Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ruxolitinib

Proprietary Product Name: Jakavi

Sponsor: Novartis Pty Ltd

January 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
alloSCT	Allogeneic stem cell transplantation
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
bd	Twice daily
BAT	Best available therapy
BCS	Biopharmaceutics classification system
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIMF	Chronic Idiopathic Myelofibrosis
C_{max}	Maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel test
CNAE	Clinically notable adverse event
COMFORT I	Study INCB 18424-351
COMFORT II	Study CINC424A2352
CSR	Clinical study report

Abbreviation	Meaning
CT	Computed tomography
CTC	Common terminology criteria
CTCAE	Common terminology criteria for adverse event
CYP	Cytochrome P-450
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Group
eCRF	Electronic case report form
Emax	Maximum effect
EORTC-QLQC30	European Organisation for Research and Treatment of Cancer-Quality of Life
ET	Essential thrombocythemia
EUMNET E	European Myelofibrosis Network
FACT-Lym	Functional Assessment of Cancer Therapy -Lymphoma
FAS	Full analysis set
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transferase
h	Hour
hERG	Human-ether-a-go-go-related gene
Hgb	Hemoglobin
HR	Hazard ratio
HU	Hydroxyurea
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
IL	Interleukin
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment

Abbreviation	Meaning
JAK	Janus kinase family of protein tyrosine kinases
kg	Kilogram
Km	Michaelis constant (substrate concentration at half maximal velocity)
LC-MS/MS	Liquid chromatographic tandem mass spectrometry
LFS	Leukemia-free survival
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
mg	Milligram
mL	Milliliter
mM	Millimolar
MPN	Myeloproliferative neoplasm
MRI	Magnetic resonance imagery
MTD	Maximum tolerated dose
nM	Nanomolar
OS	Overall survival
PD	Pharmacodynamic
PET-MF	Post essential thrombocythemia – myelofibrosis
PFS	Progression-free survival
Ph-	Philadelphia chromosome negative
PK	Pharmacokinetic
PMF	Primary myelofibrosis
PPV-MF	Post polycythemia vera – myelofibrosis
PRBC	Packed red blood cells
PV	Polycythemia vera
PXR	Pregnane X receptor

Abbreviation	Meaning
qd	once daily
QoL	Quality of life
QTc	Time from beginning of the QRS complex to the end of the T wave corrected for heart rate
RA	Rheumatoid arthritis
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA query
SOC	System organ class
STAT	Signal transducer and activator of transcription
T_{max}	Time of maximum observed concentration
TNF	Tumor necrosis factor
TPO	Thrombopoietin
WBC	White blood cell
WHO	World Health Organization
µM	Micromolar

I. Introduction to product submission

Submission details

Type of submission	New Chemical Entity
Decision:	Approved
Date of decision:	28 June 2013
Active ingredient:	Ruxolitinib

Product name:	Jakavi
Sponsor's name and address:	Novartis Pty Ltd 54 Waterloo Rd North Ryde, NSW 2113
Dose form:	Tablets
Strengths:	5, 15 and 20 mg
Containers:	Bottle and blister packs.
Pack sizes:	Bottle: 60 tablets; Blister pack: 14, 28, 56, 112, 168, 224 tablets
Approved therapeutic use:	*Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in patients with primary myelobrosis, post-polycythemia vero myelofibrosis or post-essential thrombocythemia myelofibrosis*
Route of administration:	Oral (PO)
Dosage:	The recommended starting dose is dependent on platelet count; 5 mg twice a day (bd) at 50-100 $x10^9$/L; 15 mg bd at 100-200 x 10^9/L; and 20 mg bd at >200 x 10^9/L.
ARTG numbers:	198932-198937

Product background

This AusPAR describes the application by Novartis Pharmaceuticals Australia Pty Ltd to register the new chemical entity, ruxolitinib phosphate (Jakavi), for the treatment of patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

Ruxolitinib is a new class of antineoplastic agents/protein kinase inhibitor being developed for the treatment of multiple disorders including psoriasis and rheumatoid arthritis. Ruxolitinib inhibits phosphorylation of the non-receptor Janus Associated Kinase 1 (JAK1) and JAK2 kinases and downstream signalling in the JAK-STAT (JAK signal transducer and activator of transcription) pathway. The JAK non-receptor kinases are the major downstream targets for cytokine, chemokine and growth factor receptors and cytokines like interferon, erythropoietin and growth hormone use this pathway for signal transduction. JAK1 and JAK2 signalling is important in haematopoiesis and immune function. Disruption of signalling through mutations of these kinases leads to abnormal cellular proliferation. JAK2 mutations (commonly V617F) occur in myeloproliferative cancers including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET-MF).

The sponsor has proposed the following indication for Jakavi:

Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

Treatment options for patients with myelofibrosis are limited. Allogeneic haematopoietic stem cell transplantation is potentially curative but has significant risk and is not suitable for the majority of patients. For most patients, treatment is focussed on symptoms.

Hydroxyurea is standard for symptomatic splenomegaly and corticosteroids, antihistamines and analgesics for sweats, anorexia, bone pain and pruritus.

The sponsor was granted orphan designation for the indication on 23 April 2012.

A relevant European Guideline adopted by TGA is the *Guideline on the Evaluation of Anticancer Medicinal Products in Man*[1]. *Appendix 4*, due for adoption in July 2013, has specific information on myelodysplastic syndromes[2].

Regulatory status

This is an application for a new chemical entity.

The sponsor was granted orphan designation for the indication on 23 April 2012.

Similar applications have been approved in other countries as listed in Table 1 below.

Table 1: International regulatory status of Jakavi

Country	Tradename	Submitted	Approved	Indication
US	Jakafi	June 2011	16 Nov 2011	Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post polycythemia vera myelofibrosis and post essential thrombocythemia myelofibrosis.
EU	Jakavi	June 2011	23 August 2012	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-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.
Canada	Jakavi	28 Nov 2011	19 June 2012	Jakavi is indicated for the treatment of splenomegaly and/or its associated symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.
Switzerland	Jakavi	1 Dec 2011	27 Dec 2012	Treatment of splenomegaly or disease-associated symptoms in patients with intermediate or high-risk myelofibrosis as a complication of a myeloproliferative syndrome such as primary myelofibrosis, polycythaemia vera or essential thrombocythaemia

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

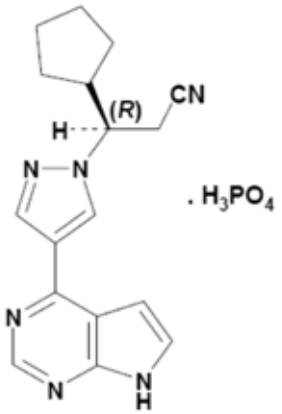
II. Quality findings

Drug substance (active ingredient)

Ruxolitinib is (*R*)-3-(4-(*7H*-pyrrolo[2,3-d]pyrimidin-4-yl)-*1H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile. It is a synthetic pyrrolopyrimidine derivative (but not closely related to for example pemetrexed). The drug is synthetic. Ruxolitinib has one chiral centre and the drug substance is the *R* enantiomer.

[1]<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500017748.pdf>
[2]<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137127.pdf>

Figure 1: Chemical structure of ruxolitinib phosphate



$C_{17}H_{18}N_6.H_3PO_4$. MW 404.4 (free base: 306.4)

Ruxolitinib is basic (pKa 4.3 and 11.8); the drug substance is the phosphate salt (1:1). The drug is crystalline. Ruxolitinib phosphate solubility varies with pH. Thus, at the maximum dose, the separate 25 mg doses would dissolve in between 46 and 150 mL of liquid across the relevant pH range.

Particle size is controlled with a limit acceptable for a BCS class 1[3] drug (a limit is appropriate to ensure good content uniformity).

There is a small amount of the S-enantiomer in the drug substance which is considered toxicologically acceptable.

Drug product

Immediate release, uncoated, unscored 5, 15 and 20 mg tablets were proposed. These are all directly scaled. The strengths are distinguished by debossing ('L5', 'L15' or 'L20') and shape. Tablets are made by wet granulation using water. Excipients are conventional. Tablets are formulated with ruxolitinib *phosphate* but labelled with ruxolitinib content, which is now the standard approach. Toxicological advice is that an *uncoated* tablet presentation is acceptable for this drug class.

Both bottle packs (60 tablet, with child resistant closure) and blister packs (14, 28, 56, 112, 168, 224 tablet) packs are proposed.

Tablet dissolution tests were provided.

There are no clear changes on storage except for an increase in two unidentified impurities.

Clinical trial formulations

An oral solution formulation was used in the Absorption, Distribution, Metabolism and Excretion (ADME) study INCB 18424-134. The first-in-man study used a powder-in capsule formulated only with drug (5 mg and 25 mg).

The Phase I and II clinical trials used immediate release 5 mg and 25 mg tablets formulated to have same weight and appearance (for blinding). The formulation included stearic acid, unlike the registration formulation.

[3] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the US Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

The two Phase III clinical trials (CT INCB 18424-351 and CINC424A2352) only used 5 mg tablets of the formulation proposed for registration. The 15 and 20 mg tablet strengths proposed for registration are direct scales of this 5 mg tablet (that is, compressed from the same blend) but were not used in clinical trials.

Biopharmaceutics

Ruxolitinib is metabolised by CYP3A4 to two significant metabolites. Excretion is chiefly renal (22% of a radiolabelled oral solution excreted in faeces). The mean elimination half life is about 3 hours. Pharmacokinetics were reported to be linear (5 to 200 mg).

Epimerisation *in vivo* does not appear to have been investigated; human pharmacokinetic data are for total ruxolitinib.

Individual pharmacokinetic profiles are conventional and show consistently rapid absorption.

Ruxolitinib phosphate is a BCS Class 1 drug (high permeability, high solubility). Such drugs, as long as formulated in rapid dissolving dosage forms, do not normally show effects of formulation on bioavailability.

The TGA adopted European Union (EU) guidance document[4] allows BCS based biowaivers for BCS Class I products which are rapidly dissolving and give 'complete absorption', which is defined as an extent of absorption ≥ 85%. The *Jakavi* tablets do show rapid initial dissolution (circa 70% in 5 minutes, although complete dissolution is strangely slow).

The draft PI states "*Based on a mass balance study in humans, oral absorption of ruxolitinib was 95% or greater*." No absolute bioavailability study was undertaken and no human intravenous dosing. In Study18424-134 single 25 mg oral solution doses of radiolabelled (^{14}C)-ruxolitinib were given to healthy subjects. Mean total recovery of radioactivity was 96%, with essentially all the administered dose recovered in urine and faeces as oxidative and glucuronated metabolites. (Phase 1 oxidative and Phase 2 conjugative metabolism can only occur after absorption, not in the gastric or intestinal fluid.) The data are consistent with extensive absorption. The Pharmaceutical Sub Committee (PSC) of the Advisory Committee on prescription Medicines (ACPM) considered the lack of an absolute bioavailability study acceptable given this data.

Novartis argued that *in vitro* and *in vivo* data show ruxolitinib meets the biowaiver criteria. Therefore, no comparative bioavailability or bioequivalence studies were presented in Module 5 of the current submission. Nevertheless, a *cross-study* comparison of pharmacokinetic data for different formulations was made. Novartis concludes that the relative bioavailability of ruxolitinib "*was similar in healthy subjects administered 25 mg of ruxolitinib as powder-in-capsule, tablet, or oral solution*".

The effect of food on bioavailability was investigated in Study INCB 18424-131. A high-fat meal decreased peak plasma concentration (C_{max}) by 24% and increased the area under the plasma concentration time curve (AUC) by 4% relative to fasted dosing of the 25 mg (Phase 2) tablet. Novartis claimed that these effects are not clinically important. There are no direct *administration* directions in the draft PI (the *Pharmacokinetics* section states that "*there was no clinically relevant change … on administration with a high-fat meal*").

[4] *Guideline on the Investigation of Bioequivalence* [CHMP/EWP/QWP/1401/98 Rev. 1/Corr]. <http://www.tga.gov.au/pdf/euguide/ewp140198rev1.pdf>

Advisory committee considerations

The submission was considered at the 149th (2013/1) meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The recommendation was (No. 2298):

- The PSC endorsed all the questions raised by the TGA in relation to the pharmaceutic and biopharmaceutic aspects of the submission by Novartis Pharmaceuticals Australia Pty Ltd to register Jakavi tablets containing 5 mg, 15 mg and 20 mg of ruxolitinib (as phosphate). In particular, the PSC supported the justification for not providing absolute bioavailability studies that is based specifically on the sponsor's reliance on the BCS class 1 classification for this product. The sponsor should however provide an explanation of the observed dissolution performance to the satisfaction of the TGA.
- The PSC advised that all outstanding issues should be addressed to the satisfaction of the TGA.
- There was no requirement for this submission to be reviewed again by the PSC before it is presented for consideration by the Advisory Committee on Prescription Medicines (ACPM).

The tablet dissolution comparisons between clinical trial and proposed formulations and between strengths are consistent with equivalence. Most of the drug from the different tablets dissolves very rapidly. Novartis has not yet commented on the strangely slow *final* dissolution (of the last 20% of drug *in vitro*) but more extensive data now provided suggest that it is an artefact from the *in vitro* apparatus.

Quality summary and conclusions

Registration was recommended with respect to chemistry, quality control and bioavailability aspects.

III. Nonclinical findings

Introduction

The maximum proposed dose is 25 mg orally twice daily. The sponsor has recommended that treatment be continued as long as the benefit:risk remains positive.

Ruxolitinib is a new class of antineoplastic agents/protein kinase inhibtors targeting the non-receptor kinases, JAK1 and JAK2, being developed for the treatment of multiple disorders including psoriasis and rheumatoid arthritis, and as a consequence, the submitted Module 4 data were in excess of that normally expected for a nonclinical dossier to support registration of an anticancer pharmaceutical (ICH S9)[5]. All pivotal safety studies were conducted under Good Laboratory Practice (GLP) conditions, using the proposed clinical route (PO) and the intended salt (phosphate). No major nonclinical deficiencies were identified.

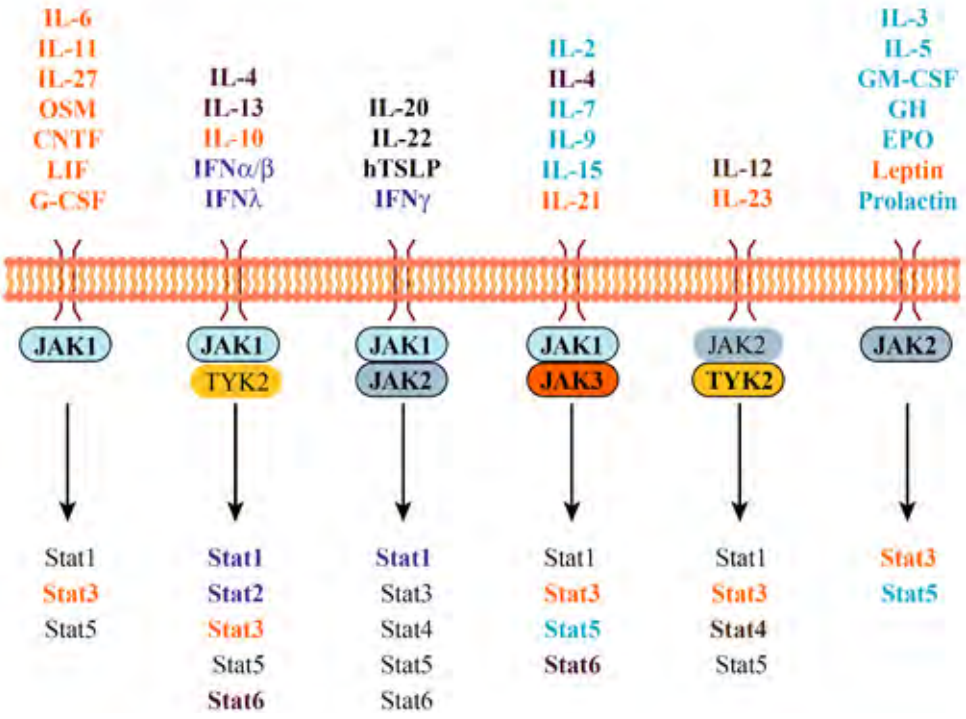
[5] <http://www.tga.gov.au/pdf/euguide/swp64610708enfin.pdf>

Pharmacology

Rationale and mechanism of action

The JAK/STAT pathway is the major signalling cascade downstream from cytokine, chemokine and growth factor receptors. There are 4 members in the non-receptor tyrosine kinase JAK family: JAK1, JAK2, JAK3 and TYK2 (Figure 2).

Figure 2. JAK/STAT signalling showing the cytokine/growth factor usage of different JAKS (from Kiu & Nicholson, 2012*)



*Kiu, H. And S.E. Nicholson. (2012) Biology and significance of the JAK/STAT signalling pathways. *Growth Factors* 30: 88–106.

Aberrant JAK/STAT signalling has been identified in patients with myeloproliferative neoplasms (MPNs). Activating mutations in JAK2 (for example JAK2-V617F, as well as others) have been shown to be present in almost all patients with polycythemia vera (PV), as well as high percentages in patients with essential thrombocythemia and idiopathic myelofibrosis (reviewed in Ghoreschi *et al.*, 2009[6] and Verstovsek, 2009[7]). These mutations confer hypersensitivity to or independence from haematopoietic cytokines, resulting in abnormal proliferation and survival of affected stem cells, thus contributing to MPN disease pathogenesis. Dysregulation may also be associated with the high levels of circulating cytokines in patients with myeloproliferative disorders or hyperactivity of JAK1 (cited in Quintás-Cardama *et al.*, 2010[8]). Ruxolitinib, as a JAK1 and JAK2 inhibitor, is anticipated to alleviate the symptoms of MPNs including splenomegaly and constitutional symptoms (that is, weight loss and fatigue) that presumably result from high levels of circulating cytokines that signal through JAK enzymes.

[6]Ghoreschi, K., A. Laurence and J.J. O'Shea. (2009) Janus kinases in immune cell signalling. *Immunol. Rev.* 228: 273–287.
[7]Verstovsek, S. (2009) Therapeutic potential of JAK2 inhibitors. *Hematology A. Soc. Hematol. Educ. Program* 636–642.
[8]Quintás-Cardama, A., K. Vaddi, P. Liu, T. Manshouri, J. Li *et al.* (2010) Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: therapeutic implications for the treatment of myeloproliferative neoplasms. *Blood* 115: 3109–3117.

Primary pharmacology

In vitro, ruxolitinib inhibited the phosphorylation of JAK2 and JAK1 (50% inhibitory concentration (IC_{50}) 2.8–3.3 nM) with equal potency but had less activity at TYK2 (IC_{50} 19 nM) and JAK3 (IC_{50} 428 nM). The IC_{50} values for JAK1, JAK2 and TYK2 kinase activity were similar to the estimated clinical steady state free plasma levels ($C_{ss, free}$ 11.7 nM[9]). At nanomolar concentrations, ruxolitinib inhibited the formation of phosphorylated STAT3 (pSTAT3; a downstream target of JAK1 and JAK2) in human blood cells exposed to various cytokines. Phosphorylated STAT3 formation was inhibited in G-CSF-exposed neutrophils, IL-6-exposed PBMCs and IL-6-exposed whole blood (all indicators of signalling through JAK1) and in GM-CSF or TPO-exposed PBMCs and TPO-exposed whole blood (indicators of signalling through JAK2). Ruxolitinib inhibited IL-23-induced IL-22 secretion from T cells, which is largely mediated through JAK2 signalling. The IC_{50} values with isolated cells were 28–68 nM (2–5.8 times higher than the $C_{ss, free}$) while IC_{50} values with whole blood cells were higher (~280 nM; 0.8 times the C_{ss}) which can be attributed to protein binding.

The main circulating human metabolites, 3-keto cyclopentyl (M9 and M11), 3-hydroxy cyclopentyl (M8, M16, M27 and M7) and 2-hydroxy cyclopentyl (M18 and M14) had inhibitory activity in JAK1, JAK2 and JAK3 kinase assays and in functional assays assessing JAK signalling effects (IL-6-induced INA-6 proliferation assays and IL-6-induced inhibition of pSTAT3 levels in IL-6-induced whole blood cells). However, the inhibitory activity was 2 to 5 times lower than the parent drug (whole blood assay). Based on potency in whole blood assays and relative percent AUC, the relative contribution to potency in human subjects of the combined metabolites (M7, M8, M9, M11, M14, M16, M18 and M27) was estimated to be 18%.

The activating mutation, JAK2-V617F has been found in a large percentage of polycythemia vera patients. Cells expressing this variant of the human kinase have constitutive phosphorylation of JAK2 and downstream targets (for example, STAT5 and ERK). At ≥51 nM ruxolitinib to cells expressing this variant, there was a dose-dependent reduction in the phosphorylated forms of JAK2, STAT5 and ERK1/2, with a maximal effect at approximately 300 nM (approximately equivalent to the C_{ss}). A dose-dependent reduction in viability was observed in cell lines endogenously expressing or engineered to express JAK2-V617F (IC_{50} 126–186 nM) with a approximately 7 fold increase in apoptosis at 400 nM. Ruxolitinib inhibited the proliferation of *ex vivo* expanded erythroid progenitors obtained from patients with JAK2-V617F positive PV (IC_{50} 223 nM; approximately 0.6 times the clinical C_{ss}). However, only marginally less inhibitory activity was observed on erythroid progenitors from healthy human subjects (IC_{50} 407 nM; 1.1 times the clinical C_{ss}), suggesting there will not be any discrimination between wild-type and mutant JAK2 in terms of inhibitory activity during clinical use as proposed.

Ruxolitinib had marginally higher inhibitory activity against IL-6-induced pSTAT3 production in assays with whole blood from rats and dogs (IC_{50} 95 and 119 nM, respectively)compared to whole blood from human subjects (IC_{50} 282 nM), whereas lower potency was seen in assays with whole blood from rabbits (IC_{50} 600 nM). This indicates ruxolitinib was pharmacologically-active in animals used in pivotal repeat-dose toxicity studies (rats and dogs) and reproductive toxicity studies (rats and rabbits).

Maximal inhibition of TPO or IL-6-induced STAT3 phosphorylation in peripheral blood samples was detectable 1 to 2 h post-dose (the earliest time point sampled) in mice, rats, rabbits, dogs and human subjects, coincident with C_{max} in all species. There was generally a dose-related extent and duration of inhibition in rabbits, dogs and human subjects (not assessed in other animal species). Greater than 30% inhibition was maintained for 4 to 8 h in mice after a 90 mg/kg oral (PO) dose, for 4 h in male rats following an oral dose of 18 mg/kg, for 6 h in female rabbits after ≥10 mg/kg PO doses and for 24 h in dogs after ≥10

[9]Based on clinical steady state plasma levels of 355 nM and an unbound fraction of 3.3%.

mg/kg PO doses. The inhibitory activity in dogs at 24 h post-dose was evident in the absence of detectable plasma levels of ruxolitinib, suggesting the inhibitory activity may be associated with pharmacologically active metabolites. *In vitro* studies with crude mixtures confirmed the inhibitory activity of rat metabolites, including metabolites generated by the male specific rat cytochrome P450 isozyme CYP2C11 isozyme, against JAK1, JAK2 and JAK3 kinase activity and IL-6-induced INA-6 cell proliferation and whole blood pSTAT3 levels. In human subjects, at least 30% inhibition was still evident 12 h post-dose in subjects that received 25–50 mg PO doses. It would be expected that pSTAT3 inhibition would be maintained for almost 24 h in human subjects with the proposed twice daily dosing.

In mice, at later time points (8–24 h), a negative percent inhibition was observed, which may reflect a rebound effect. A suggestion of a rebound effect was seen in rats but sampling past 8 h was not conducted and thus this cannot be confirmed. A rebound effect was not seen in rabbits dosed with ≥10 mg/kg PO ruxolitinib or dogs with ≥3 mg/kg PO ruxolitinib.

As inhibition was maintained for 24 h in dogs that received ≥10 mg/kg PO and some (or marginal) inhibition was still detectable at 24 h post-dose in female rabbits that received ≥10 mg/kg PO (16–19% inhibition), these species were considered suitable (based on pharmacodynamic parameters) for toxicity studies using once daily oral dosing of ruxolitinib.

The *in vivo* efficacy of ruxolitinib was assessed in a number of mouse xenograft or allograft models of cytokine-sensitive tumours. Mice engrafted with JAK2-V617F positive cells were used as an acute disease model. These mice develop progressive splenomegaly and have increased cytokine levels (13 times IL-6 and 2.4 times TNF-α), similar to that seen in patients with myeloproliferative disorders. These mice die within 2 to 3 weeks of engraftment because of penetrant haematopoietic disease progression. Treatment of 90 mg/kg PO bid ruxolitinib to these mice, beginning 1 day after engraftment and lasting for 3 weeks, prevented spleen enlargement, with fewer neoplastic features evident during histopathological analyses, and had approximately 2 times lower levels of IL-6 and TNF-α than vehicle treated animals. IL-6 levels were still elevated compared to naïve animals but splenic weights and pSTAT3 levels in the spleen were similar to those of naïve animals. Ruxolitinib also prolonged survival with >90% survival by Day 22 compared to <10% survival in vehicle-treated animals. The dose of 90 mg/kg PO twice a day (bd) is approximately 8 times the proposed clinical dose based on AUC (4 week repeat-dose study in CByB6F1 mice; Study T08-05-07) and resulted in >50% inhibition of wild-type JAK2 signalling for approximately 16 h/day.

The model chosen represents an acute disease model but is not an ideal model for the proposed indication. A better MPN model would have been JAK2V617F transgenic mice. These mice can have increased white blood cells, red blood cells, haemoglobin, haematocrit and/or platelets with bone marrow megakaryotic hyperplasia and spleens with megakaryocytic infiltrates. Varying degrees of fibrosis can be seen in the bone marrow and spleen of mice over the age of 30 weeks.[10] This model has been the chosen model to assess the efficacy of other JAK2 inhibitors.[11,12,13] While ruxolitinib has not been

[10]Xing, S., T.H. Wanting, W. Zhao, J. Ma *et al.* (2008) Transgenic expression of JAK2^{V617F} causes myeloproliferative disorders in mice. *Blood* 111**:** 5109–5117.
[11]Nakaya, Y., K. Shide, T. Niwa, J. Homan *et al.* (2011) Efficacy of NS-018, a potent and selective JAK2/Src inhibitor, in primary cells and mouse models of myeloproliferative neoplasms. *Blood Cancer J.* 1 e29; doi:10.1038/bcj.2011.29.
[12]Shide, K., T. Kameda, V. Markovstov, H.K. Shimoda *et al.* (2011) R723, a selective JAK2 inhibitor, effectively treats JAK2V617F-induced murine myeloproliferative neoplasm. *Blood* 117: 6866–6875).
[13]Kirabo, A., S.O. Park, H.L. Wamsley *et al.* (2012) The small molecule inhibitor G6 significantly reduces bone marrow fibrosis and the mutant burden in a mouse model of Jak2-mediated myelofibrosis. *Am. J. Pathol.* 181: 858–865.

assessed in an adequate MPN model, the reduction in splenic weights and cytokine levels, and the prolongation of survival in an acute disease model lends some support to the proposed indication.

