indication, and leaving a substantial number of patients without disease control and to palliation only.

In this context, the achievement of a ≥35% spleen volume reduction in approximately one third of patients, including those with no alternative treatment and compared to none in the BAT arm of the 352 study, is considered to be of clinical importance. It is noted that this volume reduction roughly corresponds to a 50% decrease in palpation length, which is a criterion for clinical improvement in the EUMNET and IWG criteria. In clinical experience, a reduced spleen size is associated with reduced abdominal symptoms and less hypersplenism and could hypothetically decrease the risk associated with splenectomy if this is to be performed. Although the duration of response remains to be fully evaluated, the median duration of response of 48 weeks seen in Study 351 is judged to be long enough to be of clinical value.

Regarding symptom relief and QoL, any improvement in this patient population is of value; the results seen in Study 351 study are considered important.

The three main safety concerns are bone-marrow depression, infections and bleeding.

As indicated by the frequencies in the control arms of the pivotal studies, cytopenias are common in the target population due to the underlying MF disease, and transfusions are given to the target population in high frequency anyway. The increase in blood transfusion frequency from 40% to 50-60% would probably be considered by most patients to be compensated by the symptom reducing effects, even though for many patients this requires hospital care. Overall, cytopenias appear manageable by dose modifications and transfusions.

Infections are also more common in the target population compared with healthy subjects, due to the underlying disease. If a markedly increased risk of severe and opportunistic infections were seen it could represent a problem for the future B/R balance. It therefore requires prospective monitoring.

Bleeding is common in the target population. As noted by the Applicant in the submitted RMP, thrombo-haemorrhagic events have been reported among principal causes of death in PMF, and in one study bleeding was the final cause of death in 2.7%of PMF patients. The MF disease in itself has been associated with impaired platelet function. Since there was no relevant increase in grade 3-4 or SAE bleeding events, it is believed that the overall increase of 7% in bleeding events in ruxolitinib treated patients in the pivotal studies can be acceptable.

Benefit-risk balance

In patients with V617F mutation positive disease, the benefits clearly outweigh the risks. The B/R balance is considered borderline positive also for the group of patients with V617F mutation negative disease, although a relatively smaller treatment effect was seen in this population.

A remaining uncertainty with regard to efficacy is whether the reduction in spleen size translates to improvements in progression free survival, leukaemia free survival or overall survival.

The safety profile of ruxolitinib is considered acceptable in relation to the benefits. Some long-term safety and questions related to interactions will be addressed as post authorisation measures.

The Applicant should therefore provide follow-up efficacy and safety data for patients in both phase III studies INCB 18424-351 and INC424A2352 annually including data on the time related endpoints (overall survival, progression free survival and leukaemia free survival) until the mature data on overall survival is available (see Annex II).

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Jakavi in the treatment of disease-related splenomegaly and symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythemia vera myelofibrosis or post essential thrombocythemia myelofibrosis is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.2 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Follow-up efficacy and safety data from the extension phase of studies INCB	Annually to

18424-351 and INC424A2352 including data on the time related endpoints (overall survival, progression free survival and leukaemia free survival) should be provided annually.	coincide with the anniversary of European birth date

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that ruxolitinib is to be qualified as a new active substance.