An oral dose of 30 mg/kg bd (90 mg/m^2 bd; 5 times the proposed clinical dose) resulted in significant (80%) tumour growth inhibition in mice bearing a human plasmacytoma xenograft. Some efficacy was also seen in other cytokine-sensitive tumour models.

Secondary pharmacodynamics

Ruxolitinib had no significant inhibitory activity at 29 unrelated human kinases (at 200 nM; 17 times the clinical $C_{ss, free}$) and there was no clinically-relevant inhibitory activity at 50 receptors. Therefore, no off-target activities are predicted.

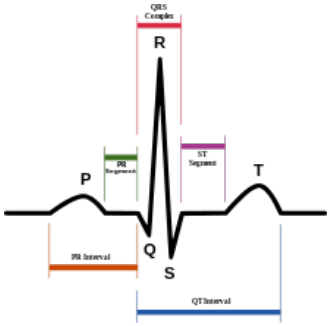
Safety pharmacology

Specialised safety pharmacology studies assessed effects on the cardiovascular, respiratory and central nervous systems. All studies were GLP compliant. A concentration-dependent inhibition of hERG K^+ tail current was seen *in vitro* (IC_{50} 131.6 µM; approximately 11 000 times the clinical $C_{ss, free}$) but no adverse effects were seen on QTc intervals[14] in electrocardiograms from dogs receiving oral doses ≤30 mg/kg (estimated C_{max} 18.5 µM [based on the 10 day repeat-dose toxicity study, Study T06-09-07]; 52 times the clinical C_{ss}). Increased heart rate (up to 117%) was seen after an oral dose of 30 mg/kg.

Respiratory changes in rats that received single oral doses of ≥50 mg/kg ruxolitinib (exposure ratio based on C_{max} [ER_{Cmax}] 2 and 8 in males and females, respectively) consisted of significantly lower respiratory frequency, increased tidal volume and, in females only, slightly lower minute volume. Abnormal breathing was also seen in repeat-dose toxicity studies in mice at ≥300 mg/kg/day PO (ER_{Cmax} 62). The decrease in minute volume was only considered adverse in females that received 150 mg/kg PO ruxolitinib (ER_{Cmax} 38). The other respiratory changes were not considered adverse.

In tissue distribution studies in rats, there was minimal penetration of the blood-brain barrier (approximately 8%). Reduced activity and darkening of the skin and mucous membranes was seen in male rats at oral doses ≥50 mg/kg (ER_{Cmax} approximately 2) and in female rats at 150 mg/kg (ER_{Cmax} 38). Lethargy was also seen in toxicity studies in mice and rats, but only at high oral doses (≥300 mg/kg/day in mice [ER_{Cmax} 62] and ≥100 mg/kg [ER_{Cmax} at least 10]). Lower body temperature was also seen in females at 150 mg/kg PO.

[14]QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated. A graphic tracing of the variations in electrical potential caused by the excitation of the heart muscle and detected at the body surface is shown below. The normal electrocardiogram is a scalar representation that shows deflections resulting from cardiac activity as changes in the magnitude of voltage and polarity over time and comprises the P wave, QRS complex, and T and U waves.



Based on large or reasonable safety margins, adverse cardiovascular, respiratory and central nervous system (CNS) effects are not predicted during clinical use.

Pharmacokinetics

Ruxolitinib was rapidly absorbed by the oral route in all species (mice, rats, rabbits, dogs, Cynomolgus monkeys and humans) with time to peak plasma concentration (T_{max}) generally ranging from 0.5 to 2 h. *In vitro* studies indicated ruxolitinib was a high permeability drug suggesting a potential for high oral absorption. The oral bioavailability was high in female rats (105%), moderate in male dogs (57%) and low in male rats and male monkeys (22–29%). The low oral bioavailability in male rats may be due to extensive first pass metabolism with ruxolitinib comprising only 7% of drug-related material in plasma at 1 h post-dose. It is unknown if this is also the case for Cynomolgus monkeys. No specific absolute bioavailability studies have been conducted in human subjects but oral absorption was estimated to be ≥95% based on a mass-balance study. Exposure to ruxolitinib (AUC) was generally dose proportional in mice, rats, dogs and human subjects, and greater than dose proportional in female rabbits. Following single dosing, exposure to male rats was consistently lower than in their female counterparts (2 times and 4–21 times lower following IV and oral dosing, respectively). This is likely due to greater metabolism in males (see below). There were no sex differences in exposure in mice, dogs or human subjects. The elimination half-life ($t_{½}$) of ruxolitinib was similar in mice, rats and monkeys ($t_{½}$ 0.8–1.5 h [PO dosing] and 0.41–0.88 h [IV dosing]) and longer in dogs and human subjects ($t_{½}$ 2.2–4 h [PO dosing] and 2.5 h in dogs [IV]). Plasma clearance was high in rats (5–9 L/h/kg) and moderate in dogs, Cynomolgus monkeys and humans (0.4–0.9 L/h/kg). There was no or only modest (≤2 times) accumulation with repeat once daily dosing to mice, rats, rabbits and dogs.

Plasma protein binding was moderate in rats, rabbits, dogs and minipigs (11–33% unbound fraction) and high in mice, monkeys and humans (2–6% unbound fraction). Binding was independent of concentration. Binding in human plasma was suggested to be due primarily to human serum albumin with 3.8% free fraction at physiologically-relevant human serum albumin concentrations. There was no specific distribution or accumulation into blood cells. The volume of distribution was greater than total body water in rats, dogs and minipigs, and similar to total body water in Cynomolgus monkeys and humans. After oral administration of ^{14}C-ruxolitinib to rats, rapid and wide distribution of radioactivity was observed. Aside from organs involved in excretion or absorption (gastrointestinal (GI) tract, kidneys, liver and bladder), the highest level of radioactivity was seen in the aorta, adrenal gland, Harderian gland, thyroid and skin. Exposure was high in pigmented tissues (skin and uveal tract). There was limited penetration of the blood-brain barrier.

Ruxolitinib was extensively metabolised in mice, rats, rabbits, dogs and humans with at least 54 metabolites detected across species and matrices. Metabolism of ruxolitinib involved 2-hydroxylation or 3-hydroxylation of the cyclopentyl group, formation of a 3-ketocyclopentyl derivative, *O*-glucuronidation of the cyclopentyl propanenitrile group, hydroxylation of the cyclopentyl propanenitrile and pyrrolidine groups and hydroxylation or dihydroxylation of the cyclopentyl propanenitrile group. These modifications resulted in various diastereomers across samples, with not all diastereomers found in human samples. While unchanged drug was the predominant circulating species at 1 h post-dose (that is, close to T_{max}) in mice, female rats, dogs and humans following oral dosing, it still only constituted 25–45% of the circulating drug-related material in animal species compared to 74% in humans. Only low levels of the parent drug (2–7% of drug-related material) were detected in the plasma of male rats and female rabbits 1–2 h post-dose. While most of the circulating human metabolites (M7, M8, M9, M11, M14, M16, M18, M27) were observed in the plasma of animals, a significant proportion of circulating drug-related material at 1–2 h post-dose consisted of animal-specific metabolites in rats

(approximately 20%), female rabbits (50–57%) and dogs (18–32%). Some of these represented diastereomers of the human metabolites and, although not specifically tested, are likely to be pharmacologically-active. The human metabolites listed above are all pharmacologically-active and together contribute approximately 18% to the *in vivo* potency of ruxolitinib. The most significant metabolites were the 2-hydroxy cyclopentyl derivative, M18 (approximately 15% of the AUC for drug-related material) and the 3-hydroxy cyclopentyl derivative, M27 (approximately 7% of the AUC for drug-related material). Of the species examined, the metabolite profile in dogs was the most similar to that in human subjects. More extensive metabolism was observed with liver microsomes from male rats compared to female rats and the male rat-specific enzymes, CYP2C11 and CYP3A2 were shown to have significant activity on ruxolitinib. This sex-specific difference in metabolism in rats probably accounts for the marked differences in ruxolitinib exposure in male and female rats. *In vitro* studies with human recombinant isozymes, indicated a major role for CYP3A4 and to a lesser extent, CYP2C9, in the metabolism of ruxolitinib.

Excretion of radioactivity following oral dosing with ^{14}C-ruxolitinib was primarily *via* the urine in mice (36% of total 49% excreted radioactivity) and humans (74%), and *via* both the urine and faeces in rats and dogs. Excreted material from mice, rats and humans consisted predominantly of metabolites, while the parent drug comprised 20–25% of the radioactivity in the faeces of dogs. The extensive role of metabolism in the clearance of ruxolitinib suggests a difference in exposure may be seen in individuals with hepatic impairment. Biliary excretion was demonstrated in rats but this consisted largely of metabolites not found in human samples. This probably accounts for the difference in excretionary profiles between rats and human subjects.

Based on pharmacokinetic parameters, mice, female rats and dogs are considered the most appropriate animal models for toxicity. Due to the extensive metabolism of ruxolitinib to pharmacologically-active metabolites as well as species-specific metabolites, the male rat and female rabbit are considered less suitable animal models.

Pharmacokinetic drug interactions

Given the extensive role of CYP3A4 in the metabolism of ruxolitinib, co-administration of an inhibitor or inducer of this isozyme may alter the exposure to ruxolitinib. The effect of this on the pharmacological activity will be somewhat dampened due to the pharmacological activity of ruxolitinib metabolites. Ruxolitinib had no significant inhibitory activity on CYP1A2, 2B6, 2C8, 2C9, 2C19 or 2D6 at concentrations up to 25 μM (approximately 2000 times the clinical $C_{ss, free}$). While there was weak inhibitory activity on CYP3A4 (IC_{50} 8.8 μM; approximately 750 times the clinical $C_{ss, free}$) this is not likely to be clinically-relevant. Ruxolitinib was not a metabolism-dependent inhibitor of CYP3A4. Ruxolitinib did not induce CYP1A2 or 2B6 activity in human hepatocytes *in vitro* (≤10 μM; 850 times the clinical $C_{ss, free}$) but was shown to have the potential to induce CYP3A in both a human PXR- and rat PXR-dependent transactivation assay. As there was only a 2 fold increase (the minimum for a positive response) in gene expression in the human PXR assay at the lowest tested concentration (3 μM; approximately 250 times the clinical $C_{ss, free}$), this induction is unlikely to be clinically-relevant. Therefore, ruxolitinib is not anticipated to alter the exposure of co-administered drugs by interactions with CYP450 isozymes.

Ruxolitinib had weak or no inhibitory activity on the BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2 transporters. The IC_{50} values were >6.5 μM, more than 550 times the clinical $C_{ss, free}$, indicating this activity is not likely to be clinically-relevant. Ruxolitinib was not a substrate of P-glycoprotein but was shown to be an inhibitor of this transporter. The IC_{50} value was 21 μM, and although this value far exceeds the clinical $C_{ss, free}$ (11.7 nM) it is less than the estimated intestinal concentrations of ruxolitinib (25 mg in 250 mL; 326 μM), suggesting ruxolitinib has the potential to increase the exposure of orally-administered drugs that are substrates of this transporter. The M18 metabolite of

ruxolitinib had no significant inhibitory activity on P-glycoprotein, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2 transport at ≤3 μM (21 times the clinical C_{max} of 143 nM).

In summary, co-administered drugs that are inducers/inhibitors of CYP3A4 have the potential to alter ruxolitinib exposure and ruxolitinib has the potential to alter the exposure of co-administered drugs that are substrates of P-glycoprotein.

Toxicology

Acute toxicity

Single dose toxicity studies were conducted in rats and dogs following PO administration. However, the conduct of the studies was not in accordance with the TGA adopted EU note for guidance on single-dose toxicity (3BS1a[15]). The studies were not GLP compliant and while more than one species was used, only one route of administration was tested (the clinical route, PO), the observation period was too short (1–5 days compared 14 days as indicated in the guideline) and necropsies were not performed. Therefore, only limited information can be gained from these studies; any evidence of delayed toxicity would not have been seen with these studies and target organs for toxicity could not be identified. The maximum non lethal oral dose was 300 mg/kg in male rats, 100 mg/kg in female rats and the maximum tested dose in dogs, 40 mg/kg. The exposures ($AUC_{0\text{-}24h}$) at these doses were approximately 5, 7 and 9 times the clinical $AUC_{0\text{-}24h}$, respectively, indicating a moderate order of toxicity when taken orally.

Repeat-dose toxicity

Repeat-dose toxicity studies of up to 28 days duration were performed in mice, 6 months in rats, 5 days in rabbits and 52 weeks in dogs. The studies in mice and rabbits were primarily conducted as pilot studies to aid in the design and dose selection of carcinogenicity and reproductive toxicity studies, respectively. The duration of the pivotal studies, group sizes and the use of both sexes were consistent with ICH guidelines (both ICH S9[16] and ICH M3(R2)[17]). The choice of species in the pivotal studies (rat as the rodent and dogs as the non-rodent species) is acceptable based on pharmacodynamic/pharmacokinetic considerations. The clinical route (PO) was used in all studies and this was considered to be acceptable. Only once daily dosing was used in the nonclinical studies as compared to the proposed clinical dosage regimen of twice daily. This is not considered a major concern for the dog studies as pharmacological studies indicated sustained activity (suppression of pSTAT3 levels) over a 24 h period with once daily dosing of ≥10 mg/kg PO to dogs, even though plasma levels of ruxolitinib are below the limit of quantification (BLQ) by 24 h post-dose. In contrast, sustained pharmacological activity is unlikely to have been achieved in rats with once daily dosing in the pivotal (6 month) study. However, exposure over a 24 h period was achieved in female rats treated with higher doses for 13 weeks. No significant difference in the toxicity profile was observed between the two studies.

Animal to human exposure comparisons were performed based on parent drug total plasma exposure (average of sexes in all species but rats) (Table 2). This would not represent comparisons of exposure based on total pharmacologically-active material as it does not take into account the presence of active metabolites. As such, the ratios are expected to be conservative as the AUC for the parent drug represents as a maximum

[15] <http://www.tga.gov.au/pdf/euguide/vol3bs1aen.pdf>
[16] <http://www.tga.gov.au/pdf/euguide/swp64610708enfin.pdf>
[17] <http://www.tga.gov.au/pdf/euguide/ich028695enfinal.pdf>

47–51% of the AUC for pharmacologically-active material in mice, female rats and dogs compared to 62% in humans, and the free fraction of parent drug is greater in plasma from rats and dogs compared to the free fraction in human plasma. The exposure ratios for male rats based on parent drug are extremely low (≤0.2). However, the AUC for the parent drug represents a maximum of only 8% of the total pharmacologically-active material in male rat plasma with the active metabolites, M8, M9 and M11 together being the main components (66%). As the majority of the toxicity findings can be attributed to pharmacological action (see below), little weight can be placed on the exposure ratios (based on ruxolitinib) for male rats.

Ruxolitinib exposures in mice, female rats and dogs were generally acceptable, reaching at least 13 times the clinical AUC, although exposures in pivotal studies were generally low (≤9 in mice, ≤3 in female rats and ≤2 in dogs). The maximum tolerated dose (MTD) was clearly used in the 28 day mouse study (based on a 5 day dose-ranging study) and the 13 week female rat study. Dosing was acceptable in male rats in the 6 month study (based on suppression of body weight gain) and dogs in the 6 month and 52 week studies (based on the incidence of demodicosis). Adequate exposures to the human metabolites were achieved in the pivotal studies (Table 3).

Table 2. Relative exposure in repeat-dose toxicity and carcinogenicity studies. Table continued across 2 pages.

Species	Study duration	Dose mg/kg/ day	$AUC_{0\text{-}24h}$ µM·h	C_{max} µM	Exposure ratio based on	
					AUC	C_{max}
Mouse (CByB6F1)	28 days [T08-05-07][a]	50	11.5	5.0	1.4	14
		100	39	10.5	5	29
		175	74	17	9	47
		250	138	23	16	64
	6 months [carcinogenicity] [T09-02-03]	15	4.85	3.66	0.6	10
		45	21	11	2	31
		125	73	19	9	53
Rat (SD) (♂/♀ data)	4 weeks [T06-08-03]	15	0.289/1.56	0.122/1.14	0.03/0.18	0.3/3
		50	1.08/11.1	1.17/3.51	0.13/1.3	3/10
		100	1.87/16.5	0.586/10.5	0.2/2	2/29
	13 weeks [T08-06-02][b]	75	32.3	8.17	4	23
		150	91.1	25.9	11	72
		250	170	21.5	20	60

Species	Study duration	Dose mg/kg/ day	AUC_{0-24h} µM·h	C_{max} µM	Exposure ratio based on	
					AUC	C_{max}
	6 months [T07-10-06]	5	0.053/0.361	0.049/0.209	0.006/0.04	0.14/0.6
		15	0.296/2.33	0.165/1.72	0.03/0.3	0.5/5
		30	0.662/7.40	0.445/4.98	0.08/0.9	1.2/14
		60	1.32/25.8	0.707/6.11	0.16/3	2/17
Dog (Beagle)	4 weeks [T06-11-03]	3	3.28	0.98	0.4	3
		10	20	4.67	2	13
		20	50	8.1	6	23
	6 months [T07-10-07]	0.5	1.12	0.61	0.13	2
		2.5	7.82	3.25	0.9	9
		5	14.7	5.3	1.7	15
		10	112	13	13	36
	T08-07-03 [52 weeks]	0.75	0.95	0.35	0.11	1
		1.5	2.5	0.74	0.3	2
		3	5.5	1.3	0.6	4
		6	17	4.4	2	12
Human	steady state	[25 mg bid]	8.5	0.36	–	–

[a]No adequate data for the 350 mg/kg/day group; [b]Female data only

Table 3. Relative exposure to the human metabolites in pivotal toxicity studies

Meta-bolite	Human $AUC_{0-24\ h}$ [a] µM.h	Mouse (6 month study) 125 mg/kg/day [b]		Female rat (6 month study) 60 mg/kg/day [b]		Dog (52 week study) 6 mg/kg/day [a]	
		AUC_{0-24h} µM.h	ER_{AUC}	AUC_{0-24h} µM.h	ER_{AUC}	$AUC_{0-24\ h}$ µM.h	ER_{AUC}
Parent	8.5	64	8	30	4	17	2
M7	0.43	29	67	3.3	8	1.2	3
M8	0.65	3.1	5	11	17	0.68	1.0
M9	0.13	11	85	2.2	17	0.95	7
M11	0.71	5.6	8	5.3	7	0.97	1.4
M14	0.17	3.8	22	0.85	5	0.48	3
M16	0.19	0.81	4	0.88	5	0.034	0.2
M18	2.0	11	6	6.8	3	12	6
M27	0.94	1.9	2	2.0	2	1.7	2

[a]Estimated data; [b]Actual data

Major toxicities

No marked differences were noted in the toxicity profiles across the species and the major findings are all associated with or secondary to the pharmacological activity of ruxolitinib (or its metabolites), including reduced red and white blood cells with effects on lymphoid tissues and bone marrow (associated with haematopoiesis). Opportunistic infections, as a result of prolonged immunosuppression, were seen in treated dogs.

Decreased red blood cell parameters (and on occasion reticulocytes), decreased white blood cells (predominantly lymphocytes and other cells of lymphoid origin but also on occasions eosinophils, monocytes or basophils) with associated lymphoid depletion in the spleen (particularly in the white pulp but also on occasion, the red pulp), lymph nodes, thymus (both cortical and medullary depletion) and sometimes gut-associated lymphoid tissue and bone marrow hypocellularity (generally erythroid but also on occasion myeloid hypoplasia) were observed in all species; mice ≥50 mg/kg/day PO (relative exposure based on AUC [ER_{AUC}] 1.4), rats ≥15 mg/kg/day in males and ≥30 mg/kg/day in females (ER_{AUC} 0.9) and dogs ≥3 mg/kg/day (ER_{AUC} 0.6). A No Observable Effect Level (NOEL) was not established in mice, while the NOEL in rats and dogs achieved subclinical exposures. These findings are consistent with the anticipated pharmacological activity of ruxolitinib (JAK inhibition)[18,19] and were reversible after cessation of treatment. The findings of anaemia are consistent with clinical findings but there was no evidence of thrombocytopaenia in animals.

[18]Rodig, S.J., M.A. Meraz, J.M. White *et al.* (1998) Disruption of the *Jak1* gene demonstrates obligatory and nonredundant roles of the Jaks in cytokine-induced biologic responses. *Cell* 93: 373–383.
[19]Neubauer, H., A. Cumano, M. Müller *et al.* (1998) Jak2 deficiency defines an essential developmental checkpoint in definitive hematopoiesis. *Cell* 93: 397–409.

As a result of sustained immunosuppression in dogs (at ≥3 mg/kg/day PO for 52 weeks [ER_{AUC} 0.6] and ≥2.5 mg/kg/day PO for 6 months [ER_{AUC} 0.9]), there were clinical as well as microscopic changes that could be attributed to an opportunistic infestation with mites as well as other infections. Clinical signs included alopecia, black/broken/dry or red skin, interdigital furunculosis, papillomatosis and pododermatitis, and secondary bacterial skin infections. Microscopic signs included pyrogranulomatous inflammation of the skin/subcutis and/or footpad associated with intrafollicular mites, and hyperkeratosis in the skin. Enlargement and inflammation of the mandibular lymph node also occurred which may be secondary to the skin inflammation as evidenced by migration of mites to the lymph node in the 6 month study. These findings indicate a risk for opportunistic infections in individuals with prolonged treatment.

Other than effects associated with pharmacological activity, there were no other significant toxicity findings in dogs. Additional findings in mice included minimal to moderate inflammation of the nasal cavity at ≥175 mg/kg/day PO for 28 days (ER_{AUC} 9) or ≥45 mg/kg/day PO for 6 months (ER_{AUC} 2), minimal to mild renal tubular dilation/ectasia at 350 mg/kg/day PO (ER_{AUC} >16) and at this same dose, hyperplasia in the non-glandular stomach. The findings in the stomach and the kidneys occurred at sufficiently high exposures not to be of particular concern for the proposed clinical use. The nasal cavity findings are peculiar. No such findings were seen in rats at similar or greater exposures or in a different mouse strain at a similar dose (CD-1; 180 mg/kg/day PO for 28 days), although exposures were lower in this strain and no nasal cavity findings were seen in dogs with long-term treatment. Therefore, the clinical relevance of the nasal inflammation is uncertain. Additional findings in rats included adrenocortical atrophy in males at 60 mg/kg/day, increased serum levels of alanine aminotransferase (ALP) and Gammaglutamyltransferase (GGT) in both sexes at ≥15 mg/kg/day PO (ER_{AUC} 0.3) and minimal fibrosis in the heart of females treated with 250 mg/kg/day PO for 13 weeks (ER_{AUC} 20). As male rats have a vastly different pharmacokinetic profile to human subjects (and other animal species), the adrenal findings observed in male rats only are not considered clinically-relevant. The increases in ALP and GGT were generally minor (<2 fold in the pivotal rat study [ER_{AUC} 3]) and were not associated with any histopathological hepatic changes. Cardiac fibrosis only occurred at sufficiently high exposures in one species and is not of particular concern.

Genotoxicity

The potential genotoxicity of ruxolitinib was investigated in the standard battery of tests, conducted under GLP conditions in accordance with ICH guidelines. All assays were appropriately validated. Appropriate bacterial strains were used in the Ames test and concentrations/doses were appropriate. Ruxolitinib was not mutagenic in the bacterial mutation assay or clastogenic *in vitro* (in human lymphocytes) or *in vivo* (in the rat micronucleus test).

Carcinogenicity

The carcinogenic potential of ruxolitinib by the oral route was assessed in transgenic Tg.rasH2 mice following daily dosing for 26 weeks. Given the intended patient group, carcinogenicity studies in a single species are considered acceptable. The sponsor indicated a 2 year rat carcinogenicity study is currently in progress. This should be submitted in the event of an extension of indication to a different patient group. The choice of transgenic model is considered acceptable. The group sizes used (25/sex) and duration of dosing (26 weeks) were appropriate for the species.[20,21] A concurrent positive

[20]Morton, D., C.L. Alden, A.J. Roth and T. Usui. (2002) The Tg rasH2 mouse in cancer hazard identification. *Toxicol. Pathol.* 30: 139–146.

control group (urethane-treated) was included and the expected pulmonary and splenic tumours were observed[22], confirming the validity of the study. There were no ruxolitinib-related neoplastic findings in any of the treated groups (≤125 mg/kg/day PO). The relative exposure at the highest tested dose was low (ER_{AUC} 9). There was no overt toxicity in this study and reduced body weight gain was only seen in female groups. Based on the findings in the 28 day study, in which the No Observable Adverse Effect level (NOAEL) was considered to be 250 mg/kg/day, higher doses may have been possible and would have provided greater confidence in the negative findings. Ruxolitinib is an immunosuppressive agent, and as such, an increased risk for the development of cancer (either lymphoproliferative disorders or as a result of latent viral infections) exists in patients on long term treatment. The Tg.rasH2 model is not a good predictor for tumourigenic potential of agents with immunosuppressive actions.[23]

Reproductive toxicity

A standard set of GLP compliant reproductive toxicity studies was submitted and examined fertility (in rats), embryofetal toxicity (rats and rabbits) and pre/postnatal development (rats). As with the repeat-dose toxicity studies, animal to human exposure comparisons were performed based on the AUC for ruxolitinib (Table 4). Exposure data for the definitive rat embryofetal development toxicity study were extrapolated from data obtained in the pilot study. Supportive toxicokinetic data did not accompany the rat fertility study and data were extrapolated from the 4 week repeat dose toxicity study (T06-08-03). Relative exposures were overall very low and were subclinical in male rats and female rabbits. As noted previously, parent drug constitutes a small portion of the pharmacologically active material in the plasma of both male rats and female rabbits. Thus little weight can be placed on the subclinical exposures in these animals.

Table 4. Relative exposure to ruxolitinib in reproductive toxicity studies

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µM·h)	Exposure ratio#
Rat (SD)	Fertility (♂/♀)	10	0.193/1.04	0.022/0.12
		30	0.578/3.12	0.068/0.37
		60	0.900/13.8	0.11/1.6
	Embryofetal development	15	0.750	0.09
		30	2.98	0.35
		60	19.0	2
	Pre/Postnatal [PND10 data]	5	0.137	0.016
		15	0.928	0.11

[21]MacDonald, J., J.E. French, R.J. Gerson *et al.* (2004) The utility of genetically modified mouse assays for identifying human carcinogens: a basic understanding and path forward. *Toxicol. Sci.* 77**:** 188–194.
[22]Ozaki, M., K. Ozaki, T. Watanabe, S. Uwagawa, Y. Okuno and T. Shirai. (2005) Susceptibilities of *p53* knockout and rasH2 transgenic mice to urethane-induced lung carcinogenesis are inherited from their original strains. *Toxicol. Pathol.* 33**:** 267–271.
[23]Cohen, S.M. (2001) Alternative models for carcinogenicity testing: weight of evidence evaluations across models. *Toxicol. Pathol.* 29(Suppl): 183–190.

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µM·h)	Exposure ratio#
		30	2.68	0.32
Rabbit (NZW)	Embryofetal development	30	0.068	0.008
		60	0.606	0.071
Human	steady state	[25 mg bid]	8.5	–

= animal:human plasma $AUC_{0-24\,h}$

Fertility was unaffected in rats when both males and females were treated with ≤60 mg/kg/day PO ruxolitinib. A number of treated female rats had prolonged dioestrus, but this did not affect mating or fertility. Female dogs that received ≥0.75 mg/kg/day PO ruxolitinib for 52 weeks (ER_{AUC} 0.11) appeared to be in different stages of oestrus compared to control females. Differences in oestrus stages were not seen in any other dog toxicity study (including the 6 month repeat dose toxicity study). As the effects on oestrus cycling were not consistently seen, a relationship with drug treatment is uncertain.

Ruxolitinib and/or its metabolites crossed the placenta in rats with fetal tissue exposures approximately 0.7 times those of maternal blood. There was no evidence of teratogenicity in either rats or rabbits. The increased incidence of post-implantation loss in rats (≥60 mg/kg/day; ER_{AUC} 2–3) and rabbits and late resorptions in rabbits (≥60 mg/kg/day; ER_{AUC} 0.07) are consistent with the embryolethality reported for a murine JAK2 mutant, which occurs as a result of impaired definitive erythropoiesis.[24] Reduced fetal weights were also observed at ≥60 mg/kg/day in rats and ≥50 mg/kg/day in rabbits. Exposures (AUC) at the NOEL were subclinical.

In a pre/postnatal study in rats, a slight increase in gestation length and a reduced litter size was observed at 30 mg/kg/day (ER_{AUC} 0.32). The reduced litter size may be a result of the embryofetal lethality observed in embryofetal development studies while the increase in gestation length (22.1 compared to 21.7 days) has an uncertain relationship with treatment. Apart from eye opening and pinna unfolding occurring earlier in pups following maternal treatment with ≥15 mg/kg/day PO ruxolitinib (which was not considered adverse), postnatal survival, pup reproductive function and other developmental parameters were unaffected by maternal treatment with ruxolitinib at ≤30 mg/kg/day. Ruxolitinib and its pharmacologically active metabolites were readily excreted into milk with exposures to drug-related material being 13 times those in maternal plasma. Unfortunately, immunocompetence was not assessed in breast-fed pups, which may have given an indication of pharmacological activity in these animals. Therefore, due to its potential adverse effects in breast-fed infants, ruxolitinib should not be used by women who are breastfeeding.

Pregnancy classification

The sponsor has not proposed a Pregnancy Category. Based on the embryofetal lethality observed in two different species, which is likely associated with the pharmacological activity of ruxolitinib, as well as the reduced fetal weights, Pregnancy Category C[25] is considered appropriate.

[24]Neubauer, H., A. Cumano, M. Müller *et al.* (1998) Jak2 deficiency defines an essential developmental checkpoint in definitive hematopoiesis. *Cell* 93: 397–409.

[25]**Australian Pregnancy Category C:** Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Immunotoxicity

No specialised immunotoxicity studies were submitted. Lymphopaenia with associated effects on lymphoid tissue were a feature in toxicity studies. Based on a single study in dogs, B cell populations were largely unaffected, while total T cell populations (helper T cells and cytotoxic T cells but comprehensive immunophenotyping was not conducted) were reduced in the circulation. Immunocompetence was not directly assessed but the reduced circulating T lymphocytes and evidence of opportunistic mite infestations in dogs following long term treatment with ruxolitinib suggest there is some impairment of the immune system. While levels of B cells were not affected, B cell function was not directly assessed. The data suggest that clinical use of ruxolitinib may be associated with an increased risk of infection.

Paediatric use

No specific studies in juvenile animals were submitted. Given the role of JAK kinases in the development of the immune system and other systems[26,27,28] there may be some concerns for adverse effects on developing systems in paediatric patients.

Nonclinical summary and conclusions

- The overall quality of the submitted dossier was high, with all pivotal toxicity studies using the proposed clinical route (PO) and conducted under GLP conditions. No major deficiencies were identified.
- Ruxolitinib belongs to a novel pharmacological class (JAK1/2 inhibitor). The JAK non-receptor kinases are the major downstream targets for cytokine, chemokine and growth factor receptors. *In vitro*, ruxolitinib inhibited JAK1 and JAK2 phosphorylation and downstream signalling with nanomolar potency. A reduction in splenic weights and serum cytokine levels with an increased life span was seen in an acute disease model in mice. The main circulating human metabolites were pharmacologically active but with lower potency than the parent.
- There was no clinically relevant inhibitory activity on 50 receptors or 29 unrelated human kinases. Therefore, no off-target activities are predicted.
- Safety pharmacology studies covered the CNS, cardiovascular and respiratory systems. A concentration-dependent inhibition of hERG K^+ tail current was seen *in vitro* at high concentrations (IC_{50} 132 µM) but no adverse effects were seen in electrocardiograms from dogs receiving oral doses ≤30 mg/kg. Some respiratory changes as well as hypoactivity were observed in rats that received single oral doses of ≥50 mg/kg ruxolitinib. Based on large or reasonable safety margins, adverse cardiovascular, respiratory and CNS effects are not predicted during clinical use.
- Ruxolitinib was rapidly and readily absorbed in animal species and human subjects. Plasma protein binding was moderate to high in animals and humans and tissue distribution of ruxolitinib and/or its metabolites was wide in rats. There was limited penetration of the blood-brain barrier. Ruxolitinib was extensively metabolised in all species. While unchanged drug was the predominant circulating species in mice, female rats, dogs and humans following oral dosing, it still only constituted 25–45% of

[26]Rodig, S.J., M.A. Meraz, J.M. White *et al.* (1998) Disruption of the *Jak1* gene demonstrates obligatory and nonredundant roles of the Jaks in cytokine-induced biologic responses. *Cell* 93: 373–383.
[27]Teglund, S., C. McKay, E. Schuetz, J.M. van Duersen *et al.* (1998) Stat5a and Statb proteins have essential and nonessential, or redundant, roles in cytokine responses. *Cell* 93: 841–850.
[28]Wagner, K.-U., A. Krempler, A.A. Triplett, Y. Qi *et al.* (2004) Impaired alveologenesis and maintenance of secretory mammary epithelial cells in Jak2 conditional knockout mice. *Molecul. Cell. Biol.* 24**:** 5510–5520.

the circulating drug-related material in animal species compared to 74% in humans. The metabolite profile in dogs was the most similar to that in human subjects. Drug-related material was excreted in both the urine and the faeces in animals, while predominantly urinary excretion was observed in human subjects.

- *In vitro* studies indicated a major role of CYP3A4 in the metabolism of ruxolitinib. Therefore, co-administration of an inhibitor or inducer of this isozyme may alter the exposure to ruxolitinib. The effect of this, however, will be somewhat dampened due to the pharmacological activity of ruxolitinib metabolites. Ruxolitinib has the potential to alter the exposure of co-administered drugs that are substrates of P-glycoprotein. No clinically relevant induction of CYP1A2, 2B6 or 3A4 or inhibition of cytochrome P450s (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4) or other transporters (BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2) was observed.
- Repeat-dose toxicity studies by the oral route were conducted in mice (up to 28 days), rats (up to 6 months) and dogs (up to 52 weeks). Dose levels were acceptable. Adequate exposures to the human metabolites were achieved in the pivotal studies. No marked differences were noted in the toxicity profiles across the species and the major findings are all associated with or secondary to the pharmacological activity of ruxolitinib (or its metabolites), including reduced red and white blood cells with effects on lymphoid tissues and bone marrow. Opportunistic infections, as a result of prolonged immunosuppression, were seen in treated dogs. These findings were reversible after cessation of treatment. Other findings either occurred at sufficiently high doses or in only one species that they are less likely to occur in patients at the proposed clinical dose.
- Ruxolitinib was not mutagenic in the bacterial mutation assay or clastogenic *in vitro* (in human lymphocytes) or *in vivo* (in the rat micronucleus test). There were no ruxolitinib related neoplastic findings in a 6 month carcinogenicity study in transgenic Tg.rasH2 mice; however, the relative exposure at the highest tested dose was low. Ruxolitinib is an immunosuppressive agent, and as such, an increased risk for the development of cancer (either lymphoproliferative disorders or as a result of latent viral infections) exists in patients on long term treatment.
- A standard set of GLP compliant reproductive toxicity studies was submitted and examined fertility (in rats), embryofetal toxicity (rats and rabbits) and pre/postnatal development (rats). Fertility was unaffected in rats when both males and females were treated with ≤60 mg/kg/day PO ruxolitinib. Ruxolitinib and/or its metabolites crossed the placenta in rats with evidence of embryolethality and fetotoxicity evident in both rats and rabbits. A slight increase in gestation length and a reduced litter size was observed in the pre/postnatal study in rats at 30 mg/kg/day but pup development was unaffected. Ruxolitinib and its pharmacologically-active metabolites were readily excreted into milk with exposures to drug-related material significantly higher than those in maternal plasma.

Conclusions and recommendation

- The reduction in splenomegaly and circulating cytokine levels in an acute animal disease model, lends some support to the proposed indication.
- *In vitro* pharmacokinetic drug interaction studies suggest inducers/inhibitors of CYP3A4 may alter the exposure to ruxolitinib. Ruxolitinib may alter the exposure of co-administered drugs that are substrates of P-glycoprotein.
- The only notable toxicities are predictable based on the pharmacology of ruxolitinib (that is, myelosuppression and immunosuppression). Prolonged immunosuppression

indicates a risk of infections and an increased risk for the development of malignancies.

- The evidence of embryolethality and fetotoxicity in two species which can be associated with ruxolitinib's pharmacology warrants a Pregnancy Category C. Ruxolitinib should not be used in pregnancy unless clearly justified.
- The excretion of ruxolitinib and/or its metabolites into milk indicates a risk for an adverse effect on immunocompetence in breast-fed infants.
- There are no objections on nonclinical grounds to the registration of ruxolitinib for the proposed indication. Amendments to the draft PI were recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The sponsor provided a clinical rationale for the use of ruxolitinib for the treatment of myelofibrosis (MF). Ruxolitinib is a small molecule (selective) inhibitor of JAK1 and JAK2. These two JAKs mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function. Dysregulation of the JAK-STAT (signal transducers and activators of transcription) pathway has been associated with MF and several other cancers, and increased proliferation and survival of malignant cells. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK-STAT pathway, gain-of function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signalling regardless of JAK2V617F mutation status.

Medicines currently used to treat the symptoms of MF include hydroxyurea (HU), danazol, erythropoiesis stimulating agents, androgens and prednisone. None of these are approved in Australia for the treatment of MF. Other drugs, including busulfan, melphalan, and 2-chlorodeoxyadenosine, have been used to treat patients refractory to HU, but have had minimal clinical effect.[29,30] Other therapeutic options include splenectomy, splenic irradiation or allogeneic stem cell transplant (alloSCT). Splenectomy and splenic irradiation are associated with various complications. AlloSCT is potentially curative, however, limiting factors include donor availability, high mortality and generally limited to patients under the age of 60 years. The low success rate of existing surgical and therapeutic interventions confirms an unmet medical need.

Comment: The sponsor's clinical rationale was considered to be acceptable. Myelofibrosis (MF) is a clinically heterogeneous myeloid malignancy with a median life expectancy of around 6 years and a median age at diagnosis of around 70 years.[31] Primary myelofibrosis (PMF) is one of the classical Philadelphia-negative chronic myeloproliferative neoplasms (MPNs).

[29]Petti MC, Latagliata R, Spadea T, et al. Melphalan treatment in subjects with myelofibrosis with myeloid metaplasia. Br J Haematol, 2002; 116(3):576–81.
[30]Tefferi A, Silverstein MN, Li CY. 2-Chlorodeoxyadenosine treatment after splenectomy in subjects who have myelofibrosis with myeloid metaplasia. Br J Haematol. 1997; 99(2):352–7
[31]Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood. 2009;113:2895-2901.

> Essential thrombocythemia (ET) and polycythaemia rubra vera (PV) are other MPNs and both of these diseases can transform into MF and are then termed post-PV MF and post-ET MF, respectively.[32,33] MF (primary or secondary) is characterised by clonal hematopoietic stem cell proliferation associated with a characteristic stromal pattern, a leuco-erythropblastic blood film and elevated levels of various inflammatory and pro-angiogenic cytokines.[6] The clinical features of MF are variable and include progressive anaemia, leucopenia or leucocytosis, thrombocytopenia or thrombocytosis and multi-organ extramedullary haematopoiesis, most commonly resulting in hepatomegaly and symptomatic splenomegaly. Patients with advanced disease experience severe constitutional symptoms due to massive splenomegaly (pain, early satiety, splenic infarction, portal hypertension and dyspnoea), progressive bone marrow failure, pulmonary hypertension, transformation to acute leukemia, and death.[34] The JAK2V617F mutation is present in around 45% to 68% of patients with PMF.[34]

There are no approved medicines in Australia for the treatment of MF. However, hydroxyurea is widely used in MF, including PMF and post-PV/ET MF, for controlling splenomegaly, leucocytosis, and thrombocytosis.[35] The sponsor provided a statement from an Australian haematologist (local expert) supporting the approval of ruxolitinib for the treatment of MF. The local expert states that hydroxyurea is the standard treatment for symptomatic splenomegaly and commented that splenomegaly may also respond to interferon-α but this agent is often poorly tolerated in patients with MF. The expert also noted that busulphan may be effective for the treatment of splenomegaly but increases the risk of secondary AML and prolonged cytopenia and is rarely used. Other treatment options for splenomegaly mentioned by the local expert include splenectomy and splenic radiation (very rarely used). The local expert commented that around a third of patients with PMF are anaemic at diagnosis (haemoglobin <100 g/L) and that most of the remaining patients will become anaemic during follow up. The local expert noted that treatments for MF associated anaemia include blood transfusion, corticosteroids, anabolic steroids (usually danazol) and erythropoiesis-stimulating agents. The expert commented that, in a minority of patients, anaemia will respond to hydroxyurea but more often cytoreduction will worsen anaemia. Other treatments that have been used for MF-associated anaemia by some haematologists include thalidomide and lenalidomide.[36]

The local expert stated that corticosteroids, antihistamines and analgesics are the mainstay of treatment for constitutional symptoms of sweats, anorexia, bone pain and pruritus. The expert noted that pruritus may also respond well to cytoreductive treatment with interferon or less often to hydroxyurea and that radiotherapy is the mainstay of treatment for localised extramedullary haematopoiesis and that hepatomegaly may respond to cytoreduction with hydroxyurea. The local expert noted that allogeneic haematopoietic stem cell transplantation is potentially curative in MF and is recommended for younger, fitter patients whose disease-related risk justifies the up-front risk of the transplant procedure. However, the expert commented that the vast majority of MF patients are not suitable for transplantation and treatment is focused on maximising quality of life, while minimising treatment-related toxicity.

[32]Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post essential thrombocythemia myelofibrosis: A consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia. 2008; 22:437-438.
[33] Hoffman R, Rondell D. Biology and treatment of primary myelofibrosis. Hematology Am Soc Hematol Educ Program. 2007;346-354.
[34]Reilly JT, McMullin MF, Beer PA, et al. Guideline for the diagnosis and management of myelofibrosis. Br J Haematol. 2012;158:453-471.
[35]Tefferi A. JAK inhibitors for myeloproliferative neoplasms; clarifying facts from myths. Blood. 2012;119:2721-2730.
[36]Tefferi A. How I treat myelofibrosis. Blood. 2011;113:3494-3504.

Scope of the clinical dossier

The submission contained the following clinical information:

- 11 clinical pharmacology studies, including 10 that provided pharmacokinetic data and 1 that provided pharmacodynamic data.
- 3 population pharmacokinetic analyses.
- 1 pivotal Phase III efficacy/safety study in patients with MF.
- 1 supportive Phase III efficacy and safety study in patients with MF
- 1 Phase I/II dose-finding study in patients with MF.
- 10 other Phase II studies and/or protocols exploring the efficacy and safety of ruxolitinib for other indications.
- Separate (sponsor) Summaries of Clinical Safety, Clinical Efficacy, and Clinical Pharmacology and an Integrated Summary of Safety,
- Literature references.

Paediatric data

The submission did not include paediatric data. This not considered a deficiency given that MF is unlikely to occur in children and adolescents.

Good clinical practice

The study protocols for Studies 351 and 352 including all amendments were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each centre. The studies were conducted according to the ethical principles of the Declaration of Helsinki and all patients provided informed consent.

Pharmacokinetics

Studies providing pharmacokinetic data

Individual studies; non-compartmental analysis (NCA)

Pharmacokinetic data for ruxolitinib based on NCA following oral administration are available from 11 studies. These studies include 198 healthy subjects administered ruxolitinib as single, repeat or multiple doses up to 10 days, 24 subjects with hepatic impairment, 32 subjects with renal impairment, 18 patients with RA, and 154 patients with MF (see Tables 5-8 below).

Table 5: Pharmacokinetics - healthy subjects and initial tolerability reports; N*= analysed for pharmacokinetics.

Study	Objectives	Doses	Duration	N*	Subjects
#131 Phase I	PK, PD, safety, tolerability, food effect,	R - 5, 10, 25, 50, 100, 200 mg R - capsules (5, 25 mg); tablets 25 mg	sd (up to 4)	23	Healthy

Study	Objectives	Doses	Duration	N*	Subjects
#132 Phase I	PK, PD, safety, tolerability	R- 15, 25, 50 mg bd; 50, 100 mg qd R – capsules (5, 25 mg) Placebo	md (10 days	71	Healthy
#134 Phase I	Mass-balance and metabolites	R – oral solution, 25 mg of 100µCI 14C-ruxolitinib	sd	6	Healthy
#138 Phase	QTc interval; PK	R – 25 mg (tablets); placebo; moxifloxacin 400 mg;	sd (x2)	48	Healthy
#139 Phase 1	Bioavailabilit y – relative) IR and SR tablets	R - IR, SR1, SR2 – 25 mg (tablets)	sd (x3)	9	Healthy

Table 6: Pharmacokinetics - hepatic and renal impairment.

Study	Objectives	Doses	Duration	N	Subjects
#137	Hepatic impairment – PK	R – 25 mg (tablet)	sd	32	Healthy HI
#142	Renal impairment - PK	R – 25 mg (tablet)	sd	40	Healthy RI

Table 7: Pharmacokinetics – interaction studies.

Study	Objectives	Doses	Duration	N	Subjects
#135	Interaction (PK and PD) – rifampin on ruxolitinib	R – 50 mg (2x25 mg tablets)	sd (x2)	12	Healthy
#133	Interaction (PK and PD) – ketoconazole, erythromycin on ruxolitinib	R – 10 mg (2x5 mg capsules); K – 200 mg bd; E – 500 mg bd;	sd (x 2)	31	Healthy
#136	Interaction (PK) –	R – 25 mg (tablet); M – 7.5	sd (x2)	18	RA

Study	Objectives	Doses	Duration	N	Subjects
	methotrexate on ruxolitinib and vice versa	to 30 mg			

Table 8: Pharmacokinetics – patients with myelofibrosis (MF).

Study	Objectives	Doses	Duration	N	Subjects
#251 Phase I/II	PKs, PDs, safety and tolerability, DLT, MTD	bd - 10, 15, 25, 50 mg; qd – 25, 50, 100, 200 mg	sd, md	154	MF

qd=once a day dosing

Population pharmacokinetic analyses

Table 9: Population pharmacokinetic reports included in the submission.

Identification	Description
INCB 18424-251 (Study #251),	Population pharmacokinetic analysis of the JAK inhibitor ruxolitinib tablets administered orally to subjects with PMF, PPV-MF or PET-MF from the Phase I/II dose escalation Study #251
INCYTE-DMB-11.04.1	Population pharmacokinetic analysis of the JAK Inhibitor ruxolitinib tablets administered orally to subjects with PMF, PPV-MF or PET-MF from Phase II/II dose escalation study #251 (Phase I/II) and the two Phase III efficacy and safety studies #351 and #352.
INCYTE-DMB-11.02.1	Analysis of ruxolitinib oral clearance and half-life in healthy subjects from Phase 1 clinical Studies #131, #132, #133, # 134, #135, #137, #138, #139, and #142.

Other studies

The clinical data also included a series of *in vitro* human biomaterial studies assessing ruxolitinib plasma protein binding, permeability in Caco-2 cell monolayers and interaction with drug transporters, metabolism, potential to inhibit CYP enzymes, and potential to induce CYP3A4 enzymes. Relevant data from these studies have been reviewed and included in the CER (Attachment 2).

Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics of ruxolitinib following oral administration have been adequately characterised in the submitted data. The submitted PK data are based on both non-compartmental analysis (primarily in healthy volunteers) and Population-PK analysis (primarily in patients with MF). In the non-compartmental studies, ruxolitinib was administered to 198 healthy subjects as single, repeat single or multiple doses up to 10 days duration, 40 subjects with varying degrees of renal impairment, 24 subjects with varying degrees of hepatic impairment, 18 subjects with rheumatoid arthritis and 154 subjects with MF. In the pivotal Population-PK analysis in patients with MF, data were analysed from 414 subjects from three clinical efficacy and safety studies. In general, the

pharmacokinetic profile of ruxolitinib was similar in healthy subjects and patients with MF.

The submission included no absolute bioavailability study. However, the sponsor provided a satisfactory justification for not providing such a study based on the drug being a BCS Category 1 compound (that is, high solubility, high permeability). The sponsor argues that ruxolitinib is a BSC Class 1 drug based on its aqueous solubility (over a pH range from 1.0 to 8.0), stability in simulated gastric and intestinal fluid, high *in-vitro* permeability in Caco-2 cells, almost complete *in-vivo* oral absorption and *in-vitro* dissolution profiles of drug product.

The submission proposes registration of three ruxolitinib tablet strengths 5, 15, and 20 mg in uncoated, immediate release dosage forms for oral administration. The submission included no comparative bioavailability study for the three proposed strengths. The sponsor provided an acceptable clinical justification for not submitting such a study primarily based on the same arguments used to justify the absence of an absolute bioavailability study. The sponsor also submitted comparative *in vitro* biopharmaceutical data showing the dissolution profiles of the three tablet strengths were similar.

The submission included no clinical studies comparing the bioavailability of the oral formulations of ruxolitinib used in the clinical development program with that proposed for registration and no justification for the absence of such studies could be identified in the provided data.

In humans, mass-balance data from Study #134 showed that absorption of ruxolitinib is nearly complete following oral administration with at least 95% of the dose being absorbed. Following oral administration, ruxolitinib is rapidly absorbed with mean T_{max} values ranging from 0.75 to 1.3 h following a single oral fasted dose of 25 mg (Studies #131, #137, #138, #139 and #142). In the pivotal Population-PK analysis in patients with MF, the estimated population mean absorption half-life of ruxolitinib after oral administration was approximately 0.168 h (approximately 10 minutes) following an estimated population mean absorption lag-time of less than 5 minutes (0.0545 hours). The population mean first-order absorption rate constant (ka) was 4.12 h^{-1} and demonstrated high intersubject variability (75%CV).

Administration of a single-dose 25 mg tablet with a high-fat, high-calorie meal reduced the gmean C_{max} by ~24% relative to fasting (ratio = 75.7% [90% CI: 62.7, 91.3%]) and increased the gmean $AUC_{0\text{-}inf}$ by 4% (ratio = 104% [95% CI: 96.8, 113%]) (Study #131). There was no substantial change in the oral apparent clearance or the terminal elimination half-life of ruxolitinib when administered with food, while the T_{max} increased by 1.4 hours. Overall, the fed/fasting PK data suggest that ruxolitinib can be administered with or without food.

Based on mean C_{max} and AUC values, the pharmacokinetics of ruxolitinib were linear in healthy subjects following single oral doses over the range 5 mg to 200 mg (Study #131), and at steady state for 15 mg, 25 mg, and 50 mg bd and 50 mg and 100 mg qd regimens (Study #132). There is no accumulation of ruxolitinib following multiple dosing and no marked differences were observed between single-dose and steady-state PK parameters in healthy subjects (Study #132). Serial trough plasma ruxolitinib concentrations indicate that steady-state is reached by the morning of Day 2, which is consistent with the short observed plasma terminal half-life of the drug of about 3 h (Study #132).

The mean steady state apparent volume of distribution (V_z/F) in healthy subjects ranged from 82 to 111 L (Study #132), and in patients with MF ranged from 53 to 65 L (Study #251). Ruxolitinib binding to human serum albumin (HAS) *in vitro* is approximately 96% to 97% at HSA concentrations expected in healthy subjects (40 to 50 mg/mL) (INCYTE-DMB-10.05.1). The protein binding data suggest that clinical conditions resulting in a 30% to 50% decrease in HSA concentrations are likely to result in only a 2 fold or less increase

in the unbound fraction of ruxolitinib. In healthy males subjects, after a single oral dose of ^{14}C-ruxolitinib (25 mg), the mean ratio of AUC_{inf} for blood cell radioactivity compared with plasma radioactivity was 2.9 (range: 2.0 to 3.3), suggesting a minor degree of preferential partitioning into blood cells (Study #134).

Ruxolitinib is eliminated almost completely by oxidative metabolism, with renal excretion of unchanged ruxolitinib being negligible. Oxidation, primarily resulting in hydroxylated and ketone metabolites, is the major Phase I metabolic pathway and the hydroxylated metabolites can undergo conjugation. Less than 1% of an administered dose of ruxolitinib is excreted unchanged in the urine and feces. The mass-balance study showed that the ruxolitinib (parent compound) was the major circulating entity in the plasma representing 74%, 66% and 58% of the total radioactivity at 1, 2 and 6 h post-dose, respectively. The predominant metabolite was M18 which represented 7.3%, 9.1% and 14% of the total radioactivity at 1, 2 and 6 h post-dose, respectively. Eight other minor mono and dihydroxylated metabolites were identified in the plasma with each averaging less than 5% of the radioactivity. M18 was the only metabolite with both a plasma concentration and $AUC_{0\text{-}24h}$ value > 10% that of ruxolitinib (18% and 30%, respectively).

Data from INCYTE-DMB-10.55.1 on the pharmacokinetics of the metabolites in healthy subjects from Study #138 (n=20) showed that the major metabolites of ruxolitinib in plasma were M18 and M27, representing 25% and 11%, respectively, of the parent drug systemic exposure based on $AUC_{0\text{-}inf}$ values. All other six metabolites were present in the plasma at concentrations < 10% or the parent drug. The total percent for all eight metabolites combined was approximately 65% of the parent drug systemic exposure based on $AUC_{0\text{-}inf}$ values. All metabolites of ruxolitinib are pharmacologically active with weaker potencies (approximately 2 to 5 fold) relative to the parent being observed in a human whole blood assay of IL-6 induced pSTAT3 (INCYTE-IN VITRO-09.11.1). After adjusting the *in vitro* pSTAT3 IC_{50} values for the metabolites relative to the parent, the metabolites were estimated to have about 18% combined PD activity relative to ruxolitinib.

In vitro studies in human recombinant CYP enzymes and human liver microsomes suggest that CYP3A4 is the predominant CYP enzyme responsible for the metabolism of ruxolitinib. These studies also showed that CYP1A2, CYP2C9, CYP2C19 and CYP2D6 appear to have little role in the metabolism of ruxolitinib. No data could be identified on the role of CYP2B6 or CYP2C8 in the metabolism of ruxolitinib.

In healthy subjects, co-administration of oral ketoconazole (a potent CYP3A4 inhibitor) 200 mg bd for 4 days with a single-dose of ruxolitinib 10 mg significantly increased gmean ruxolitinib $AUC_{0\text{-}inf}$ by 91% relative to ruxolitinib alone, which appears to be due to a 48% reduction in apparent oral clearance (CL/F) (Study #133). This result indicates that the ruxolitinib dose should be reduced by 50% when co-administered with potent CYP3A4 inhibitors. When erythromycin (a moderate CYP3A4 inhibitor) 500 mg bd for 4 days was co-administered with a single-dose of ruxolitinib 10 mg to healthy subjects (Study #131) the gmean ruxolitinib $AUC_{0\text{-}inf}$ significantly increased by 27% relative to ruxolitinib alone and the apparent oral clearance (CL/F) decreased by 14%. This result suggests that no change in the ruxolitinib dose appears to be required when co-administered with moderate CYP3A4 inhibitors. However, it should be noted that the ruxolitinib dose used in this interaction study (10 mg) in healthy subjects was notably lower than that being proposed for treatment of MF (15 or 20 mg bd). Consequently, caution is required when ruxolitinib is co-administered with moderate CYP3A4 inhibitors.

In healthy subjects, co-administration of rifampin (a potent CYP3A4 inducer) 600 mg once a day (qd) for 10 days with a single dose of ruxolitinib 50 mg significantly decreased ruxolitinib geometric mean C_{max} and $AUC_{0\text{-}inf}$ by 52% and 71%, respectively, relative to ruxolitinib alone (Study #135). The reduced systemic exposure to ruxolitinib following co-administration with rifampin appears to be due to a significant 3.7 fold increase in oral

apparent clearance (CL/F). Furthermore, the effect on ruxolitinib exposure due to rifampin was still present 21 days after rifampin had been discontinued. However, the PD effect of ruxolitinib when co-administered with rifampin was much less than predicted from the PK effects. The sponsor explained this apparent discrepancy on the characteristics of the sigmoidal dose-response curve relating ruxolitinib plasma concentration to cytokine-induced inhibition of pSTAT3 and increased PD activity of ruxolitinib metabolites relative to the parent compound following co-administration with rifampin. Based on the PD results and a conservative approach to safety the sponsor proposes no increase in the ruxolitinib dose when co-administered with CYP3A4 inducers. This was considered to be acceptable.

The mass-balance study (#134) showed that, following a single oral dose of ^{14}C-ruxolitinib (25 mg), recovery of the administered radioactivity was ~ 96%, with ~74% and ~22% being recovered in the urine and feces, respectively. Elimination of the administered dose was rapid with greater than 70% of dosed radioactivity being excreted within 24 h for all subjects, except for one subject with recovery of 50%. Urinary elimination was the major route of excretion for ruxolitinib derived radioactivity (consisting of various hydroxylation and ketone metabolites with glucuronide conjugates). Less than 1% of the ruxolitinib derived radioactivity recovered in the urine and feces was parent drug.

The mean±standard deviation (SD) apparent oral clearance (CL/F) of ruxolitinib was 19.2±6.94 L/h, based on data from 290 healthy subjects from 9 Phase I studies. There was a 2 fold difference in mean CL/F cross the studies from ranging from 14.1 L/hr to 28.2 L/hr and the sponsor speculates that this most likely reflects variability in metabolic clearance. However, there were no data in the submission confirming the sponsor's explanation. In the pivotal Population-PK analysis in patients with MF, gender was found to be a significant predictor of oral clearance, with male subjects having a slightly higher CL/F compared with female subjects (22.1 and 17.1 L/h, respectively), although the results were within the variability of CL/F for the total population (39.1% CV).

The mean±SD terminal elimination half-life ($t_{1/2}$) of ruxolitinib was 3.1±1.0 hours, based on data from 290 healthy subjects from 9 Phase I studies. There was an approximate 2 fold difference in $t_{1/2}$ across the studies ranging from 2.3 to 4.0 hours and this was consistent with the results for CL/F. Gender had not significant effect on $t_{1/2}$ with the estimates from the Population-PK model in patients with MF being ~3.8 h for males and ~4.1 h for females.

In patients with MF (Study #251), mean ruxolitinib C_{max} and $AUC_{0-\tau}$ steady state values increased approximately linearly proportional to doses over the range of 10 mg to 100 mg. The apparent clearance (CL/F) in MF patients ranged from 19.7 L/h to 25.6 L/h, and the estimated terminal half was approximately 2 hours. Intersubject variability at steady state ranged from 2.2% to 44.1% for C_{max} and from 20% to 57% for $AUC_{0-\tau}$. Intersubject variability in these parameters in patients with MF was greater than in healthy subjects. In the Population-PK analysis in patients with MF, the estimated intersubject variabilities (CV%) for the following parameters were 75.0% for k_a, 39.1% for CL/F, 28.0% or V_c/F, and 102.0% for V_p/F.

In the pivotal Population-PK analysis in patients with MF, ruxolitinib plasma concentrations were adequately described by a two-compartment model with first-order absorption, absorption lag time and linear elimination. Gender was found to be a statistically significant predictor of apparent oral clearance (CL/F) with the value in males being approximately 25% higher than in females (22.1 L/h versus 17.7 L/h, respectively). However, the difference in CL/F between the genders was within the inter-subject variability (CV) of CL/F in the total population of 39.1%. Body weight was a statistically significant predictor of apparent central volume of distribution (V_c/F), and was described by a linear function which predicts a Vc/F of 56.3 L for a typical 70 kg individual and an approximate 8 L increase in Vc/F for every 10 kg increase in body weight. However, the

magnitude of the covariate effects of gender (male versus female) and weight (72.9 kg versus > 72.9 kg) based on the gmean ratios for AUC_{ss} were maintained within prespecified bounds of 0.5 to 2 for both the 15 mg bd and 20 mg bd dosage regimen. Consequently, the AUC_{ss} ratios suggest that the effects of gender on CL/F and weight on Vc/F are unlikely to be clinically significant.

In subjects with hepatic impairment, exposure to ruxolitinib based on the $AUC_{0\text{-}inf}$ increased by 87%, 28%, and 65% in patients with mild, moderate, and severe impairment, respectively, relative to subjects with normal renal function following administration of a single fasted ruxolitinib 25 mg tablet (Study #137). The "no effect" boundary for hepatic impairment based on the $AUC_{0\text{-}inf}$ ratio (impaired/normal) was pre-specified at 80% to 125%, and the 90% confidence interval (CI) for the relevant ratios for subjects with mild, moderate and severe hepatic impairment were all well outside the boundary. The upper bound for 90% confidence interval (CI) for the $AUC_{0\text{-}inf}$ ratios (impaired/normal) was 2.71, 1.85, and 2.40 for patients with mild, moderate and severe hepatic impairment. These results suggest that the ruxolitinib starting dose should be reduced by 50% for patients with hepatic impairment.

In subjects with renal impairment, exposure to ruxolitinib based on the $AUC_{0\text{-}inf}$ increased by 10%, 22% and 3% in patients with mild, moderate and severe impairment, respectively, relative to subjects with normal renal function following administration of a single fasted ruxolitinib 25 mg tablet (Study #137). The "no effect" boundary for renal impairment based on the $AUC_{0\text{-}inf}$ ratio (impaired/normal) was 80% to 125%, and the 90% CI for the relevant ratios for subjects with mild, moderate and severe renal impairment were all outside the boundary. However, the upper bound of the 90% CI for $AUC_{0\text{-}inf}$ ratio was ≤ 150% for patients with mild, moderate and severe renal impairment. In a PD analysis, the pharmacological activity (IC_{50}) adjusted AUC of ruxolitinib plus metabolites, expressed as a percent of parent AUC, was 117% for patients with normal renal function, 123%, 134% and 153% for patients with mild, moderate and severe renal impairment, respectively, and 212% and 192% for subjects with ESRD dosed after dialysis and before dialysis, respectively. The sponsor proposes that no dosage adjustments are required for patients with mild renal impairment but recommends an approximate 50% reduction in starting dose for patients with moderate and severe renal function.

In vitro studies demonstrated that ruxolitinib and its M18 metabolite are unlikely to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 at ruxolitinib concentrations (C_{max}) at the highest proposed therapeutic dose for treatment of patients with MF (25 mg bd). *In vitro* studies have also demonstrated that clinically significant induction of CYP3A4, CYP1A2 and CYP2B6 is unlikely at clinically relevant ruxolitinib plasma concentrations associated with the highest proposed therapeutic dose.

*In vitr*o intestinal permeability studies showed that ruxolitinib crosses Caco-2 cell monolayers through a passive mechanism and is not a substrate for transporters including P-gp. *In vitro* studies have also demonstrated that it is unlikely that ruxolitinib at therapeutic concentrations will inhibit P-gp mediated transport of drugs that are P-gp substrates. In addition, *in vitro* studies have demonstrated that ruxolitinib and its M18 metabolite at clinically relevant therapeutic concentrations are unlikely to inhibit the transport of drugs that are substrates for the transporters BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1 and OAT3.

Pharmacodynamics

Studies providing pharmacodynamic data

The following pharmacodynamic data were submitted and have been evaluated:

- effect of ruxolitinib in health subjects on the QTcF[14] interval in a "Thorough QT/QTc study" complying with the relevant TGA adopted ICH E14 guidelines[37] (Study #138);
- effect of ruxolitinib on inhibition of IL-6 stimulated pSTAT3 in healthy subjects (INCYTE-IN VITRO-11.01.1), and in patients with MF (Studies #251 and #351)
- PK/PD analyses of the relationship between average steady state ruxolitinib concentration and efficacy outcomes of reduction in spleen volume and change in total symptom score (assessed by the Myelofibrosis Symptom Assessment Form [MFSAF]), and safety outcomes of platelet count, absolute neutrophil count and haemoglobin concentration in patients with MF from the pivotal Phase III efficacy and safety study (#351)

Evaluator's overall conclusions on pharmacodynamics

There is no evidence from the "Thorough QT/QTc study" in healthy subjects that ruxolitinib is associated with clinically significant increases in the QTcF interval. Based on the relevant TGA annotated ICH guideline E14 it can be concluded that the results from the "Thorough QT/QTc study" suggests that ruxolitinib is not of "regulatory concern" as regards a "threshold pharmacologic effect on cardiac repolarisation".

Baseline elevations in a number of inflammatory markers were noted in patients with MF compared with healthy subjects (Study #251). These markers have been associated with constitutional symptoms such as fatigue, pruritus and night sweats. In Study #351, many of the inflammatory markers demonstrated a rapid and significant change in subjects who were treated with ruxolitinib (that is, CD40, CRP, ICAM-1, IL-1ra, MCP-1, MIP-1β, TNFα, TNFRII, and VCAM-1) In contrast, none of these markers showed significant changes from baseline in the placebo group after 4 or 24 weeks. In addition, observed changes from baseline and differences at Weeks 2 and 24 between the ruxolitinib and placebo groups for a number of other markers were consistent with the postulated mechanisms of action of ruxolitinib (for example, VEGF, EPO, leptin, MPO and β2M).

The submitted data showed that (*ex vivo*) ruxolitinib inhibits IL-6 stimulated STAT3 phosphorylation in both healthy subjects and patients with MF. In patients with MF, inhibition was demonstrated to be time and dose dependent. The data establish a pharmacological rationale supporting the clinical use of ruxolitinib for the treatment of MF.

The PK/PD analyses in patients with MF demonstrated exposure-response relationships between ruxolitinib and efficacy outcomes of reduction in spleen volume and total symptom score, and safety outcomes of change in platelet counts, absolute neutrophil counts and haemoglobin concentration. The PK/PD analyses support the sponsor's proposed dosage proposed starting dose of 15 mg bd or 20 mg bd based on baseline platelet counts, and dosage adjustments of 5 mg bd based on efficacy (inadequate reductions in spleen volume) and safety (changes in platelet and/or neutrophil counts).

Efficacy

Dosage selection for the pivotal studies

Dosage selection in both the pivotal Phase III study (#351) and the supportive Phase III study (#352) was based on the results from an open-label, non-randomised, non-controlled, dose-escalation Phase I/II study (#251) in patients with PMF, PPV-MF), or

[37] CHMP/ICH/2/04. ICH E14. The Clinical Evaluation Of Qt/Qtc Interval Prolongation And Proarrhythmic Potential For Non-Antiarrhythmic Drugs. <http://www.tga.gov.au/pdf/euguide/ich000204entga.pdf>

PET-MF (see Table 10, below). This study included objectives relating to identification of dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of oral ruxolitinib for patients with MF, in addition to numerous other exploratory objectives relating to efficacy, safety, pharmacodynamics and pharmacokinetics. The study was conducted in the USA at two centres and was initiated on 21 June 2007 and the data cut-off date for the ongoing study was 31 December 2009. The study complied with all ethical requirement and has been published.[11]

Table 10: Overview of Phase I/II Study #251.

Study No./design	Data cut-off date/Study status/ Duration of treatment and follow-up	Primary objective/ Study population/	Treatment and dose regimen		Number of patients/Number of centers/countries
			Ruxolitinib	Control	
INCB 18424-251	31-Dec-2009 Ongoing	Determine dose-limiting toxicity and maximum tolerated dose of ruxolitinib Evaluate safety, tolerability and preliminary effectiveness of ruxolitinib in patients with PMF, PPV-MF, or PET-MF.	25 mg b.i.d. as first of 7 twice daily dose-escalation cohorts, or 25 mg q.d. as first of 4 once daily dose-escalation cohorts, or 10 mg b.i.d., or 25 mg b.i.d. (2 cycles) then 10 mg b.i.d. as first of several induction/ maintenance regimens.	Not applicable	N=154 (ruxolitinib) 2 centers in the United States

The study included patients aged at least 18 years of age with PMF, PPV-MF, or PET-MF, regardless of JAK2 mutational status, with a life expectancy of at least 12 weeks. If newly diagnosed, patients were to be classified as intermediate or high risk according to the Lille (Dupriez) Scoring System (adverse prognostic risk factors were: Hgb < 10 g/dL; WBC count < 4 or > 30 x 10^9/L; or risk group: 0 factors = low, 1 factor = intermediate, 2 factors = high), or symptomatic splenomegaly that was > 10 cm below costal. The study analysed 154 patients for efficacy, safety and pharmacokinetics.

The study consisted of 3 parts:

- Part 1 (dose escalation) was planned in the original protocol and
- Parts 2 and 3 were added by protocol amendment.

Part 1 (dose escalation) was designed to determine the DLT and MTD of ruxolitinib. The starting dose was determined using a standard algorithm based on nonclinical studies for Phase 1 multiple-dose oncology studies in patients.[12] The nonclinical studies identified the rat as the most sensitivity species and the dose causing severe toxicity or death in 10% of rats was between 100 and 250 mg/kg. Using a dose of 100 mg/kg in the rat, an appropriate safe starting dose in humans was determined to be 96 mg/day. However, the starting dose was reduced to 50 mg/day (25 mg bd) because it was expected to result in pharmacologically active ruxolitinib plasma concentrations.

Sequential cohorts of 3-6 patients were to be assigned to escalating doses of ruxolitinib, starting with a total daily dose of 50 mg (25 mg bd). Dose escalation followed a modified Fibonacci series with the exception that the 2 initial doses were in 100% increments. The maximum planned total daily dose was 900 mg, which was less than 10 times the safe clinical starting dose. However, only 2 of the proposed 7 dose levels were tested (25 and 50 mg bd). The starting dose of 25 mg bd was well tolerated in the initial 3 subjects. However, of the 5 patients enrolled at the 50 mg bd dose, 3 had a dose DLT of Grade 3 thrombocytopenia and 1 had Grade 4 thrombocytopenia. In these patients the 50 mg bd dose was stopped and resumed at a lower dose following platelet recovery, the patient who experienced Grade 4 thrombocytopenia was also given a prophylactic platelet transfusion. Three additional patients were enrolled in the 25 mg bd cohort without further DLTs, and the 25 mg bd dosage was confirmed as the MTD for the bd regimen. A significant and sustained reduction in spleen size was demonstrated with the 25 mg bd dose but was associated with clinically meaningful reductions in platelet counts and/or haemoglobin concentrations leading to dose interruption or study discontinuation in 25% of patients. Therefore, the sponsor considered that it was important to study other doses

and dose regimens to define the dosing options that best combined the efficacy benefits of ruxolitinib, while minimizing the negative impact on haematologic parameters.

Part 2 examined 3 alternative dose regimens in three Schedules (A, B, C). Schedule A evaluated the MTD in sequential cohorts of 3-6 patients for up to 4 single daily dose regimens of 25, 50, 100, and 200 mg. Once daily doses of 25, 50, and 100 mg were well tolerated but the once daily dose of 200 mg in the initial 3 patients resulted in thrombocytopenia. Three additional patients were given 100 mg qd, which was well tolerated and 100 mg qd was confirmed as the MTD for the qd regimen. However, 2 of 6 patients who received 100 mg qd developed Grade 3 thrombocytopenia during the second month of therapy. Therefore, the 50 mg qd cohort was chosen for expansion with additional subjects, even though 100 mg qd met the criteria for MTD. Schedule B examined the efficacy and tolerability of a low dose regimen of 10 mg bd. Schedule C examined the efficacy and tolerability of an induction and maintenance regimen in which patients initially received 25 mg bd for two 28 day cycles (induction) and then 10 mg bd (maintenance).

Part 3 included 3 groups of patients (Groups I, II, and III) to further evaluate safety and efficacy of selected dose levels from Parts 1 and 2, to explore dose selection and modification based on platelet counts, to evaluate quality of life and symptoms of MF using the EORTC QLQ-C30[38] questionnaire and the modified MFSAF[39] and to evaluate other measures such as activity and exercise capacity assessments, body composition, organ and muscle size, and grip strength. Group I examined one or more of the dosing regimens 10 mg bd, 25 mg bd, and 50 mg bd. Group II examined the same regimens as Group 1 with the addition of 100 mg qd. Group III examined different starting doses bases on the baseline platelet count; patients with baseline platelet counts > 200 x 10^9/L started treatment at 15 mg bd, and patients with baseline platelet counts 100 to 200 x 10^9/L, inclusive, started treatment at 10 mg bd.

Of the 154 patients enrolled, 88 (57.1%) were still in the study as of 31 December 2009. For the 66 (42.9%) patients who discontinued from the study, the most frequently reported reasons were withdrawal of consent (9.7%) and physician decision to discontinue (9.7%). Reasons for termination classified as "other" included subject choice after splenectomy (1 subject), lack of response (2 subjects), loss of response (2 subjects), anaemia (development of Grade 3 anaemia and persistent anaemia, 1 subject each) and other medical condition (not specified in 1 subject). Four of the 15 patients who withdrew consent and 5 of the 15 patients who were discontinued by the physician had an AE leading to discontinuation of study medication at the time of discontinuation.

Comment: The sponsor commented that it appeared from the Study #251 data that there was individual variability in terms of sensitivity to thrombocytopenia and clinical response such that the optimal dose for a given individual patient was likely to be between 10 mg bd and 25 mg bd. In addition, the data indicated that dose titration within this range might offer the best balance of efficacy and safety for an individual patient. Therefore, starting doses in both the pivotal Phase III study (#351) and the supportive Phase III study (#352) were based on baseline platelet count. Patients with baseline platelet counts > 200 x 10^9/L started on 20 mg bd and patients with baseline platelet counts between 100 and 200 x 10^9/L, inclusive, started on 15 mg bd. In addition, individual dose titration rules based on platelet count and absolute neutrophil count and efficacy measured by change in palpable spleen length, were provided in the protocols of both

[38] The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of patients.
[39] The Myelofibrosis Symptom Assessment Form (MFSAF) is a daily diary capturing quality of life and symptomatic response to treatment.

studies. Overall, dosage selection for the pivotal and supportive Phase III studies was considered to be appropriate.

In Study #251, spleen volume assessed by magnetic resonance imaging (MRI) (or computed tomography (CT) in patients ineligible for MRI) was examined in 27 subjects. At Week 4, 40.7% of patients had a ≥ 35% reduction from baseline in spleen volume. The proportion of patients who had a ≥ 35% reduction from baseline in spleen volume varied over time (36.4% to 44.4%) and was 40.7% at Week 72. Of the 12 (44.4%) patients who were responders at Week 12, 7 patients maintained that response for over 1 year, through to Week 72. There was a dose response over time in the proportion of patients with a ≥ 35% reduction from spleen volume. Based on average treatment, median percent reduction from baseline to Week 24 was 12% in subjects receiving ≤ 10 mg bd (n=2), 32% in subjects receiving > 10 to ≤ 15 mg bd (n=13), 38% in subjects receiving > 15 to ≤ 20 mg bd (n=7) and 48% in subjects receiving > 20 mg bd (n=3). The percent reduction in total symptom score at Week 24 from baseline (ITT population) was 55% in all patients (n=79), 25% in the 10 mg bd group (n=9), 52% in the 15 mg bd (n=26), 50% in the 25 mg bd group (n=11) and 73% in the all qd group (n=17).

The conclusions drawn from the study with regard to safety and efficacy are limited by the absence of an appropriate control group. However, with respect to efficacy, the observed reductions in spleen size are clearly treatment related. If untreated, spleens typically continue to increase in size or stay at approximately the same size in patients with MF. Therefore, the notable decreases in spleen size observed in the majority of patients in this study can be reasonably considered to be related to ruxolitinib treatment. Similarly, improvements in the symptoms of MF observed in the study are also likely to be related to treatment with ruxolitinib.

Overview of clinical efficacy studies

The submission to register ruxolitinib for the treatment of MF is based on two, good quality, Phase III efficacy and safety studies (#351 and #352). The sponsor identified both of these studies as being pivotal. However, it is considered that Study #351 is pivotal (randomised, placebo-controlled, double-blinded) while Study #352 is supportive (randomised, best available therapy [BAT] controlled, open-label). Study #352 is considered to be supportive rather than pivotal as although it is controlled, it is open-label rather than double-blinded. The basic design features of the Studies #351 and #352 are summarised below in Table 11.

Table 11: Overviews of Phase III Studies #351 (pivotal) and #352 (supportive).

Study No./design	Data cut-off date/Study status/ Duration of treatment and follow-up	Primary objective/ Study population/	Treatment and dose regimen		Number of patients/Number of centers/countries
			Ruxolitinib	Control	
INCB 18424-351 randomized, placebo-controlled trial Randomization ratio: Ruxolitinib:placebo 1:1	02-Nov-2010** Ongoing Duration of treatment and follow-up: Until marketing approval or when the last randomized patent completed Week 144 (36 months)	Evaluate efficacy, safety and tolerability of ruxolitinib given twice daily (b.i.d.) in patients with PMF, PPV-MF, or PET-MF compared to placebo	Starting dose: 20 mg b.i.d. for patients with baseline platelet count >200,000/µL 15 mg b.i.d. for patients with baseline platelet count of 100,000 to 200,000 µL	Placebo to match ruxolitinib 5 mg tablets	Total: N=309 Ruxolitinib: N=155 Placebo: N=154 68 centers in the United States, 6 sites in Canada, and 15 centers in Australia
CINC424A2352 randomized, reference therapy-controlled trial Randomization ratio: Ruxolitinib:BAT 2:1	04-Jan-2011** Ongoing Duration of treatment and follow-up: Until disease progression (unless clinically beneficial according to Investigator) or study conclusion. Follow-up until patient death.*	Evaluate efficacy, safety and tolerability of ruxolitinib in patients with PMF, PPV-MF, or PET-MF compared to BAT.	Starting dose: 20 mg b.i.d. for patients with baseline platelet count >200,000/µL 15 mg b.i.d. for patients with baseline platelet count of 100,000 to 200,000 /µL	Choice of BAT including watchful waiting (i.e. no drug therapy).	Total: N=219 Ruxolitinib: N=146 BAT: N=73 58 centers in 9 countries: Austria, Belgium, France, Italy, Germany, the Netherlands, Spain, Sweden, and the United Kingdom

** For OS, analyses were presented using a cut-off through 1 March 2011.

Evaluator's conclusions on clinical efficacy

The efficacy of ruxolitinib for the proposed indication was supported by two good quality Phase III efficacy and safety studies, both of which have recently been published. The pivotal Phase III study (#351) was a multinational, multicentred, randomised, placebo-controlled, double-blind, ongoing clinical trial in 309 patients with MF (155 randomised to ruxolitinib, 154 randomised to placebo). The supportive Phase III study (#352) was a multinational, multicentred, randomised, open-label, ongoing clinical trial in 219 patients with MF (145 randomised to ruxolitinib, 73 randomised to BAT).

Both the pivotal and supportive studies included patients with PMF, PPV-MF and PET-MF diagnosed according to WHO (2008) criteria and the median time from initial diagnosis to study entry was 2.2 years in Study #351 and 3.1 years in Study #352. In both studies, the proportion of patients with PMF was greater than the proportion of patients with PPV-MF or PET MF: that is, 49.8%, 31.4% and 18.4%, respectively, in Study #351; and 53.0%, 31.1% and 16.0%, respectively, in Study #352.

In both studies, all patients were required to be IWG intermediate risk level-2 or high risk. In Study #352, randomisation was stratified based on the two IWG categories while in Study #351 randomisation was unstratified. In Study #351, high risk patients were more common than intermediate risk level-2 patients (61.2% versus 38.2%, respectively), while in Study #352 high risk and intermediate risk level-2 patients occurred with similar frequencies (49.3% versus 50.7%, respectively). In both studies, ECOG PS could be 0 to 3, inclusive In Study #351, the percentages of patients with baseline ECOG PS 0, 1, 2, and 3 were 28.3%, 56.3%, 13.0% and 2.9%, respectively, and in Study #352 the corresponding percentages were 38.4%, 52.1%, 8.7% and 0.9%, respectively. All patients in both studies were required to have palpable splenomegaly, with the spleen measuring ≥ 5 cm below - the costal margin. The mean palpable spleen length in the total population was similar in both studies being 16.2 cm (range: 0, 34) in Study #351 and 15.2 cm (range: 5, 37) in Study #352.

The mean age of patients in Study #351 was 67.7 years (range: 40, 91), 39.5% were aged ≤ 65 years, 60.5% were aged > 65 years, 54.0% were male, 45.6% were female, and 89.6 were White. In Study #352, the mean age of patients was 65.2 years (range: 35, 85), 47.9% were aged ≤ 65 years and 52.1% were aged > 65 years, 57.1% were male, 42.9% were female and 84.5% were White. Patients could be included in the study irrespective of JAK2 mutation status, and in Study #351 76.4% were positive and 21.7% were negative at baseline, and the corresponding figures in Study #352 were 72.6% and 25.1%.

In both studies, the starting dose of ruxolitinib was based on baseline platelet count. Patients with a platelet count between 100 and 200 x 10^9/L were started on 15 mg bd and patients with a platelet count greater than 200 x 10^9/L were started on 20 mg bd. Doses were then individualised based on tolerability and efficacy with maximum doses of 20 mg bd for patients with platelet counts 100 to ≤ 125 x 10^9/L, 10 bd for patients with platelet counts 75 to ≤ 100 x 10^9/L and 5 mg bd for patients with platelet counts 50 to ≤ 75 x 10^9/L.

In both studies, the primary efficacy analysis of ≥ 35% reduction in spleen volume measured by MRI (or CT if applicable) from baseline to Week 24 (pivotal study) or Week 48 (supportive study) statistically significantly favoured ruxolitinib compared with placebo. In the pivotal study (ITT population), the response rate of ≥ 35% reduction in spleen volume from baseline to Week 24 in patients in the ruxolitinib group (n=155) was 41.9% (95% CI: 34.1, 50.1) compared with 0.7% (95% CI: 0.0, 3.6) in the placebo group (n=154); p<0.0001, Fisher's exact test. In the supportive study (FAS), the response rate of ≥ 35% reduction in spleen volume from baseline to Week 48 in the ruxolitinib (n=144) group was 28.5% (95% CI: 21.3, 36.6) compared with 0% (95%: 0.0, 5.0) in the BAT group

(n=72); p<0.0001, CMH exact test. The reduction in spleen volume in the ruxolitinib groups in both studies is considered to be clinically meaningful.

In the pivotal study, the results for the secondary efficacy endpoints of duration of maintenance of ≥ 35% reduction in spleen volume, proportion of patients with a ≥ 50% reduction in total symptom score measured (MFSAF) from baseline to Week 24 and change in total symptom score (MFSAF) from baseline to Week 24 all supported the primary efficacy analysis. The median duration of response was 48.1 weeks (95% CI: 37.4, NE) in patients (n=81) in the ruxolitinib group who had a ≥ 35% reduction from baseline in spleen volume at any point during the study and who either had at least 1 subsequent measurement or who subsequently dropped out prior to another assessment. The Kaplan-Meier analysis suggests that response diminishes over time, with the probability of maintaining a response for at least 12, 24, 36 or 48 weeks being 91%, 75%, 65% and 60%, respectively.

In the pivotal study, there was a statistically significant and clinically meaningful reduction in the percentage of patients who achieved a ≥ 50% improvement from baseline in Week 24 total symptom score in the ruxolitinib group compared with the placebo group (45.9% versus 5.3%, respectively, p<0.0001, Chi-square test). There was a statistically significant and clinically meaningful difference in the change in total symptom score from baseline to Week 24 in the ruxolitinib group compared with the placebo group (p<0.0001, Wilcoxon rank-sum test). In the ruxolitinib group, the mean±SD percent change from baseline to Week 24 in total symptom score was -8.6±10.0 (mean±SD percent change -46±48.6%) compared with a mean±SD change of +3.2±9.4 (mean±SD percent change +41.8±99.3%) in the placebo group.

In the supportive study, the key secondary efficacy endpoint of ≥ 35% reduction in spleen volume at 24 weeks supported the primary efficacy endpoint analysis. The response rate for patients with ≥ 35% reduction in spleen volume at 24 weeks was statistically significantly higher in the ruxolitinib group compared with the BAT group (31.9% versus 0%, respectively, p<0.0001, CMH exact test). The response rate at Week 24 (31.9%) was marginally higher than the response rate at Week 48 (28.5%). Other secondary efficacy endpoints in the supportive study showed that: (1) the median duration of maintenance of ≥ 35% reduction in spleen volume was 48 weeks (95% CI: 35.9, N/A) in patients who had ≥ 1 measurement of ≥ 35% reduction from baseline in spleen volume at any time during the study and ≥ 1 subsequent measurement or who withdrew prior to another assessment; and (2) the median time to first occurrence of reduction in spleen volume ≥ 35% was 12.3 weeks in the ruxolitinib group. The Kaplan-Meier analysis of maintenance of response of ≥ 35% in spleen volume suggests that response diminishes over time, with the probability of maintaining a response for at least 12, 24, 36, or 48 weeks being 78%, 67%, 58% and 39%, respectively.

Nearly all patients in the ruxolitinib groups in both studies achieved some reduction in spleen volume over time. In the pivotal study, nearly all patients in the ruxolitinib with both baseline and Week 24 data had a reduction in spleen volume (median reduction approximately 33%) compared with the majority of patients in the placebo group who had an increase in spleen volume (median increase approximately 8.5%). In the supportive study, 97.1% of patients in the ruxolitinib group had a reduction in spleen volume as best percentage change from baseline (median reduction approximately 28.4%) compared with 55.6% of patients in the BAT group (median increase approximately 8.5%).

In the supportive study, progression free survival (PFS), leukemia free survival (LFS) and overall survival (OS) were secondary efficacy endpoints. The stratified analyses of these three time-to-event endpoints showed no statistically significant differences between the ruxolitinib group and the BAT group. The PFS analysis showed that the median time to an event was 60.4 weeks in the ruxolitinib group and 60.1 weeks in the placebo group, while the median times to events were not reached in the LFS and OS analyses. In the pivotal

study, OS was a secondary efficacy endpoint and the total number of deaths with a median of 51 weeks of follow-up was 13 (8.4%) in the ruxolitinib group and 24 (15.6%) in the placebo group. The hazard ratio (ruxolitinib:placebo) was 0.499 (95% CI: 0.254, 0.980), p=0.0395 but median durations of survival could not be determined as the majority of patients in both treatment groups were censored at the date of the data cut-off. The statistically significant result for the OS should be considered to be nominal as no adjustment was made for repeat testing. Future assessments of PFS, LFS and OS in both the pivotal and supportive study will be difficult to interpret due to the likelihood that most patients randomised to placebo (pivotal study) or BAT (supportive study) will cross-over to ruxolitinib.

There were limited efficacy data in the Phase III studies beyond 12 months and all data need to be interpreted cautiously due to the relative small patient numbers. In the pivotal study at Week 60, of the 28 patients in the ruxolitinib group who had ≥ 35% reduction in spleen volume at the prior visit 11 continued to achieve a ≥ 35% reduction, 1 no longer had a ≥ 35% reduction and 16 were censored, while 1 additional patient newly achieved a ≥ 35% reduction. In the supportive study, the mean±SD percent change in spleen volume from baseline to Week 60 was a reduction of 28.6±26.9% in 19 patients in the ruxolitinib group and an increase of 12.1±14.1% in 5 patients in the BAT group.

Exploratory subgroup analyses in of the primary efficacy endpoint in ruxolitinib treated patients in the pivotal Phase III study showed notably higher responses (non-overlapping 95% CIs) in females compared with males (59.2% versus 25.3%) and in patients with started on 20 mg bd compared with 15 mg bd (53.0% versus 21.8%, respectively). In the supportive Phase III study, none of the subgroup analyses of the primary efficacy endpoint showed overlapping 95%CIs but there was a trend towards higher response in the 20 mg bd starting dose group compared with the 15 mg bd group and in females compared with males. In both Phase III studies, there was a trend towards higher response rates in the primary efficacy endpoint in patients aged ≤ 65 years compared with ≥ 65 years, in patients with PPV-MF compared with PMF and PET-MF, in patients with intermediate risk-2 disease compared with high risk disease and in JAKV617F mutation positive patients compared with JAKV617F mutation negative patients.

Exploratory efficacy analyses showed that both QoL and symptoms generally improved over time in patients treated with ruxolitinib compared with controls as assessed by the EORTC QLC-C30 questionnaire (Phase III pivotal and supportive studies) and the FACT-Lym questionnaire (Phase III supportive study).

Exploratory efficacy analyses of change in *JAK2*V617F allele burden showed that in the pivotal Phase III study there was a median decrease of 7.8% (range: -83.7% to +35.7%) at Week 24 in the ruxolitinib group (n=101) compared with a median increase of 1.1% (range: -23.3% to +100.0%) in the placebo group (n=154), and in the supportive Phase III study there was median decrease of 9.7% (range: -97.9% to +19.0%) at Week 48 in the ruxolitinib group (n=59) compared with no median change (range -91.5% to +15.4%) in the BAT group (n=22).

Safety

Studies providing evaluable safety data

The submission included a Summary of Clinical Safety (SCS). The safety database used for the analyses presented in the SCS included 787 patients from 6 studies evaluating patients with MF, prostate cancer, multiple myeloma, ET and PV (see Table 12, below). In addition, the SCS included data on 50 healthy volunteers treated in a "Thorough QT" study.

The 6 clinical studies included a total of 617 patients treated with at least one dose of ruxolitinib, including 345 (55.9%) patients treated with ruxolitinib for MF (PMF, PPV-MF or PET-MF). In this CER, the evaluation of safety focuses primarily on the data from the 2 Phase III studies in patients with MF as these data are considered to be directly relevant to the object of the submission (Studies #351, #351). The two Phase III studies allow the safety of ruxolitinib at the dosage regimen proposed for approval to be directly compared with placebo (Study #351) or BAT (Study #352). Safety data from the Phase I/II open-label, ruxolitinib dose escalation study in patients with MF (#251), the 3 clinical studies for indications other than MF and the 1 study in healthy volunteers have been examined. Information from these studies has been referred to in the CER if considered to provide relevant additional safety data to that observed in the Phase III MF studies. In all studies, safety and tolerability were assessed by monitoring adverse events (AE) and serious AEs (SAE), measuring vital signs, physical examinations, 12-lead electrocardiograms (ECG) and clinical laboratory blood and urine samples.

Table 12: Summary of the 6 clinical studies providing safety data.

Study	Study type	Population	Patients treated	Initial Dose	Median exposure (range) (months)
INCB 18424-251	Phase I/II open-label	PMF, PPV-MF PET-MF	154 total		
			117	Ruxolitinib 10, 15, 25, 50 mg b.i.d.	14.8 (1.2 – 30.2)
			37	Ruxolitinib 25, 50, 100, 200 mg q.d.	19.6 (0.5 – 23.1)
INCB 18424-351	Phase III double-blind, randomized	PMF, PPV-MF, PET-MF	306 total		
			155[1]	Ruxolitinib 15-20 mg b.i.d.	7.8 (2.6-13.6)
			151	Placebo	7.1 (1.1-13.4)
			36[2]	Ruxolitinib 10-20 mg b.i.d.	
CINC424A2352	Phase III open-label, randomized	PMF, PPV-MF, PET-MF	219 total		
			146[1]	Ruxolitinib 15-20 mg b.i.d.	11.8 (0.5 – 17.3)
			73	BAT	10.4 (0 – 15.4)
			18[3]	Ruxolitinib 5-20 mg b.i.d.	
INCB 18424-254	Phase II open-label	metastatic, androgen-independent prostate cancer	22	Ruxolitinib 25 mg b.i.d.	2.0 (0.8 – 5.8)
INCB 18424-255	Phase II open-label	relapsed or refractory multiple myeloma	13[4]	Ruxolitinib 25 mg b.i.d. + dexamethasone 40 mg	4.6 (0 – 24.8)
INCB 18424-256	Phase II open-label	hydroxyurea-refractory patients with PV or ET	73	Ruxolitinib 10, 25 mg b.i.d. 50 mg q.d.	16.0 (4.8 – 21.7)
Total number of patients treated			**787**		
Total number of patients treated with ruxolitinib			**617**		

[1]Patients randomised to and treated with ruxolitinib. [2] Patients receiving ruxolitinib after cross-over from placebo could begin ruxolitinib at 10 mg bd. according to their platelet count. [3]Patients receiving ruxolitinib after cross-over from BAT could begin ruxolitinib at 5 mg bd. 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

Exposure in the phase III MF population

In the Phase III MF population, overall exposure to ruxolitinib was 238.70 patient years. The median duration of exposure to ruxolitinib was 9.6 months (range: 0.49, 17.25), and the majority of patients (55.8%) were treated for 9 months. The overall the median ruxolitinib dose intensity was 30 mg/day (range: 7.3, 49.4), and the intensities were similar in both studies. Duration of exposure in the Phase III MF population are summarised below in Table 13.

Table 13: Phase III MF population - Duration of exposure; safety set.

	Study INCB 18424-351		Study CINC424A2352		Total
	ruxolitinib	placebo	ruxolitinib	BAT	Ruxolitinib
	N=155	N=151	N=146	N=73	N=301
Exposure categories - n (%)					
< 1 month	0	0	3 (2.1)	3 (4.1)	3 (1.0)
1 - < 3 months	1 (0.6)	16 (10.6)	4 (2.7)	3 (4.1)	5 (1.7)
3 - < 6 months	15 (9.7)	31 (20.5)	11 (7.5)	23 (31.5)	26 (8.6)
6 - < 9 months	85 (54.8)	71 (47.0)	14 (9.6)	5 (6.8)	99 (32.9)
9 - < 12 months	49 (31.6)	28 (18.5)	45 (30.8)	15 (20.5)	94 (31.2)
≥ 12 months	5 (3.2)	5 (3.3)	69 (47.3)	24 (32.9)	74 (24.6)
Duration of exposure (months)					
Mean	8.255	7.018	10.855	8.675	9.516
SD	2.0995	2.7660	3.5202	4.3585	3.1538
Median	7.786	7.064	11.811	10.382	9.626
Range	2.56 – 13.57	1.08 – 13.40	0.49 – 17.25	0.03 – 15.41	0.49 – 17.25
Patient-years	106.63	88.31	132.07	52.77	238.70

Comment: The Phase III MF population included only 74 (24.6%) patients who had been exposed to ruxolitinib for ≥ 12 months. This is a small number of patients and raises concerns about the adequacy of the ruxolitinib long-term safety data. In the all MF safety set (n=509) there were 187 (36.7%) patients exposed for ≥ 12 months. In all cancer safety set (n=617), 252 (40.8%) patients were exposed to ruxolitinib exposed for ≥ 12 months. In the all cancer safety set (n=617), median ruxolitinib dose intensity was 30 mg/day which was identical to that in the Phase III MF population.

Evaluator's overall conclusions on clinical safety

Overall, exposure to ruxolitinib in the Phase III MF population (n=301) was adequate (238.7 patient years) with median duration of exposure of 9.6 months (range: 0.5, 17.3). While the majority of patients exposed to ruxolitinib were treated for more than 9 months (55.8%), exposure for ≥ 12 months was limited to 74 (24.6%) patients. However, concerns relating to the long-term safety of ruxolitinib for the treatment of MF arising from the relatively small number of patients exposed for ≥ 12 months in the Phase III studies (n=74) are mitigated by the long-term safety data in the all MF safety set (n=509) in which 187 (36.7%) patients were treated with ruxolitinib for ≥ 12 months, and the all cancer safety set (n=617) in which 252 (40.8%) patients were treated with ruxolitinib for ≥ 12 months. The median dose intensity in the Phase III MF population was 30 mg/day (range: 7.3, 4.9) and was identical to that in the all cancer safety set.

In both the Phase III MF studies, a greater of proportion of patients in the ruxolitinib groups were still receiving randomised treatment at the date of the data cut-off than patients in the control groups (ruxolitinib, 87.1% versus 51.7%, placebo [#351]; ruxolitinib, 62.3% versus 42.5%, BAT [#352]). In the control groups, the major reason for discontinuing randomised treatment was crossing-over to ruxolitinib due to disease progression (23.8%, placebo [#351]; 24.7%, BAT [#352]). In Study #351, discontinuation from randomised treatment due to adverse events occurred in 10.3% of patients in the ruxolitinib group and 9.3% in the placebo group and the corresponding figures for Study #352 were 8.2% of patients in the ruxolitinib group and 5.5% in the BAT group. Discontinuations from randomised treatment due to disease progression were notably more common in the control groups than in the ruxolitinib groups (ruxolitinib, 1.9% versus 8.6%, placebo [#351]; ruxolitinib, 0.7% versus 4.1%, BAT [#352]) as were discontinuations due to withdrawn consent (ruxolitinib, 0.6% versus 4.6%, placebo [#351]; ruxolitinib, 1.4% versus 12.3%, BAT [#352]).

In the Phase III MF studies, AEs by SOC were reported in 98.3% of patients in the combined ruxolitinib group (#351 plus #352), 98.0% of patients in the placebo group

(#351) and 90.4% of patients in the BAT group (#352). The most common AEs by SOC, regardless of relationship to study drug and reported in ≥ 50% of patients in the combined ruxolitinib group were "Blood and lymphatic system disorders" (62.5%), "Gastrointestinal disorders" (58.8%), "General disorders and administration site conditions" (53.8%), and "Infections and infestations" (50.5%). SOC disorders with ≥ 2% more patients in the combined ruxolitinib group than in the control group in both the Phase III studies were "Blood and lymphatic system disorders", "Investigations" "Nervous system disorders", "Injury, poisoning and procedural complications", "Cardiac disorders", "Psychiatric disorders" and "Ear and labyrinth disorders". SOC disorders with ≥ 2% more patients in the control groups than the combined ruxolitinib group in both the Phase III studies were "Skin and subcutaneous tissue disorders", "Renal and urinary disorders" and "Hepatobiliary disorders".

In the Phase III MF studies, AEs regardless of relationship with study drug were reported in nearly all patients in both the pivotal study (ruxolitinib, 97.4% versus 98.0%, placebo) and the supportive study (ruxolitinib, 99.3% versus 90.4%, placebo). However, there were a number of specific AEs reported notably more commonly in patients treated with ruxolitinib compared with patients treated with placebo or BAT. AEs reported in ≥ 10% of patients in the combined ruxolitinib group and more commonly than in the placebo and BAT groups were, respectively: thrombocytopenia (39.2% versus 9.3% versus 9.6%); anaemia (35.9% versus 13.9% versus 12.3%); diarrhoea (23.3% versus 21.2% versus 12.3%); headache (12.6% versus 5.3% versus 4.1%); pyrexia (12.3% versus 7.3% versus 9.6%); pain in extremity (12.0% versus 9.9% versus 4.1%); arthralgia (11.6% versus 8.6% versus 6.8%); dizziness (11.3% versus 6.6% versus 5.5%); and vomiting (10.6% versus 9.9% versus 1.4%). Other less frequently reported AEs occurring more commonly in the ruxolitinib group than in the control group in both the Phase III studies were constipation, contusion, weight increased, urinary tract infection, haematoma, bronchitis, cardiac murmur, exertional dyspnoea, chills, cystitis and flatulence.

In the Phase III MF studies, Grade 3 AEs regardless of relationship with study drug were reported with similar frequencies in the ruxolitinib and placebo groups in the pivotal study (35.3% versus 35.1%, respectively), but more frequently in the ruxolitinib group than in the BAT group in the supportive study (38.3% versus 12.3%, respectively). Grade 3 AEs occurring more commonly in patients in the ruxolitinib group than in the control group in both the Phase III studies were (Study #351 and Study #352, respectively): thrombocytopenia (7.1% versus 1.3%; 6.8% versus 4.1%); anaemia (10.3% versus 4.6%; 11.0% versus 2.7%); diarrhoea (1.9% versus 0%; 1.4% versus 0%); pain in extremity (1.3% versus 0%; 0.7% versus 0%); arthralgia (1.9% versus 0.7%); and platelet count decreased (1.3% versus 0%; 0.7% versus 0%). Grade 4 AEs regardless of relationship to treatment occurred more commonly in the ruxolitinib group than in the placebo group in the pivotal study (11.6% versus 9.3%), while in the supportive study Grade 4 AEs occurred more commonly in the BAT group than in the ruxolitinib group (12.3% versus 6.8%, respectively).

AEs occurring in ≥ 10% of patients in the control group in both the pivotal Phase III and supportive Phase III studies and more commonly in both studies than in the combined ruxolitinib group were (placebo versus BAT versus combined ruxolitinib): abdominal pain (41.1% versus 13.7% versus 10%); peripheral oedema (22.5% versus 2.0% versus 20.3%); and pruritus (15.2% versus 12.3% versus 4.7%). Other less frequently reported AEs occurring more commonly in the control group than in the ruxolitinib group in both the pivotal Phase III and supportive Phase III studies were back pain, anorexia, hepatomegaly, tachycardia, pain, blast cell increased and weight decreased. Pneumonia (Grade 3) was the only Grade 3 or 4 event that occurred more commonly in the control group than the ruxolitinib group in both the pivotal study (3.3% versus 3.2%, respectively) and the supportive study (2.7% versus 1.4%, respectively).

There were no marked differences in the frequency of SAEs in patients in the ruxolitinib and placebo groups in the pivotal Phase III study (27.7% versus 35.1%, respectively) or in the ruxolitinib and BAT groups in the supportive Phase III study (30.1% versus 28.8%, respectively). The only SAE reported in ≥ 2% of patients in the ruxolitinib group in both studies and occurring more commonly than in both control groups was anaemia (ruxolitinib, 3.2% versus 2.0%, placebo; ruxolitinib, 4.8% versus 4.1%, BAT). The only other SAE occurring in ≥ 1% of patients in the combined ruxolitinib group, and more commonly than in both control groups (ruxolitinib versus placebo versus BAT) was diarrhoea (1.0% versus 0% versus 0%). The only SAE occurring in ≥ 5% of patients in any treatment group was pneumonia (ruxolitinib, 6.5% versus 3.3%, placebo; ruxolitinib, 0.7% versus 5.5%, BAT).

There were no significant differences in AEs associated with death between the ruxolitinib and control groups in the Phase III studies. In the pivotal Phase III study (safety set), death during treatment or within 28 days after treatment discontinuation was reported in 9 (5.8%) patients in the ruxolitinib group, 11 (7.3%) patients in the placebo group and 1 patient in the placebo crossed-over to ruxolitinib group. There was 1 death in the ruxolitinib group and 2 deaths in the placebo group occurring more than 28 days after treatment discontinuation. In the supportive Phase III study (safety set), death during treatment or within 28 days after discontinuation of treatment was reported in 4 (2.7%) patients in the ruxolitinib group, 3 (4.1%) patients in the BAT group and 1 patient in the BAT group crossed-over to ruxolitinib group. There were 2 deaths in the ruxolitinib group reported more than 28 days of treatment discontinuation.

The data from the Phase III MF populations showed that most AEs occurring in patients treated with ruxolitinib were managed by temporary dose interruptions or reductions rather than permanent treatment discontinuations. In the Phase III MF population, in the pivotal study discontinuations due to AEs regardless of the relationship to the study drug were reported in 11.0% of patients in the ruxolitinib group and 10.6% in the placebo group, and in the supportive study 8.2% of patients in both the ruxolitinib and BAT groups. None of the discontinuations due to AEs were reported in more than 2 patients in any group and discontinuations in 2 patients were uncommon in all groups.

In the Phase III PMF population, study drug dose interruptions or reductions resulting from AEs occurred notably more commonly in the combined ruxolitinib group than in the placebo and BAT groups (56.8% versus 25.8% versus 15.1%, respectively). The most frequent AE resulting in dose interruptions or reductions in the treatment groups (combined ruxolitinib versus placebo versus BAT) was thrombocytopenia (34.9% versus 6.0% versus 1.4%). The predominance of thrombocytopenia was accounted for by protocol mandated dose interruptions or reductions for this AE. The only other AEs of note resulting in more frequent dose interruption or reduction in the ruxolitinib groups than in the control groups were platelet count decreased and anaemia. All other AEs resulting in dose interruption or reduction occurred in ≤ 1% of patients (n ≤ 3) in the total ruxolitinib group.

Data from the pivotal Phase III study showed that in the ruxolitinib group, AEs were managed notably more frequently by dose reductions rather than interruptions. In this study, 40% (n=62) of patients in the ruxolitinib group had an AE resulting in dose reduction compared with 9.3% (n=14) of patients in the placebo group. The most frequent AEs leading to dose reduction were combined thrombocytopenia/platelet count decreased (32.9%, ruxolitinib versus 6.6%, placebo). AEs resulting in dose interruption or reduction occurred in 51.0% (n=79) of patients in the ruxolitinib group compared with 25.8% (n=39) of patients in the placebo group. The most frequent AEs leading to dose interruption or reduction were combined thrombocytopenia/platelet count decreased (37.4%, ruxolitinib versus 8.0, placebo).

In the Phase III MF population, AEs defined as clinically notable and selected on their frequency and relatedness to ruxolitinib were analysed. The clinically notable haematological AEs (cytopenias) were thrombocytopenia, erythropenia and leukopenia. Thrombocytopenia SMQ occurred in 45.8% of patients in the total ruxolitinib group compared with 10.6% and 12.3% in the placebo and BAT groups, respectively, and resulted in dose reduction in 39.2%, 7.3% and 0% of patients in the three groups, respectively. Erythropenia SMQ also occurred commonly and was reported in 38.9% of patients in the total ruxolitinib group compared with 15.2% and 12.3% in the placebo and BAT groups, respectively, and resulted in dose reduction in 5.3%, 0% and 2.7% of patients in the three groups, respectively. Leukopenia SMQ occurred relatively uncommonly compared with thrombocytopenia and anaemia and was reported in 4.7% of patients in the total ruxolitinib group compared with 2.6% and 1.4% in the placebo and BAT groups, respectively, and resulted in dose reduction in 0.7%, 0% and 0% of patients in the three groups, respectively.

In the Phase III MF population, clinically notable haemorrhagic SMQ events occurred commonly in the total ruxolitinib group, placebo and BAT groups (29.6% versus 25.2% versus 16.4%, respectively) but dose reductions or treatment discontinuations were infrequent for these events in all treatment groups. The imbalance between the treatment groups in haemorrhagic SMQ events was primarily accounted for by the increased frequency of bruising AEs in the ruxolitinib groups compared with the control groups.

In the Phase III MF population, clinically notable malignancies SMQ occurred more commonly in the placebo (7.9%) and BAT (5.5%) groups than in the total ruxolitinib group (4.0%). No malignancies occurred in more than 2 patients in the total ruxolitinib group. The only malignancy reported in 2 patients in the total ruxolitinib group, and more commonly than in both the placebo and BAT groups, was acute myeloid leukemia (0.7%, 0% and 0%, respectively).

In the Phase III MF population (clinical laboratory data), newly occurring or worsening Grade 3 platelet counts were reported in 7.6% of patients in the combined ruxolitinib group, 1.3% of patients in the placebo group and 4.1% in the BAT group, and the corresponding percentages for Grade 4 platelet counts were 3.0%, 0% and 2.7%. The majority of Grade 3 or 4 thrombocytopenia reported in the combined ruxolitinib group occurred within the first 3 months of treatment. Kaplan-Meier estimates of median time to resolution of first episode of Grade 3 or 4 thrombocytopenia to Grade 2 or less in the combined ruxolitinib group was 2 weeks (95% CI: 1.29, 2.14). Platelet transfusions while on ruxolitinib were infrequent. In the pivotal study (safety set), 8 (5.2%) patients in the ruxolitinib group received a platelet transfusion compared with 5 (3.3%) patients in the placebo group. Of the 8 patients transfused with platelets in the ruxolitinib group, 3 were transfused on treatment and 5 after withdrawal from the study. In the supportive study (safety set), more patients in the BAT group received platelet transfusions than in the ruxolitinib group (8 patients [11.0%] versus 6 patients [4.1%]). The results indicate that the majority of cases of thrombocytopenia in the ruxolitinib groups resolved with dose interruption or reduction and did not require platelet transfusion.

In the Phase III MF population (clinical laboratory data), newly occurring or worsening Grade 3 haemoglobin levels were reported in 30.9% of patients in the combined ruxolitinib group, 12.6% of patients in the placebo group and 11.0% of patients in the BAT group and the corresponding percentages for Grade 4 haemoglobin levels were 9.6%, 2.6% and 9.6%. Kaplan-Meier estimates of median time to onset of first new or worsening episode of Grade 2 or higher grade anaemia in the total ruxolitinib group was 1.5 months (95% CI; 1.4, 1.9). In the pivotal study approximately 22% more patients in the ruxolitinib group compared with the placebo group received at least one PRBC transfusion while on treatment (59.4% versus 37.1%, respectively) and the mean number of transfusions per month were 0.92 and 0.75, respectively. In the supportive study, 13% more patients in the

ruxolitinib group compared with the BAT group received at least one PRBC transfusion while on treatment (51.4% versus 38.4%, respectively) and the mean number of transfusions per month were 0.86 and 0.91 respectively. The combined data from the two studies showed the percentage of patients started on ruxolitinib 20 mg bd who received at least one PRBC transfusion while on treatment was greater than that for patients started on ruxolitinib 15 mg bd (57.4% versus 52.3%, respectively) but the results for the individual studies were inconsistent.

In the Phase III MF population, significant abnormalities in liver function tests (clinical laboratory data) were uncommon in the total ruxolitinib group. Worsening (any) grade alanine aminotransferase (ALT) levels in the combined ruxolitinib group occurred in 26.2% of patients compared with 7.9% and 6.8% of patients in the placebo and BAT groups, respectively, and worsening (any) grade AST levels in the combined ruxolitinib group occurred in 18.6% of patients compared with 6.6% and 2.7% of patients in the placebo and BAT groups, respectively. Nearly all reports of worsening in ALT and aspartate aminotransferase (AST) levels in all treatment groups were Grade 1 events, with ALT Grade 3 events being reported 1.3% of patients in the combined ruxolitinib group compared with no patients in the placebo and BAT group and no reports of ALT Grade 4 or AST Grade 3 or 4 events being reported in any treatment group. However, liver failure was reported as one of the causes of death in a patient treated with ruxolitinib in the supportive study and liver function tests in this patient appear to satisfy Hy's law criteria for drug-related hepatotoxicity.

There were no significant changes in creatinine levels associated with ruxolitinib (clinical biochemistry laboratory data) and apart from changes in LFTs the only other notable change in the clinical laboratory findings was an increase in median total cholesterol levels in patients in the ruxolitinib group compared with a decrease in the placebo group in the pivotal study (+21% versus -4%).

In the Phase III MF population, changes in pulse rate, blood pressure and respiratory rate were generally comparable between patients treated with ruxolitinib or control and there were no significant differences among the treatment groups in change in ECG QTc interval duration. In the Phase III MF population, there were a number of specific AEs in the combined ruxolitinib group that occurred more frequently in patients aged > 65 years compared with patients aged < 65 years and in female compared with male patients (and vice versa).

First round benefit-risk assessment

First round assessment of benefits

The evaluator considered that the pivotal and supportive Phase III studies have satisfactorily demonstrated the efficacy of ruxolitinib for the treatment of MF in a subgroup of patients with symptomatic splenomegaly, constitutional symptoms and higher risk disease with adequate bone marrow reserve. In both Phase III studies, the primary efficacy endpoint of higher proportion of patients in the ruxolitinib group compared with the control group achieving a ≥ 35% reduction in spleen volume measured by MRI (or CT if applicable) from baseline to Week 24 (pivotal Study #351) or Week 48 (supportive Study #352) was met. In the pivotal study, the primary efficacy endpoint analysis was supported by the key secondary efficacy endpoint of proportion of patients with ≥ 50% reduction in total symptom score from baseline. In addition, in the pivotal study the difference between the ruxolitinib and placebo groups for the secondary efficacy endpoint of OS was nominally statistically significant based on the HR but the median survival time had not been reached in either treatment group due to the high percentage of censored patients. In the supportive study, the primary efficacy endpoint was supported

by the secondary efficacy endpoint of reduction in spleen volume of ≥ 35% from baseline to Week 24 but the secondary efficacy endpoints of PFS, OS and LFS showed no statistically significant difference between ruxolitinib and BAT.

In the pivotal study (ITT population), the proportion of patients achieving the primary efficacy endpoint of ≥ 35% reduction in spleen volume measured by MRI (or CT if applicable) from baseline to Week 24 was statistically significantly in favour of ruxolitinib compared with placebo (41.9%, [n=65/155] versus 0.7%, [n=1/154], respectively, p<0.0001, Fisher's exact test). In the supportive study (FAS), the proportion of patients achieving the primary efficacy endpoint of ≥ 35% reduction in spleen volume measured by MRI (or CT if applicable) from baseline to Week 48 was statistically significantly in favour of ruxolitinib compared with BAT (28.5% [n=41/144] versus 0% [n=0/72], respectively, p<0.0001, CMH exact test). In both studies, the reductions in spleen volume of ≥ 35% from baseline in the ruxolitinib group compared with control are considered to be clinically meaningful.

In the pivotal study, the median duration of reduction in spleen volume of ≥ 35% from baseline was 48.1 weeks (95% CI: 37.4, NE) in patients (n=81) in the ruxolitinib group calculated by Method 1 (that is, loss of response is date of < 35% reduction from baseline). The Kaplan-Meier analysis suggests that response decreases over time with the probability of maintaining a response for at least 12, 24, 36 or 48 weeks being 91%, 75%, 65% and 60%, respectively. Median duration of response was not calculated in the placebo group as only 1 patient in this group achieved a ≥ 35% reduction in spleen volume during the study.

In the pivotal study, there was a statistically significant and clinically meaningful reduction in the percentage of patients who achieved a ≥ 50% improvement from baseline in Week 24 total symptom score in the ruxolitinib group compared with the placebo group (45.9% [n=68/148] versus 5.3% [n=8/152], respectively, p<0.0001, Chi-square test). In addition, there was a statistically significant and clinically meaningful difference in change in mean total symptom score from baseline to Week 24 in favour of the ruxolitinib group compared with the placebo group (improvement of 46.1% compared with worsening of 41.8%, respectively, p<0.0001, Wilcoxon rank-sum test).

In the supportive study, the response rate for patients with ≥ 35% reduction in spleen volume at 24 weeks (key secondary efficacy endpoint) was statistically significantly higher in the ruxolitinib group compared with the BAT group (31.9% [n=46/146] versus 0% [n=0/73], respectively, p<0.0001, CMH exact test). Other secondary efficacy endpoints in the supportive study showed that the median duration of maintenance of ≥ 35% reduction in spleen volume was 48 weeks (95% CI: 35.9, NA) in the ruxolitinib group analysed by Method 1 and the median time to first occurrence of reduction in spleen volume ≥ 35% in the ruxolitinib group was 12.3 weeks. The Kaplan-Meier analysis suggests that response decreases over time with the probability of maintaining a response for at least 12, 24, 36 or 48 weeks being 78%, 67%, 58% and 39%, respectively.

In the supportive study, there were no statistically significant differences between the ruxolitinib and BAT in time-to-event endpoints of PFS, OS and LFS. However, median duration of OS and LFS had not been reached in either the ruxolitinib or placebo groups at the date of the data cut-off. In the updated analysis of the OS in the pivotal study (secondary efficacy analysis), the total number of deaths with a median of 51 weeks of follow-up was 13 (8.4%) in the ruxolitinib group and 24 (15.6%) in the placebo group. The hazard ratio was 0.499 (95% CI: 0.254, 0.980), p=0.0395, but median survival durations could not be determined because the majority of patients in both treatment groups were censored at the date of the data cut-off. The OS data in the pivotal study are considered too immature to confirm a survival benefit in patients in the ruxolitinib arm compared with the placebo arm.

Exploratory efficacy analyses showed that both quality of life and symptoms associated with MF generally improved over time in patients treated with ruxolitinib compared with controls, as assessed by the EORTC QLC-C30 questionnaire (Phase III pivotal and supportive studies) and the FACT-Lym questionnaire (Phase III supportive study).

There are limited long-term efficacy data from the two Phase III studies. In the pivotal study at Week 60, of the 28 patients in the ruxolitinib group who had ≥ 35% reduction in spleen volume at the prior visit 11 continued to achieve a ≥ 35% reduction, 1 no longer had a ≥ 35% reduction and 16 were censored, while 1 additional patient newly achieved a ≥ 35% reduction. In the supportive study, the mean±SD percent change in spleen volume from baseline to Week 60 was a reduction of 28.6±26.9% in 19 patients in the ruxolitinib group and an increase of 12.1±14.1% in 5 patients in the BAT group.

Overall, the data from the pivotal and supportive studies are considered to have satisfactorily demonstrated meaningful clinical benefits relating to reduction in spleen volume and improvement in symptoms in patients with MF with IWF high risk and intermediate risk level-2 disease. However, the data are considered not to have satisfactorily established a treatment benefit relating to PFS, OS or LFS in patients treated with ruxolitinib compared with patients treated with placebo or BAT.

Based on the efficacy results and the patient population in the pivotal and supportive Phase III studies the evaluator recommended that the proposed indication be amended. The evalutor recommended that indication for ruxolitinib be "*for the treatment of disease-related splenomegaly or symptoms in patients with high-risk or intermediate-risk level-2 primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis*".

It was noted that the local expert nominated by the sponsor considers that the *"inclusion and exclusion criteria of the COMFORT studies defined a small subset of MF patients with adequate haematopoiesis and higher risk disease. Since ruxolitinib is likely to be used primarily for the relief of symptoms I would see the selection of patients being based on their symptom burden, not their risk score".* However, while noting the local expert's opinion, it was considered that the indication should reflect the risk scores of the patient population in the two Phase III studies (that is, intermediate risk level 2 and high risk). There are no efficacy data on patients with lower risk disease.

First round assessment of risks

Nearly all patients exposed to ruxolitinib, placebo or BAT experienced at least one AE. However, the risks of treatment with ruxolitinib were notably greater for a number of specific AEs than the risk of treatment with placebo or BAT. In particular, the risks of thrombocytopenia and anaemia were markedly greater in patients treated with ruxolitinib compared with controls. Other risks of treatment with ruxolitinib notably greater than treatment with controls included diarrhoea, headache, pyrexia, pain in extremity, arthralgia, dizziness and vomiting. In addition clinically notable AEs of bruising, urinary tract infection, herpes zoster and weight gain all occurred more frequently in the combined ruxolitinib group compared with the control groups in the Phase III MF population. There were no marked differences in the risks associated with SAEs in patients treated with ruxolitinib compared with controls, and there was no increased risk of death due to AEs in patients treated with ruxolitinib compared with controls. In patients treated with ruxolitinib there were increased risks of specific AEs in patients aged ≥ 65 years compared with patients aged ≤ 65 and in females compared with males. Overall, in the Phase III MF population, the risks of treatment due to AEs in the combined ruxolitinib group were managed by temporary dose reduction or interruption (56.8%) rather than by permanent treatment discontinuation (9.6%).

In the Phase III MF population, thrombocytopenia occurred in 39.2% of patients in the combined ruxolitinib group compared with 9.3% of patients in the placebo group and 9.6% of patients in the BAT group. The majority of thrombocytopenic events were Grade 1 or 2 in severity. Grade 3 and Grade 4 thrombocytopenia occurred in 7.0% and 1.0% of patients, respectively, in the combined ruxolitinib group compared with 1.3% and 0.7% of patients, respectively, in the placebo group and 4.1% and 0% of patients, respectively, in the BAT group. In the combined ruxolitinib group, SAEs of thrombocytopenia occurred in 1.0% of patients compared with 0.7% and 1.4% of patients in the placebo and BAT groups, respectively. The majority of Grade 3 or 4 thrombocytopenia (clinical laboratory data) reported in the combined ruxolitinib group occurred within the first 3 months of treatment. Kaplan-Meier estimates of median time to resolution of first episode of Grade 3 or 4 thrombocytopenia to Grade 2 or less in the combined ruxolitinib group was 2 weeks (95% CI: 1.29, 2.14).

In the Phase III MF population, most cases of thrombocytopenia occurring in the combined ruxolitinib group were managed by temporary dose interruptions or dose reductions (34.9%) rather than permanent treatment discontinuation (0.7%). Despite the frequency of thrombocytopenia in ruxolitinib treated patients platelet transfusions were uncommon. In the pivotal Phase III study (safety set), 8 (5.2%) patients in the ruxolitinib group received a platelet transfusion compared with 5 (3.3%) patients in the placebo group. In the supportive Phase III study (safety set), more patients in the BAT group received platelet transfusions than in the ruxolitinib group (8 patients [11.0%] versus 6 patients [4.1%]).

In the Phase III MF population, anaemia occurred in 35.9% of patients in the combined ruxolitinib group compared with 13.9% of patients in the placebo group and 12.3% of patients in the BAT group. The majority of anaemia events were Grade 1 or 2 in severity. Grade 3 and Grade 4 anaemia occurred in 10.6% and 2.7% of patients, respectively, in the combined ruxolitinib group compared with 4.6% and 0% of patients, respectively, in the placebo group and 2.7% and 1.4% of patients, respectively, in the BAT group. Anaemia was the most commonly reported SAE in the combined ruxolitinib group (4.0% of patients) and was reported in 3.2% of patients in the ruxolitinib group compared with 2.0% of patients in the placebo group in the pivotal study and in 4.8% of patients in the ruxolitinib group compared with 4.1% of patients in the BAT group in the supportive study. Kaplan-Meier estimates of median time to onset of first new or worsening episode of Grade 2 or higher anaemia (clinical laboratory date) in the total ruxolitinib group was 1.5 months (95% CI; 1.4, 1.9).

In the Phase III MF population, in the combined ruxolitinib group a higher proportion of AEs of anaemia were managed by temporary dose interruptions or dose reductions (5.3%) rather than permanent treatment discontinuation (0.3%). These data suggest that most cases of anaemia were managed without either temporary dose interruptions or dose reductions or permanent treatment discontinuation. However, data from the Phase III studies suggest that anaemia commonly required PRBC transfusions in both the ruxolitinib and control groups. In the pivotal study, approximately 22% more patients in the ruxolitinib group compared with the placebo group received at least one PRBC transfusion while on treatment (59.4% versus 37.1%, respectively), with the mean number of transfusions per month being 0.92 and 0.75, respectively. In the supportive study, 13% more patients in the ruxolitinib group compared with the placebo group received at least one PRBC transfusion while on treatment (51.4% versus 38.4%, respectively), with the mean number of transfusions per month being 0.86 and 0.91 respectively.

In the Phase III MF population, AEs in addition to thrombocytopenia and anaemia reported in ≥ 10% of patients in the combined ruxolitinib group and more commonly than in the placebo and the BAT groups were, respectively: diarrhoea (23.3% versus 21.2%

versus 12.3%); headache (12.6% versus 5.3% versus 4.1%); pyrexia (12.3% versus 7.3% versus 9.6%); pain in extremity (12.0% versus 9.9% versus 4.1%); arthralgia (11.6% versus 8.6% versus 6.8%); dizziness (11.3% versus 6.6% versus 5.5%); and vomiting (10.6% versus 9.9% versus 1.4%).

In the Phase III MF population (clinical laboratory data), significant abnormalities in liver function tests were uncommon in the total ruxolitinib group. However, there was one case of liver failure contributing to death in a patient treated with ruxolitinib in the supportive study in which the reported liver function abnormalities appear to satisfy Hy's law criteria for drug-related hepatotoxicity. There were no significant changes in creatinine levels associated with ruxolitinib, however there was an increase in total cholesterol level in the ruxolitinib group in the pivotal study compared with a decrease in the placebo group. In the Phase III MF population, changes in pulse rate, blood pressure and respiratory rate were generally comparable between patients treated with ruxolitinib or control and there were no significant differences among the treatment groups in ECG QTc interval increases.

First round assessment of benefit-risk balance

The benefit-risk balance of ruxolitinib, given the amended proposed usage, was considered to be favourable. However, the benefits of treatment in patients with MF relate to reduction in splenomegaly and improvement in symptoms rather than increased PFS and/or OS. Furthermore, there are number of significant risks associated with ruxolitinib treatment, particularly thrombocytopenia and anaemia. The evaluator considered that the absence of PFS and OS benefits associated with ruxolitinib and the presence of significant risks of thrombocytopenia and anemia results in the benefit-risk assessment being relatively finely balanced. However, the notably greater clinical benefits associated with reduction in spleen volume and improvement in symptoms in patients treated with ruxolitinib compared with patients treated with placebo or BAT are considered to result in a favourable benefit-risk balance, despite the identified risks associated with the drug.

There were no adequate efficacy and safety data in the submission relating to the appropriate ruxolitinib starting dose for patients with baseline platelet counts < 100 x 10^9/L. In the pivotal Phase III study, patients were required to have a baseline platelet count > 100 x 10^9/L in order to be included in the study, and in the supportive Phase III study patients with baseline platelet counts < 100 x 10^9/L were excluded from the study. Based on the absence of adequate data, it is considered that treatment with ruxolitinib should not be initiated in patients with platelet counts < 100 x 10^9/L despite the recommendation in the PI that patients with platelet counts between 50 and 100 x 10^9/L can be started on 5 mg bd and cautiously titrated. The sponsor acknowledges that there is limited information to recommend a starting dose in patients with platelet counts between 50 and 100 x 10^9/L (see statement in PI, *Dosage and Administration* section).

There are no efficacy or safety data in patients with IWG low or intermediate risk level-1 categories comparing ruxolitinib with control and the evaluator considered that treatment with ruxolitinib should not be initiated in these patients.

First round recommendation regarding authorisation

The evaluator recommended that ruxolitinib be approved for the treatment of disease-related splenomegaly or symptoms in patients with high-risk or intermediate-risk level-2 primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis.

The evaluator recommended that the proposed ruxolitinib dosage regimen should be approved, apart from the proposed starting dose of 5 mg bd in patients with platelet

counts 50 to 100 x 109/L. The evaluator recommended that ruxolitinib should not be started in patients with baseline platelet counts < 100 x 10^9/L.

List of questions

Pharmacokinetics

1. No clinical studies could be identified in the submission comparing the bioavailability of ruxolitinib oral formulations used in the Phase I/II/III development program and the oral formulations proposed for registration. Please justify the absence of such studies.
2. In the PK interaction study between erythromycin (a moderate CYP3A4 inhibitor) and ruxolitinib, ruxolitinib gmean C_{max} and $AUC_{0\text{-}inf}$ increased by 8% and 27%, respectively, following co-administration relative to ruxolitinib alone (Study #135). Based on these results, the sponsor proposes no ruxolitinib dosage adjustment when co-administered with erythromycin or other moderate CYP3A4 inhibitors. However, the ruxolitinib dose used in the interaction study (10 mg single-dose) was notably lower than that proposed for the treatment of MF (that is, starting dose of 15 mg bd or 20 mg bd depending on baseline platelet count). Does the sponsor intend repeating the PK interaction study between ruxolitinib and erythromycin using a clinically relevant ruxolitinib dose? If not, then please justify the recommendation that no adjustment of ruxolitinib is required when the drug is co-administered with moderate CYP3A4 inhibitors.
3. No data could be identified on the role of CYP2B6 or CYP2C8 in the metabolism of ruxolitinib. Please comment on this matter.

Pharmacodynamics

Nil.

Efficacy

1. In Phase III Study #351, there were a total of 53 unique protocol violations resulting in patients being excluded from the pre-protocol population: 14 due to violation of inclusion/exclusion criteria; 33 because compliance with treatment was < 80% (3 with compliance < 50%, 10 with compliance > 50% but < 70%, 20 with compliance ≥ 70% but < 80%); 4 because of use of prohibited medications; and 2 because the subject never took the study medication. Please provide a tabulated summary of these 53 unique protocol violations by treatment group. Please comment on the potential of the identified violations to have biased the analyses of the primary and secondary efficacy analyses in the ITT population.

Safety

1. In the Phase III Study #352, one patient treated with ruxolitinib had an ALT or AST > 3.0 x upper limit of normal (ULN) and bilirubin ≥ 2 x ULN and alkaline phosphates (ALP) < 2 x ULN. This patient was a 66 year old male who died due to hepatic failure, portal vein thrombosis and cerebral hemorrhage. The liver function abnormalities described for this patient appear to fit the criteria for Hy's law. Please comment on likelihood that the hepatic failure observed in this case was due to ruxolitinib related hepatoxicity. Have any other cases meeting Hy's law criteria been reported in the studies with ruxolitinib for indications other than for MF?

2. Does the sponsor have any specific data on withdrawal/rebound effects on patients discontinuing ruxolitinib? If so, please provided the data. It is noted that the *Precautions and Adverse effects* section of the PI includes information on withdrawal effects.

Second round evaluation of clinical data submitted in response to questions

Pharmacokinetics

Question a

No clinical studies could be identified in the submission comparing the bioavailability of ruxolitinib oral formulations used in the Phase I/II/III development program and the oral formulations proposed for registration. Please justify the absence of such studies.

Sponsor's response:

Ruxolitinib drug product is an oral immediate-release (IR) dosage form. In the pivotal Phase III trials [INCB 18424-351] and [INCB 18424-352/CINC424A2352], a 5 mg strength tablet was used. This Phase III formulation (5 mg tablet) corresponds to the intended commercial formulation along with other strengths, 15 mg and 20 mg, which have a quantitatively proportional composition using the same manufacturing process of compressing a common blend containing compendial-grade excipients. These excipients are well established standard pharmacopoeial excipients in common use for tableting. None of these excipients are expected to significantly affect the absorption of the active pharmaceutical ingredient (API).

Bioavailability of ruxolitinib oral formulations used across the development program and the oral formulation intended for registration was not compared,and justification for lack of such study (ies) is contained within the "*justification for biowaiver from EMA*[40]" seeking an exemption from providing *in-vivo* bioavailability studies for the (a) 5 mg batches used in Phase III studies versus commercial material and (b) 5 mg commercial batch and the higher strength 15, and 20 mg ruxolitinib IR tablets.

Ruxolitinib is a BCS Class 1 drug (that is, high solubility > 25 mg/250 mL over pH range 1.0 to 8.0, high permeability (21.5 x 10^{-6} cm/s across Caco-2 cell monolayers) and demonstrating rapid dissolution at three pH conditions (0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer). Ruxolitinib shows near complete oral absorption (approximately 95%) based on results of radiolabelled (^{14}C)- ruxolitinib mass balance study (Study #134) and it is not considered to be a narrow therapeutic index drug. In addition to being readily soluble and rapidly absorbed *in vivo*, pharmacokinetics of ruxolitinib was dose proportional following single dose administration over a wide dose range, from 5 mg to 200 mg [β estimated of AUC using a power-function regression analysis between dose-$AUC_{0\text{-inf}}$ was 0.974 (90% CI, 0.921-1.03)] and multiple doses from 15 mg to 100 mg [β estimated of AUC using a power-function regression analysis between dose-$AUC_{0\text{-tau}}$ was 0.947 (90% CI, 0.715-1.18)] [CTD 2.7.2 Studies 131 and 132]. Dose proportionality of systemic exposure to ruxolitinib was also observed in healthy subjects (N=47) administered single doses of 25 mg and 200 mg ruxolitinib tablets in a randomised crossover study [INCB 18424-138].

Further, to evaluate whether ruxolitinib bioavailability was formulation-dependent, a cross-study comparison of pharmacokinetic data was conducted. The relative bioavailability of ruxolitinib was found to be similar in healthy subjects administered 25 mg of ruxolitinib as powder-in-capsule [INCB 18424-131, Part 1], tablet [INCB 18424-131,

[40] EMA=European Medicines Agency

Part 2]; [INCB 18424-137]; [INCB 18424- 138]; [INCB 18424-139]; and [INCB 18424-142] or oral solution [INCB 18424-134].

In summary since ruxolitinib is a BCS Class I drug, and the 15 and 20 mg tablets are proportional in composition to the 5 mg tablet, have rapid and similar dissolution profiles in three different pH media and follow dose-proportional PK, these tablet strengths meet the BE waiver criteria [CHMP Guideline on the investigation of bioequivalence, January 2010[41]] and per the similar bioavailability across various formulations investigated during the development program, a formal BA/BE study evaluating bioavailability across the formulations used in development program and the oral formulation proposed for registration is not warranted.

Comment: The sponsor's response was considered to be satisfactory.

Question b

In the PK interaction study between erythromycin (a moderate CYP3A4 inhibitor) and ruxolitinib mean C_{max} and AUC_{inf} increased by 8% and 27% respectively, following co-administration relative to ruxolitinib alone (Study #135). Based on these results, the sponsor proposes no ruxolitinib dosage adjustment when co-administered with erythromycin or other moderate CYP3A4 inhibitors. However, the ruxolitinib dose used in the interaction study (10 mg single dose) was notably lower than that proposed for the treatment of MF (that is, starting dose of 15 mg bd, or 20 mg bd depending on baseline platelet count). Does the sponsor intend repeating the PK interaction study between ruxolitinib and erythromycin using a clinically relevant ruxolitinib dose? If not, then please justify the recommendation that no adjustment of ruxolitinib is required when the drug is co-administered with moderate CYP3A4 inhibitors.

Sponsor's response:

The sponsor does not intend to repeat the PK interaction study between ruxolitinib and erythromycin using a higher ruxolitinib dose. The impact on ruxolitinib pharmacokinetics by erythromycin at higher doses of ruxolitinib (for example, 15 or 20 mg) is expected to be smaller than that observed at 10 mg ruxolitinib.

Per guideline on investigation of drug interactions, *"if the victim drug has linear pharmacokinetics, it is sufficient to investigate the pharmacokinetics of the victim drug after a single dose with and without treatment with the perpetrator (e.g., erythromycin) drug"* [CHMP Guideline on investigation of drug reactions, June 2012[42]].

Linearity in ruxolitinib pharmacokinetics has been demonstrated over a dose range of 5 to 200 mg when administered as single doses therefore use of single 10 mg dose of ruxolitinib in drug interaction study with erythromycin is considered to be an appropriate dose.

Additionally, conduct of drug interaction study at low dose of victim drug (when permissible per above guidance) assures that in conditions when a true drug interaction is seen with a moderate inhibitor such as erythromycin, an exposure increase in the 2 to 5 fold range would still maintain the victim drug concentrations within safe limits.

The sponsor thereby believed that the drug interaction study conducted at the 10 mg single ruxolitinib dose is more sensitive and sufficient. Per the results of this study, the sponsor did not propose any dose adjustments when ruxolitinib is administered with moderate CYP3A4 inhibitors.

Comment: The sponsor's response was considered to be satisfactory.

[41]<http://www.tga.gov.au/pdf/euguide/ewp140198rev1.pdf>
[42]<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf>

Question c

No data could be identified on the role of CYP2B6 or CYP2C8 in the metabolism of ruxolitinib. Please comment on this matter.

Sponsor's response:

The role of CYP2B6 and CYP2C8 on the metabolism of ruxolitinib was investigated in [Study DMPK R1100644]. The cytochrome P450 enzymes involved in the oxidative metabolism of ruxolitinib were identified by using seven different recombinant human cytochrome P450 isoenzymes. Ruxolitinib was incubated with the recombinant CYPs at two concentrations (20 and 200 μM) for 20 minutes. The observed metabolism rates for these concentrations were 160 and 850 pmol/min/nmol CYP for CYP2B6 and 837 and 4725 pmol/min/nmol CYP for CYP2C8. These metabolism rates were scaled with CYP expression rates in human liver to calculate the relative contribution of the CYP enzymes to total oxidative liver metabolism. Based on the observed recombinant CYP enzyme kinetics [Study DMPK R1100644], the contributions of CYP2B6 and CYP2C8 to the oxidative liver metabolism of ruxolitinib were small and could be calculated as 0.12% and 1.44% of the total metabolism. Hence, CYP2B6 and CYP2C8 play only a minor role in the metabolism of ruxolitinib.

Comment: The sponsor's response was considered to be satisfactory.

Efficacy

In Phase III Study #351, there were a total of 53 unique protocol violations resulting in patients being excluded from the pre-protocol population: 14 due to violation of inclusion/exclusion criteria; 33 because compliance with treatment was <80% (3 with compliance <50%, 10 with compliance >50% but <70%, 20 with compliance ≥70% but <80%), 4 because of use of prohibited medications; and 2 because the subject never took the study medication. Please provide a tabulated summary of these 53 unique protocol violations by treatment group. Please comment on the potential of the identified violations to have biased the analyses of the primary and secondary efficacy analyses in the ITT population.

Sponsor's response:

Table 14 presents a summary of protocol violations in Study 351 by treatment arm. Overall, 22 patient (14.2%) and 31 patients (20.1%) were excluded from the per-protocol population in the ruxolitinib and placebo arms, respectively. The main reasons were due to inclusion/exclusion criteria (5.2% and 3.9% in ruxolitinib and placebo arms) and compliance between 70-80% (4.5% versus 8.4%). Other than the slight trend toward more patients in the 70-80% compliance group in the placebo arm than in the ruxolitinib arm, the reasons for exclusion from the per protocol group appear to be distributed between the arms in a similar way.

It is unlikely that the protocol violations biased the results of the primary and key secondary results, both of which were highly significant. Results of the analysis of spleen volume of the per-protocol population were similar to the primary analysis, with a significantly higher proportion of subjects in the ruxolitinib group (42.9%) achieving a ≥ 35% reduction from Baseline at Week 24 compared with the placebo group (0.8%, $p < 0.0001$, 351 CSR).

Table 14: Summary of patients with major protocol violations leading to an exclusion from the per protocol population in Study 351 (ITT subjects).

	Ruxolitinib (N=155)	Placebo (N=154)	Total (N=309)
Number (%) of Subjects of PP Exclusion	22 (14.2)	31 (20.1)	53 (17.2)
Primary Reason of PP Exclusion:			
Inclusion/Exclusion Criteria	8 (5.2)	6 (3.9)	14 (4.5)
Compliance <=50%	0	3 (1.9)	3 (1.0)
Compliance >50% to <70%	4 (2.6)	5 (3.2)	9 (2.9)
Compliance >=70% to <80%	7 (4.5)	13 (8.4)	20 (6.5)
Prohibited Medication	3 (1.9)	1 (0.6)	4 (1.3)
Never Dosed/Lost Data	0	3 (1.9)	3 (1.0)

Note 1. The subject was in both Incl/Excl criteria and compliance 65% and was summarised on the Incl/Excl criteria only. Note 2. Subject's data were lost.

Comment: The sponsor's response was considered to be satisfactory.

Safety

Question a

In the Phase III Study #352, one patient treated with ruxolitinib had an ALT or AST > 3.0 x ULN and bilirubin ≥ 2 x ULN and ALP < 2 x ULN. This patient was 66 year old male who died due to hepatic failure, portal vein thrombosis, and cerebral haemorrhage. The liver function abnormalities described for this patient appear to fit the criteria for Hy's law. Please comment on the likelihood that the hepatic failure observed in this case was due to ruxolitinib related hepatotoxicity. Have any other cases meeting Hy's law criteria been reported in the studies with ruxolitinib for indications other than MF?

Sponsor's response:

Ongoing safety monitoring and pooled data analyses identified no report meeting the Hy's law criteria in ruxolitinib studies. Pooled data analysis of liver function test abnormalities identified one patient in the ruxolitinib group that had an AST or ALT > 3 x ULN with concurrent bilirubin ≥ 2 x ULN without alkaline phosphatase > 2 x ULN.

Table 15. Liver function tests abnormalities in Phase III patients (Safety set).

	Study INCB 18424-351				Study INC424A2352				Total	
	ruxolitinib N=155		Placebo N=151		ruxolitinib N=146		BAT N=73		ruxolitinib N=301	
Test	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
ALT > 3.0 x ULN	155	3 (1.9)	147	1 (0.7)	145	2 (1.4)	69	0	300	6 (1.7)
AST > 3.0 x ULN	155	1 (0.6)	147	0	145	1 (0.7)	69	0	300	2 (0.7)
ALT or AST > 3.0 x ULN	155	3 (1.9)	147	1 (0.7)	145	2 (1.4)	69	0	300	6 (1.7)
Bilirubin ≥ 2 x ULN	155	5 (3.2)	147	4 (2.6)	145	9 (6.2)	69	3 (4.1)	300	14 (4.7)
ALT or AST > 3.0 x ULN and Bilirubin ≥ 2 x ULN and ALP < 2 x ULN	155	0	147	0	145	1 (0.7)	69	0	300	1 (0.3)

Total = number of patients who had at least one post-baseline value for the lab parameter.
n = number of patients out of Total who satisfied the criterion.

Comment: The sponsor's response was considered to be acceptable. In addition to the above information, the sponsor's response included a detailed case narrative for the 66 year old male referred to in the question. The sponsor concluded that the reported case did "*not qualify as a Hy's law case for*

several reasons. Firstly, the time to onset of enzyme elevation of about 10 months is not consistent with a Hy's law case [FDA DILI guidance[43]]. Secondly, the hepatic failure developed in the context of massive portal vein thrombosis, which is [a] known complication of Myelofibrosis and is therefore plausibly explained. Valla and Condat have found evidence of overt or latent myeloproliferative disorders in 48% of cases of isolated portal vein thrombosis. [Valla 2000]."

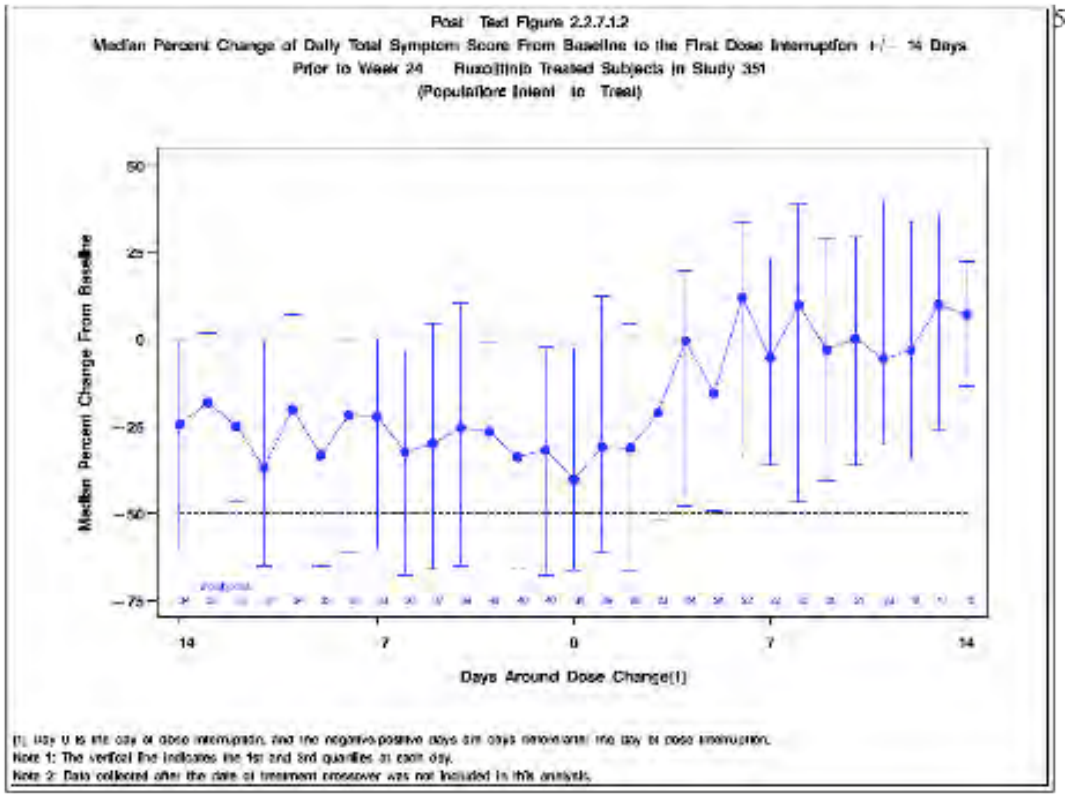
Question b

Does the sponsor have any specific data on withdrawal/rebound effects on patients discontinuing ruxolitinib? If so, please provide the data. It is noted that the Precautions and Adverse effects section of the PI includes information on withdrawal effects.

Sponsor's response:

When ruxolitinib therapy is discontinued, patients typically sustain a recurrence in clinical manifestations of their disease (Figure 3), including regrowth of an enlarged spleen and return of disease related symptoms such as fevers, night sweats, anorexia, abdominal discomfort and others.

Figure 3: Median percent change in daily total symptom score from baseline to first dose interruption.



Data presented in the RMP v2 table 1-19:

In Study 352, 26.7% (39/146) of patients randomised and treated with ruxolitinib discontinued treatment by 1 March 2011. Of these, 53.8% (21/39) reported 128 AEs with an onset after and up to 28 days after treatment discontinuation. For the other 46.2% of patients (18/39) no AEs after discontinuation were reported. Most AEs reported after discontinuation (68.0%; 87/128) were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2; 32.0% (41/128) were Grade 3 or higher. The mean last dose for

[43] <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf>

patients who discontinued was higher in patients who had no AEs compared to patients who experienced AEs after discontinuation (30.5 mg [range 10 mg to 50 mg] versus 20.3 mg [range 10 mg to 50 mg]).

Out of the 21 patients who were reported with AEs after discontinuation 38.1% (8/21) had one or more CTCAE grade 1 or 2 AE and no Grade 3 or 4 AEs. One or more CTCAE grade 3 or higher AEs were reported in 52.4% (11/21) patients; out of these 11 patients, 2 patients died. Both patients discontinued ruxolitinib due to an AE. In both patients the first AE started on the first day after discontinuation and the patients died within a week after discontinuing treatment: [one subject a] 66 year old male patient died due to hepatic failure, portal vein thrombosis and cerebral hemorrhage; [one subject a] 73 year old male patient died due to multi-organ failure and septic shock assessed as suspected to be related to the study drug by the investigator.

AEs compatible with MF symptoms after treatment discontinuation

To identify AEs which may be compatible with the return of myelofibrosis disease symptoms all terms included in the disease symptoms scoring system Myelofibrosis Symptom Assessment Form (MFSAF) 2.0[44,45] and reported after treatment discontinuation in protocol 352 [were summarised]. Fifteen AE terms with relevance to the MF symptom score were reported in 9 patients (4.3%; 9/21). Median time to onset after discontinuation was 8 days (range 1 to 23 days). Ten AEs were reported as CTCAE Grade 1 or 2, five were reported as CTCAE Grade 3. No CTCAE Grade 4 AEs were reported.

All other AEs (other than MFSAF symptom score related)

Overall 111 AE terms were reported in 20 patients, which represent 95.2% (20/21) of all patients who reported AEs after discontinuation. Preferred terms were grouped to enhance signal detection into the following:

Hematopoietic erythropenia, leukopenia and thrombocytopenia SMQ (broad)

Twenty-three AE reports of anemia, thrombocytopenia or neutropenia were reported in six patients (28.6%; 6/21) after discontinuation of ruxolitinib. The most commonly reported was anaemia and related terms (10 reports). Median time to onset of event after discontinuation was 8 days (range 4 to 18 days). Ten AEs were reported as CTCAE Grade 1 or 2, thirteen were reported as CTCAE Grade 3 or 4 (anaemia, thrombocytopenia, neutropenia).

Gastrointestinal disorders SOC

Fourteen AE reports of gastrointestinal disorders were reported in seven patients (33.3%; 7/21) after discontinuation of ruxolitinib. The three most commonly reported were nausea (5 reports), diarrhoea (3 reports) and vomiting (2 reports). Median time to onset after discontinuation was 11.5 days (range 1 to 26 days). Twelve AEs were reported as CTCAE Grade 1 or 2, two were reported as CTCAE Grade 3 (gastrointestinal telangiectasia and nausea).

Hemodynamic edema, effusions and fluid overload SMQ (broad)

Seven AE reports of edema and related terms were reported in four patients, (19.0%; 4/21) after discontinuation of ruxolitinib. The most commonly reported were peripheral edema and fluid retention. Median time to onset after discontinuation was 21.0 days (range 9 to 28 days). Five AEs were reported as CTCAE Grade 1 or 2, three were reported as CTCAE Grade 3 or higher (fluid retention).

[44]<http://www.proqolid.org/instruments/myelofibrosis_symptom_assessment_form_mfsaf>
[45]Mesa RA, Schwager S, Radia D, Cheville A, Hussein K, Niblack J, Pardanani AD, Steensma DP, Litzow MR, Rivera CE, Camoriano J, Verstovsek S, Sloan J, Harrison C, Kantarjian H, Tefferi A. The Myelofibrosis Symptom ssessment Form (MFSAF): An evidence-based brief inventory to measure quality of life and symptomatic response to treatment in myelofibrosis. Leuk Res. 2009 Sep;33(9):1199-203

Infection and infestations SOC

Six AE reports of infections were reported in five patients (23.8%; 5/21) after discontinuation of ruxolitinib. The most commonly reported were respiratory tract infections (6 reports). Median time to onset after discontinuation was 9.0 days (range 1 to 24 days). Three AEs were reported as CTCAE Grade 1 or 2, three were reported as CTCAE Grade 3 or higher (septic shock and respiratory tract infection).

Other AEs

The remaining 61 AE terms were reviewed showing a broad variety of signs symptoms and conditions and no particular pattern was identified.

MFSAF symptom score and treatment interruption due to AEs

In the placebo-controlled Study 351, disease symptoms were assessed prospectively using the validated disease-specific MFSAF 2.0 instrument as a secondary efficacy endpoint (Mesa 2009). The MFSAF included the assessment of myelofibrosis symptoms such as fatigue, bone pain, fever pruritus, night sweats, symptomatic splenomegaly and weight loss by the patient. The effect of withdrawal of ruxolitinib on total symptom scores in the 2 weeks preceding and following the first dose interruption was analysed. Beginning at the time of dose interruption, median percent change from Baseline in total symptom score gradually returns to Baseline levels over approximately 7 days. Mean scores after withdrawal slightly exceeded the Baseline score, as a result of 1 subject who had a large increase on Day 6 after discontinuation which improved starting on Day 7 but reported no new or worsening adverse events at that time.[46]

SAEs after treatment discontinuation

SAEs after discontinuation of ruxolitinib reported up to 1 September 2011 in MF studies 251, 351 and 352 were reviewed. Overall 301 SAEs were reported for 55 patients. Out of these 55 patients 27.3% (15/55) reported SAE compatible with MF related symptoms (Mesa 2009). These reports were consistent with disease progression. Infections were reported in a further 27.3% (15/55) of patients. A further 10.9% of patients (6/55) reported anaemia, thrombocytopenia or neutropenia.

Deaths occurring after withdrawal or discontinuation

Ten deaths occurred due to disease progression: Ruxolitnib groups: 7/697 (1.0%) and comparator groups: 3/224 (1.3%). In addition, there was one death occurring in the comparator group after crossover to ruxolitinib.

Conclusions

In summary, AE and SAE data after treatment discontinuation were examined as well as MF symptom scores during dose interruption. The available evidence from the Phase III Study 351 suggests that myelofibrosis symptoms may return within approximately a week after treatment discontinuation. The general pattern, frequency and severity of AEs reported after treatment discontinuation were often consistent with those expected for untreated MF patients. Other frequent conditions reported after discontinuation of treatment were infections and cytopenias. No relationship between last dose level and AEs after discontinuation was observed. Thus upon careful examination of AE data and disease symptom scores after treatment discontinuation in MF trials the hypothesis of withdrawal syndrome after ruxolitinib treatment discontinuation was not confirmed. However, myelofibrosis related symptoms do appear to return upon discontinuation of ruxolitinib.

Comments: The sponsor's response is satisfactory. The data suggest that the symptoms of myelofibrosis rapidly return when ruxolitinib is discontinued.

[46]Verstovsek S, Kantarjian H, Mesa RA, et al. Safety and Efficacy of INCB018424, a JAK1 and JAK2 Inhibitor, in Myelofibrosis. *N Engl J Med*. 2010;363:1117-27.

Question 7 (Indication)

The evaluator recommended that the indication be amended to read "the treatment of disease-related splenomegaly or symptoms in patients with high-risk or intermediate-risk level-2 primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis". The benefits of treatment observed in the Phase III studies in patients with MF relate to reduction in splenomegaly and improvement in symptoms rather than increased PFS and/or OS. Consequently, the evaluator considered that the indication should specifically include reference to disease disease-related splenomegaly or symptoms. The two Phase III studies included patients with high-risk or intermediate-risk level-2 MF and there are no data comparing the efficacy or safety of ruxolitinib with controls in patients with less severe disease. Consequently, the evaluator considered that the indication should specifically refer to patients with high-risk or intermediate- risk level-2 MF.

Sponsor's response:

The key benefits (and hence the goals) of therapy with ruxolitinib are converging to the control of splenomegaly, disease-related symptoms and prolongation of life. These potential benefits extend generally to patients with MF, irrespective of their prognostic risk status.

Patients across all risk categories may experience disabling MF associated symptoms. As shown in the Table 16, unpublished data available from the IPSS analysis (Cervantes 2011[47], data on file) indicate that splenomegaly was present across all risk groups including 54% of low risk patients. In addition, although by definition low risk patients cannot have night sweats, fever or 10% unintended weight loss over a 6 month period, they may have pruritus and bone/muscle pain and would be expected to have symptoms of splenomegaly if present, all of which have been shown to improve upon treatment with ruxolitinib. Further, patients with low risk MF by definition have Hgb > 10.0 g/dL, indicating preserved bone marrow function and therefore are likely to tolerate ruxolitinib as well or better than intermediate and high risk patients.

Table 16: IPSS Analysis.

	IPSS risk group			
	Low	**Intermediate-1**	**Intermediate-2**	**High**
Frequency of constitutional symptoms at presentation (26% of patients[a])	0%*	14%	30%	67%
Frequency of palpable splenomegaly at presentation (64% of patients)	54%	62%	70%	68%

[a] Frequency of acquisition of constitutional symptoms during the evolution (following diagnosis as per DIPSS): 14% of patients acquired this factor during follow-up and the actuarial frequency of acquisition of constitutional symptoms was 22% at 15 years, therefore, 26% + 14% = 40% (actual) or 26% + 22% = **48% (actuarial)**

* By definition, the low-risk group has 0%, since constitutional symptoms are a poor prognosis factor and patients in this group have no poor prognostic factor

Source: Unpublished data from the IPSS database (Cervantes 2011, data on file)

[47]Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood. 2009;113:2895-2901.

Since the first publication of prognostic criteria for MF, known as the Lille criteria[48], several additional prognostic classifications have been published including the International Working Group Classification which is known as IPSS 2009[49], DIPSS 2010[50] and DIPSS-Plus 2011[51] creating substantial confusion in the field. These scoring systems have been used primarily by expert physicians participating in clinical trials; understanding in the broader community is limited and their use in every day clinical practice is mostly limited to helping physicians and patients to make calculated judgments together regarding when to potentially pursue alloSCT. It must also be noted that most prescribers manage only a few patients with this orphan disease a year. They make decisions based on what can be done to safely and effectively treat the individual patient and are unlikely to focus on these evolving and increasingly complex scoring systems.

In summary, restricting the indication to intermediate-2 and high risk patients would deny effective therapy to a group of patients who would be expected to benefit from the drug and should be at lower risk of cytopenias. Additionally, this restriction will cause unnecessary confusion to physicians treating the disease.

Data from a recent publication demonstrated that patients with intermediate-1 disease experience a comparable benefit from ruxolitinib therapy to patients with intermediate-2 and high-risk disease.[52] This reasoning is supported by Australian clinical physicians.

Comment: No pivotal data has been presented indicating that the benefits of ruxolitinb extend to patients with MF outside those treated in the two clinical studies (that is, patients with high risk or intermediate-2 risk disease). In Study 351, there was 1 (0.6%) patient in the ruxolitinib group (n=155) and 1 (0.6%) patient in the placebo group (n=154) with IWG (IPSS) risk category less than intermediate-2 or unknown, and no patients in Study 352 in either the ruxolitinib group (n=146) or the BAT group (n=73) in these categories. Nevertheless, the sponsor states that the potential benefits of treatment with ruxolitinib generally extend to patients with MF, irrespective of their prognostic risk factors.

The sponsor comments that MF classification systems (such as the IPSS), *"have been used primarily by expert physicians participating in clinical trials [and that] understanding in the broader community is limited and their use in every day clinical practice is mostly limited to helping physicians and patients to make calculated judgments together regarding when to potentially pursue alloSCT"*. The submission from the Haematology Society of Australia & New Zealand (HSANZ) notes that the IPSS for MF *"was developed primarily to guide decisions about allogenic transplantation"* and that the inclusion criteria of the COMFORT studies defined a small subset of MF patients with adequate haematopoiesis and intermediate-2 to high risk disease" which was appropriate to *"ensure adequate statistical power to demonstrate study endpoints, but does not indicate that patients outside those criteria will not benefit."*

[48]Dupriez B, Morel P., Demory J.L. (1996). Prognostic factors in agnogenic myeloid metaplasia: a report on 195 cases with a new scoring system. Blood 88:1013-1018.
[49]Cervantes F., Dupriez B., Pereira A *et al* (2009). New prognostic scoring system for primary myelofibrosis based on a study of the Internation Working Group for Myelofibrosis Research and Treatment. Blood. 113:2895-2901.
[50] Passamonti F., Cervantes F., Vannucchi A. M., et al. (2010). Dynamic International Prognostic Scoring System (DIPSS) predicts progression to acute myeloid leukemia in primary myelofibrosis. Blood October 14, 2010 vol. 116 no. 15 2857-2858
[51]*Gangat N., Caramazza D., Vaidya r. et al.(2011)* DIPSS Plus: A Refined Dynamic International Prognostic Scoring System for Primary Myelofibrosis That Incorporates Prognostic Information From Karyotype, Platelet Count, and Transfusion Status. *J Clin Oncol* 29:392-397
[52]Barosi, G, et al. An individual patient supply program for ruxolitinib for the treatment of patients with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis. 2012 ASH Poster #2844

The HASNZ submission expresses concern that patients with intermediate-1 risk (about 29%) would be excluded from treatment if the indication were to be restricted to patients with intermediate-2 risk or high-risk disease. In addition, the HASNZ is concerned that patients younger than 65 with equivalent symptoms to patients older than 65 years will be ineligible for treatment (that is, intermediate-risk 1 versus intermediate-risk 2, respectively). However, based on IPSS risk group categories median survival time is notably longer in patients with intermediate-1 risk disease compared with intermediate-2 risk disease (see Table 17 below). Furthermore, there are no data on the risk-benefit balance for ruxolitinib treatment of intermediate-1 risk patients.

Table 17: Cervantes *et al*,., 2009 - Definition, frequency, and survival of the risk groups of the prognostic scoring system of primary myelofibrosis.

Risk Group	No. of factors	Proportion of patients	Median survival (months: 95%CI)	Proportion of deaths
Low	0	22%	135 (117, 181)	32%
Intermediate-1	1	29%	95 (79, 114)	50%
Intermediate-2	2	28%	48 (43, 59)	71%
High	> 3	21%	27 (23, 31)	73%

Source: Cervantes *et al*., 2009.

The HASNZ states that "*logical selection of patients for treatment with ruxolitinb on the degree of symptom burden*". However, there are no pivotal data on treatment of patients with ruxolitinib based only on symptom burden. Constitutional symptoms are a component of the IPSS scoring system included with four other risk factors considered to have an effect on survival.[53] The risk factors contributing to the IPSS are summarised below in Table 18.

Table 18: Cervantes *et al*,., 2009. Risk factors at presentation of primary myelofibrosis selected at the stepwise Cox regression model for significant association with shorter survival*.

Risk Factor	Frequency in the series	Hazard Ratio	z test	p value
Age > 65	44.6 %	1.96 (1.16, 2.36)	6.84	< 0.001
Constitutional symptoms	26.4%	1.97 (1.62, 2.40)	6.77	< 0.001
Hb < 10 g/dL	35.2%	2.89 (2.46, 3.61)	11.24	< 0.001
WBC count > 25 x 10^9/L	9.6%	2.40 (1.83, 3.14)	6.37	< 0. 001

[53] Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood. 2009;113:2895-2901.

Risk Factor	Frequency in the series	Hazard Ratio	z test	p value
Blood blasts > 1%	36.2%	1.80 (1.50, 2.17)	6.29	< 0.001

* In 1001 patients with the 5 variables available.

The sponsor and the HSANZ refer to data from a recent publication[52] showing that patients with intemediate-1 risk disease experience a comparable benefit from ruxolitinib therapy to patients with intermediate-2 risk and high-risk disease. However, it should be noted that the publication referred to is an abstract of data presented at the 2012 meeting of the American Society of Hematology (ASH). The abstract reports the results of a retrospective observational analysis on the use of ruxolitinib provided through an individual patient supply program (IPSP) outside the US. The analysis included data on 1240 patients for whom access to ruxolitinib was approved. Of the 1240 patients, 460 (37%) were classified as high-risk, 418 (34%) as intermediate-2, 234 (19%) as intemediate-1, and 42 (3%) as low-risk. The results for change in spleen size and change in constitutional symptoms based on risk score were available on 247 and 203 patients from the total patient population, respectively. The median spleen length of the total population was 16 cm (range: 0-40 cm). The results for changes in spleen size and constitutional symptoms based on MF risk score are summarised below in Table 19. There were no data on the percentage decrease in spleen size. The observational data in a limited number of patients with intermediate-1 risk disease suggest that treatment with ruxolitinib was associated with an improvement in spleen size and constitutional symptoms that were similar to those observed for patients with high-risk and intermediate-2 risk disease. The number of patients with low-risk disease with response data for both spleen size and constitutional symptoms are considered to be too small to allow meaningful conclusions to be drawn.

Table 19: Barosi *et al*., 2012 - Response in spleen size and constitutional symptoms based on MF risk score (IPSS).

Response				
Spleen Size				
Decreased	79 (80.6%)	74 (87.1%)	32 (74.4%)	4 (57.1%)
Unchanged	16 (16.3%)	9 (10.6%)	8 (18.6%)	3 (42.9%)
Increased	3 (3.0%)	1 (1.2%)	3 (7.0%)	0
Total	98	85	43	7
Constitutional Symptoms				
Decreased	53 (69.7%)	56 (81.2%)	26 (70.2%)	4 (57.1%)
Unchanged	20 (26.3%)	13 (18.8%)	11 (29.8%)	3 (42.9%)
Increased	3 (3.9%)	0	0	0
Total	76	69	37	7

Source: Barosi *et al*., 2012.

In summary, the sponsor commented on the roles of classification systems, such as the IPSS, in contributing to the understanding of MF and speculated that these systems might

have little role in the decisions physicians make when treating patients with MF. However, these observations are considered to be of tangential relevance to the deliberations concerning the content of the indication. The Barosi *et al.,* 2012[52] abstract is considered to be the only relevant additional evaluable data submitted to support the sponsor's proposed indication. The data from this abstract are considered to be promising and provide limited support for the treatment of patients with intermediate-1 risk MF. However, the data are derived from a retrospective observational study rather than from a prospective, Phase III, randomised, double-blind, placebo-controlled study. Furthermore, the published data are from an abstract of a presentation to the ASH Meeting in 2012 and not from a peer-reviewed journal article. No pivotal data have been presented that allows a benefit-risk balance assessment to be made for ruxolitinib for the treatment of intermediate-1 or low risk MF. The data from Barosi *et al,* 2012[52] are considered to be exploratory and suggest that the efficacy and safety of ruxolitinib should be investigated in a Phase III trial of similar design to Study 351 in patients with intermediate-1 risk MF and possibly low-risk MF.

Overall, the additional information provided in the sponsor's response to TGA's request for information was not considered to be sufficient to change the indication from that recommended in the round one clinical evaluation report, namely, "*the treatment of disease-related splenomegaly or symptoms in patients with high-risk or intermediate-risk level 2 primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis".*

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of ruxolitinib for *"the treatment of disease-related splenomegaly or symptoms in patients with high-risk or intermediate-risk level 2 primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis"* were unchanged from those identified in the first round evaluation report.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of ruxolitinib for *"the treatment of disease-related splenomegaly or symptoms in patients with high-risk or intermediate-risk level 2 primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis"* were unchanged from those identified in the first round evaluation report.

Second round assessment of benefit-risk balance

The benefit-risk balance of ruxolitinib was considered to be favourable for *"the treatment of disease-related splenomegaly or symptoms in patients with high-risk or intermediate-risk level 2 primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis"*.

Second round recommendation regarding authorisation

The evaluator recommended that ruxolitinib be approved for *"the treatment of disease-related splenomegaly or symptoms in patients with high-risk or intermediate-risk level 2 primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis"*.

Indications:

The indication should be

"Jakavi® is indicated for the treatment of disease-related splenomegaly or symptoms in patients with high-risk or intermediate-risk level 2 primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis".

The reasons for this recommendation have been provided in this second round clinical evaluation report.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown in Table 20.

Table 20. Ongoing Safety Concerns provided by the sponsor in their Australian RMP submission.

Important identified risks	Thrombocytopenia Erythropenia (Anemia) Neutropenia Urinary tract infection Herpes zoster Use in patients with hepatic impairment Use in patients with severe renal failure or end stage renal failure requiring hemodialysis Raised transaminases
Important potential risks	Infections (excluding UTI and Herpes zoster) Bleeding (Hemorrhage) Withdrawal syndrome with return of MF symptoms
Important identified interactions	Use with strong CYP3A4 inhibitors
Important missing information	MF patients with a platelet count below 100,000 at baseline Pediatric patients

The following table (Table 21) summarises the OPR's evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the second round OPR evaluation of the sponsor's responses.

Table 21. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these include a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.		
2. To align the ongoing safety concerns with the European market, the list of ongoing safety concerns should be revised to include the following: increased systolic blood pressure, developmental toxicity, MF patients with an ANC <500/µL, non-Caucasian patients, risks in off-label use, long-term safety data (including secondary malignancies), disease severity different from those in CTs, elderly patients over 75 years of age, sub-populations with genetic polymorphisms, and effect on bone marrow fibrosis.	*'The Jakavi RMP has been updated to version 2 release date 02 May 2012. Each of the ongoing safety concerns raised by the TGA are included in this updated version.'*	This was considered acceptable.
3. The following potential interactions should be included: haematopoietic growth factors or cytoreductive therapies, CYP3A4 inducers, orally administered CYP3A4 substrates, and oral contraceptives.	*'The Jakavi RMP has been updated to version 2 release date 02 May 2012. Each of the ongoing safety concerns raised by the TGA are included in this updated version.'*	This was considered acceptable.
4. Infections and bleeding should be re-assigned as	*'The Jakavi RMP has been updated to version 2 release date 02 May 2012. Each of the ongoing safety concerns*	This was considered

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
important identified risks.	*raised by the TGA are included in this updated version.'*	acceptable.
5. In regard to additional pharmacovigilance activities, the sponsor should: a. align Australia with the activities planned or conducted in the European Union; and b. provide study protocols or synopses for studies mentioned in the First Round Evaluation of the RMP (including dates for estimated planned submission of final data).	*'The Jakavi RMP has been updated to version 2 release date 02 May 2012. This RMP includes the global pharmacovigilance plan that includes the studies listed in the TGA's evaluation of the Jakavi RMP version 1. Therefore, these studies are applicable to the Australian registration of Jakavi.'*	This was considered acceptable. Study protocols, synopsis and/or reports have been provided.
6. In the 'Use in Lactation' section, the sponsor should include a statement that Jakavi must not be used in breastfeeding and that risks to the breast-fed child cannot be excluded.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.
7. In the 'Interaction with other medicines' section, the sponsor should include examples for each group of medications discussed to assist clinicians referring to this section.		
8. In the 'Interaction with other medicines' section, the PI should include examples of strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) to assist clinicians referring to this section.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
9. In the 'Interaction with other medicines' section, the PI should include examples of mild to moderate CYP3A4 inhibitors (for example, diltiazem and erythromycin) to assist clinicians referring to this section.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.
10. In the 'Interaction with other medicines' section, the PI should include examples of CYP3A4 inducers (e.g. dexamethasone, carbamazepine, phenytoin, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) to assist clinicians referring to this section.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.
11. In the 'Interaction with other medicines' section, the PI should include examples of dual CYP2C9 and CYP3A4 inhibitors to assist clinicians referring to this section.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.
12. In the 'Interaction with other medicines' section, the PI should include examples of CYP3A4 substrates to assist clinicians referring to this section.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.
13. In the 'Interaction with other medicines' section, the PI should include examples of drugs that inhibit P-glycoprotein (such as tacrolimus, cyclosporine, diltiazem, amiodarone, carvedilol, nifedipine, verapamil, ketoconazole, itraconazole, quinidine, ritonavir, saquinavir, nelfinavir, ranolazine valspodar, and isradipine) to assist clinicians referring to this section.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.
14. In the 'Interaction with other medicines' section, the PI should include examples of drugs that inhibit P-	[recommendation repeated accidentally]	[recommendation

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
glycoprotein (such as tacrolimus, cyclosporine, diltiazem, amiodarone, carvedilol, nifedipine, verapamil, ketoconazole, itraconazole, quinidine, ritonavir, saquinavir, nelfinavir, ranolazine valspodar, and isradipine) to assist clinicians referring to this section.		repeated accidentally]
15. In the 'Interaction with other medicines' section, the PI should include examples of substances transported by P-glycoprotein or other transporters to assist clinicians referring to this section.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.
16. In the 'Interaction with other medicines' section, the PI should include examples of cytoreductive therapies to assist clinicians referring to this section.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.
17. In the 'Adverse events' section, the sponsor should include increased systolic blood pressure.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.
18. In the 'Dosage and administration' section, the sponsor should include more detailed dosing recommendations for patients with thrombocytopaenia to assist prescribers with dose adjustments.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.
19. In the 'Dosage and administration' section, the sponsor should add information on dose modification based on response.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.
20. In the 'Dosage and administration' section, the sponsor should add that Jakavi should be avoided in patients with	Appropriate PI changes were made by the sponsor.	This was considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
moderate to severe renal impairment or hepatic impairment where platelet counts are less than 100 x 10^9/L.		
21. In the 'Dosage and administration' section, the sponsor should add information on method of administration with or without food and by nasogastric tube, and information on gradual tapering when discontinuing the drug.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.
22. The sponsor should change the statement 'Treatment may be continued as long as the benefit: risk remains positive' to 'Treatment may be continued as long as the benefit-risk ratio remains positive'.	Appropriate PI changes were made by the sponsor.	This was considered acceptable.

Summary of recommendations

It was considered that the sponsor's response to the TGA request for information has adequately addressed all of the issues identified in the RMP evaluation report.

Suggested wording for conditions of registration

· RMP

Implement EU-RMP Version 2 (dated 02 May 2012, DLP 01/03/2011 (INCB018424-351 and INC424A2352), DLP 31 December 2009 (INCB 18424-251)) and any future updates as a condition of registration.

· Provide Periodic Safety Update Reports (PSURs) in line with the European Union reference dates and frequency until the period covered by such reports is not less than three years from the date of this letter. The reports are to meet the requirements of the ICH E2C (R2) guideline on Periodic Benefit-Risk Evaluation Reports and Module VII of the EMA Guideline on Good Pharmacovigilance Practices relating to PSURs. Submission of the report must be within 70 days of the data lock point for PSURs covering intervals up to and including 12 months and within 90 days of the data lock point for PSURs covering intervals in excess of 12 months. The submission may consist of two PSURs each covering six months.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Ruxolitinib was well characterised and stable. The proposed 5 mg tablet was used in the Phase III trials. The proposed 15 mg and 20 mg tablets are direct scales of the 5 mg. The tablets initially dissolve rapidly, but complete dissolution is slow. Most (≥ 95%) of the administered dose was absorbed; thus, gastrointestinal permeability was high. The sponsor claimed the product is BCS1 and entitled to a biowaiver. On this basis, an absolute bioavailability study was not performed.

The Pharmaceutical Subcommittee supported the BCS1 classification and biowaiver at the meeting on 21 January 2013. Strangely slow final dissolution was an artefact.

The sponsor satisfactorily addressed all questions raised.

The evaluator supported registration.

Nonclinical

The toxicity of ruxolitinib was predictable from its pharmacology. The major toxic effects in the animal studies (mice, rats and dogs) were immunosuppression and myelosuppression. Opportunistic infections were seen in dogs in a 12 month study. No malignancy was seen in a 6 month carcinogenicity study in mice; however, malignant effects are possible with longer exposure.

Ruxolitinib did not affect fertility in rats. However, it crossed the placenta and was toxic to the embryos and fetuses of rats and rabbits. Pregnancy Category C is recommended.

The evaluator supported registration.

Clinical

Pharmacokinetics

- Absorption of ruxolitinib after oral administration is rapid (T_{max} about 1 h) and almost complete (≥ 95%). The pharmacokinetics are linear over the dose range 5 to 200 mg. There is minimal accumulation of ruxolitinib with twice daily dosing. The steady state apparent volume of distribution is about 60 L in myelofibrosis patients. Ruxolitinib is predominantly eliminated through metabolism with mean elimination half-life of 3 h. The metabolites contribute about 18% to activity.
- Ruxolitinib exposure based on $AUC_{0-¥}$ is increased in all degrees of hepatic impairment (based on data from eight subjects each with normal, mild, moderate and severe impairment). There was considerable variability. Starting dose reduction of 50% is recommended.
- Ruxolitinib exposure is also increased in renal impairment again with considerable variability (based on data from eight subjects each with normal, mild, moderate and severe impairment and eight subjects each with end-stage renal disease four dosed before and four dosed after haemodialysis). The pharmacological activity adjusted AUC of ruxolitinib plus metabolites, expressed as a percentage of parent AUC, is 117%, 123%, 134% and 153% in patients with normal renal function and mild, moderate and severe renal impairment respectively. In patients with end-stage renal disease dosed before and after haemodialysis, the pharmacological activity adjusted AUC of ruxolitinib plus metabolites, expressed as a percentage of parent AUC, is 192% and 212% respectively. Therefore, the contribution of ruxolitinib metabolites increases with increasing renal impairment. Ruxolitinib starting dose reduction of 50% is recommended in patients with moderate to severe renal impairment (creatinine clearance < 50 mL/min) and approximately 200% in patients on haemodialysis (based on once daily dosing on dialysis days only and three dialyses per week).
- Concomitant ketoconazole (a strong CYP3A4 inhibitor) significantly increased ruxolitinib exposure by a mean 91%. It is recommended that the ruxolitinib dose be reduced by 50% when co-administered with strong CYP3A4 inhibitors. Concomitant erythromycin (a moderate CYP3A4 inhibitor) significantly increased ruxolitinib exposure by a mean 27%. No dose reduction but close monitoring is recommended when ruxolitinib is co-administered with moderate CYP3A4 inhibitors.
- Concomitant rifampin (a strong CYP3A4 inducer) significantly decreased ruxolitinib exposure by a mean 71%. However, the loss of activity of ruxolitinib was partially offset by activity from increased ruxolitinib metabolites. No dose increase but close monitoring is recommended when ruxolitinib is co-administered with CYP3A4 inducers.

Pharmacodynamics

- Ruxolitinib inhibited IL-6 stimulated STAT3 phosphorylation which is a rationale for its clinical use. Ruxolitinib also had effects on inflammatory and other markers consistent with its postulated mechanism of action.
- PK/PD analyses showed an exposure-response relationship between ruxolitinib and decreases in spleen volume and symptom score (efficacy) and changes in platelet count, absolute neutrophil count and haemoglobin concentration (safety).
- There was no evidence of a clinically significant prolongation of the QTcF interval in a thorough QT/QTc study in healthy subjects.

- The ruxolitinib dose for the pivotal trials was based on the dose escalation Study #251. There was considerable variability in clinical response and sensitivity to thrombocytopenia. It was concluded that the optimal dose for an individual patient was between 10 mg bd and 25 mg bd. The recommended starting doses were 15 mg bd if the baseline platelet count was 100-200 x 10^9/L and 20 mg bd if the baseline platelet count was > 200 x 10^9/L. The dose was then titrated up to 25 mg bd depending on a balance between efficacy and safety.

Efficacy

- Efficacy was assessed in two multinational randomised controlled trials, #351 and #352, also referred to as COMFORT-I and COMFORT-II respectively (published). Trial #351 was the pivotal trial and was double-blind and placebo-controlled. Trial #352 was open-label, randomisation was 2:1 and the control group was investigator-determined best available therapy (BAT).
- Subjects had intermediate level-2 or high risk primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythaemia myelofibrosis according to WHO (2008) and International Working Group (IWG) criteria and palpable splenomegaly at least 5 cm below the costal margin. About half the subjects had PMF, one-third PPV-MF and the remainder PET-MF. A baseline platelet count > 100 x 10^9/L was required for trial entry. The median age of subjects was 68 years, range 40-91 in Study 351 and 66 years, range 35-85 in Study 352. Slightly more subjects were male.
- The starting dose of ruxolitinib was 15-20 mg bd based on platelet count (see *Pharmacodynamics*). The dose was then titrated based on efficacy and safety to a maximum of 25 mg bd if the platelet count was > 125 x 10^9/L, 20 mg bd for platelet count 100 to ≤ 125 x 10^9/L, 10 mg bd for platelet count 75 to ≤ 100 x 10^9/L and 5 mg bd for platelet count 50 to ≤75 x 10^9/L. If the platelet count fell below 50 x 10^9/L, the ruxolitinib dose was withheld. The median duration of ruxolitinib treatment was approximately 8 months in Study 351 and 12 months in Study 352.
- The primary efficacy endpoint was the percentage of subjects achieving ≥ 35% reduction in spleen volume measured by MRI or CT at Week 24 Study 351) or Week 48 (Study 352). This endpoint was considered acceptable since about 90% of patients with MF have splenomegaly and this order of reduction in spleen volume is likely to result in reduced splenomegaly symptoms.
- Significantly more subjects treated with ruxolitinib than control achieved ≥ 35% reduction in spleen volume in both trials (Tables 22-23). The reduction in spleen volume was maintained for a median 48.1 weeks in Study 351 and 48 weeks in Study 352. It was not clear from the subgroup analyses if ruxolitinib reduced spleen volume to a similar extent regardless of JAK2 V617F mutation status or myelofibrosis subtype.
- In Study 351, ruxolitinib also significantly reduced symptoms. Withdrawal of ruxolitinib led to a return to baseline symptom score within a week. Reduction in symptoms was not assessed in Study 352. Quality of life (EORTC QLQ-C30) was an exploratory endpoint in both trials with a significant increase (more than 10 points difference from control) being observed in Study 351.

Table 22: Trial #351 Results – Intent-to-Treat Population

	Ruxolitinib n=155	Placebo n=154	Difference [95% CI]
Duration of Treatment median (range) mths	*7.8 (2.6-13.6)*	*7.1 (1.1-13.4)*	-
% Subjects with ≥ 35% reduction in spleen volume at Week 24	41.9%	0.7%	41.3% [33.2%, 49.2%][1] p<0.0001[2]
Duration of reduction in spleen volume *median weeks*[3]	48.1	Not applicable	-
% Subjects with ≥ 50% reduction in symptom score[4] at Week 24	45.9%	5.3%	40.6% [?, ?] p<0.0001[5]
EORTC QLQ-C30 quality-of-life score – mean change at Week 24	+12.3	-3.4	15.7[6] [?, ?]

[1] Newcombe-Wilson method without continuity correction – *CE R1*, p.68. [2] Fisher's exact test.[3] Kaplan-Meier estimate in subjects with ≥ 35% reduction in spleen volume at week 24. [4] Night sweats, itch, abdominal discomfort, pain under left ribs, feeling of fullness, muscle bone pain scored 0-10 daily from Week -1 to Week 24 using Modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 developed by the sponsor and agreed with the US FDA. [5] χ^2 test. [6] Difference < 10 not clinically significant. *? Sponsor requested to provide data in Pre-ACPM Response.*

Table 23: Trial #352 Results – Intent-to-Treat Population

	Ruxolitinib n=144	BAT n=72	Difference [95% CI]
Duration of Treatment median (range) months	*11.8 (0.5-17.3)*	*10.4 (0.03-15.4)*	-
% Subjects with ≥ 35% reduction in spleen volume *at Week 48*	28.5%	0.0%	28.5% [?, ?] p<0.0001[1]
% Subjects with ≥ 35% reduction in spleen volume *at Week 24*	31.9%	0.0%	31.9% [?, ?] p<0.0001[1]
Duration of reduction in spleen volume *median weeks*[3]	48	Not assessable	-
EORTC QLQ-C30 quality-of-life	?	?	?[4]

	Ruxolitinib n=144	BAT n=72	Difference [95% CI]
score – mean change at Week 48			[?, ?] not sig
EORTC QLQ-C30 quality-of-life score – mean change at Week 24	?	?	?[4] [?, ?]

[1] Cochran-Mantel Haenszel exact test. [2] Kaplan-Meier estimate that spleen volume will not increase more than 25% above nadir in responders. [3] Kaplan-Meier estimate in subjects with ≥ 35% reduction in spleen volume at any time during study. [4] Difference < 10 not clinically significant. *? Sponsor requested to provide data in Pre-ACPM Response.*

- In Study 351, 24% of placebo subjects crossed over to ruxolitinib. If subjects crossed over before Week 24 (10% of subjects), they were considered not to have achieved ≥ 35% reduction in spleen volume or ≥ 50% reduction in symptom score in the efficacy assessment.
- Overall survival data were supportive despite crossover from control to ruxolitinib. In Study 351, at median follow-up 12 months, there were 13 deaths (8%) with ruxolitinib and 24 (16%) with placebo. At median 26 months follow- up[54], there were 27 deaths (17%) with ruxolitinib and 41 (27%) with placebo. In Study 352, at median follow-up 14 months, there were 13 deaths (9%) with ruxolitinib and 5 (7%) with BAT (EU product information). At median 26 months follow-up[55], there were 20 deaths (14%) with ruxolitinib and 16 (22%) with BAT.
- To support extending the indication to low to intermediate-1 risk patients, a retrospective observational analysis was provided.[56] Ruxolitinib appeared to reduce spleen size and constitutional symptoms to a similar extent in intermediate-1 risk patients (n=43) as intermediate-2 and high risk patients (n=183). There were too few low risk patients (n=7) for meaningful analysis. There was no benefit-risk assessment. Overall, the data in intermediate-1 and low risk patients were considered exploratory.
- To support extending the treatment population to patients with baseline platelet counts of 50-100 x 10^9/L, the sponsor presented two abstracts from ASH 2012 reporting preliminary data from ongoing trials.[57,58] The starting dose of ruxolitinib was 5 mg bd in both trials. The Talpaz trial had more experience with 19 subjects completing 24 weeks of ruxolitinib treatment. The efficacy of ruxolitinib appeared comparable to that in the pivotal Study 351. Although the data from these trials was promising, it was considered too limited for meaningful assessment. The sponsor also referred to data in the pivotal and supportive trials in which patients developed

[54]Verstovsek, S, et al. Long-term outcome of ruxolitinib treatment in patients with myelofibrosis: Durable reductions in spleen volume, improvements in quality of life, and overall survival advantage in COMFORT-I. Abstract, American Society of Haematology (ASH) 2012

[55] Cervantes, F, et al. Long-term safety, efficacy, and survival findings from COMFORT-II, a Phase III study comparing ruxolitinib with best available therapy for the treatment of myelofibrosis. Abstract, American Society of Haematology (ASH) 2012

[56]Barosi, G, et al. An individual patient supply program for ruxolitinib for the treatment of patients with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis. 2012 ASH Poster #2844

[57]Talpaz, M, et al. Efficacy, hematologic effects, and dose of ruxolitinib in myelofibrosis patients with low starting platelet counts (50–100 x 10^9/L): A comparison to patients with normal or high starting platelet counts. 2012 ASH Oral Talpaz Abstract 176.

[58]Harrison, C, et al. *EXPAND:* a Phase 1b, open-label, dose-finding study of ruxolitinib in patients with myelofibrosis and baseline platelet counts between 50 × 10^9/L and 99 × 10^9/L. 2012 ASH Oral Harrison. Abstract 177.

platelet counts < 100 x 10^9/L after receiving ruxolitinib; however, this data could not be extrapolated to patients with platelet counts < 100 x 10^9/L at baseline before receiving ruxolitinib.

Safety

- The primary safety data is from Studies 351 and 352 (n=310 ruxolitinib subjects). The median ruxolitinib dose was 30 mg/day (range 7, 49) and the median duration of treatment with ruxolitinib 9.6 months (range 0.5, 17.3). Only 74 subjects were exposed to ruxolitinib for ≥ 12 months. The primary safety data was supported by a summary of safety from six trials including Studies 351 and 352 (n=617 ruxolitinib subjects). In this summary, there were 252 subjects exposed to ruxolitinib for ≥ 12 months.
- In Studies 351 and 352, common adverse events with a notably higher incidence with ruxolitinib than control included (ruxolitinib versus placebo; ruxolitinib versus BAT): thrombocytopenia (34% versus 9%; 45% versus 10%), anaemia (31% versus 14%; 41% versus 12%), headache (15% versus 5%; 10% versus 4%), pyrexia (11% versus 7%; 14% versus 10%), dizziness (15% versus 9%; 8% versus 6%) and contusion (14% versus 5%; 2% versus 1%).
- In Studies 351 and 352, common severe (Grade 3-4) adverse events with a notably higher incidence with ruxolitinib than control included (ruxolitinib versus placebo; ruxolitinib versus BAT): thrombocytopenia (8% versus 2%; 8% versus 4%) and anaemia (10% versus 5%; 11% versus 3%).
- The incidences of serious adverse events, deaths and adverse events leading to treatment discontinuation were similar for ruxolitinib and control. Adverse events requiring dose interruption or reduction were notably more frequent with ruxolitinib than control (ruxolitinib 51% versus placebo 26%; ruxolitinib 63% versus BAT 15%. Most of the difference was accounted for by dose interruption or reduction for thrombocytopenia.
- During the evaluation, the sponsor advised TGA of a potentially emerging safety issue associated with ruxolitinib, four cases of progressive multifocal leucoencephalopathy (PML).

The evaluator recommended restricting the indication as follows based on the population in the clinical trials:

"Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in patients with high-risk or intermediate-risk level-2 primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis".

The evaluator also recommended restricting ruxolitinib treatment to patients with platelet count ≥100 x 10^9/L and reducing the starting dose in moderate to severe renal impairment as in the USA.

Risk management plan

The sponsor satisfactorily addressed the issues raised by the RMP evaluator.

The evaluator recommended the Risk Management Plan and Periodic Safety Update Reports as conditions of registration as below:

Risk management plan

Implement European Union Risk Management Plan Version 2 dated 2 May 2012 (data lock points 1 Mar 2011 for trials INCB018424-351 and INC424A2352 and 31 Dec 2009 for trial INCB18424-251) and any future updates agreed with the TGA Office of Product Review.

Periodic safety update reports

Provide Periodic Safety Update Reports (PSURs) in line with the European Union reference dates and frequency until the period covered by such reports is not less than three years from the date of this letter. The reports are to meet the requirements of the ICH E2C (R2) guideline on Periodic Benefit-Risk Evaluation Reports and Module VII of the EMA Guideline on Good Pharmacovigilance Practices relating to PSURs. Submission of the report must be within 70 days of the data lock point for PSURs covering intervals up to and including 12 months and within 90 days of the data lock point for PSURs covering intervals in excess of 12 months. The submission may consist of two PSURs each covering six months.

Risk-benefit analysis

Delegate considerations

The efficacy of ruxolitinib in myelofibrosis was based on two randomised controlled trials one of which was placebo-controlled. The primary endpoint, percentage of subjects achieving ≥ 35% reduction in spleen volume, was unusual. However, it appeared to be durable and correlated with reduced symptoms and improved quality-of-life in the placebo-controlled trial (see *Efficacy* Table 22). Symptoms returned quickly (within one week) on withdrawal of ruxolitinib. It was not clear if ruxolitinib had an impact on the disease process. Overall survival data were supportive despite being confounded by crossover.

The incidence of adverse events and severe adverse events was greater with ruxolitinib than the control group (placebo, best available therapy) in both trials. In particular, there was a higher incidence of thrombocytopenia and anaemia with ruxolitinib (see *Safety* above).

In spite of the higher incidence of adverse events, the benefit-risk balance of ruxolitinib is favourable in the trial population. There are limited other treatment options.

Only high risk and intermediate-2 risk patients were included in the trials. However, if patients are experiencing splenomegaly or symptoms, they are likely to benefit from ruxolitinib regardless of their risk level. Although most low and intermediate-1 risk patients would not have splenomegaly or symptoms, some would and may benefit from ruxolitinib. This was supported by a retrospective observational analysis. However, the benefit-risk balance of ruxolitinib is unclear in low and intermediate-1 risk patients.

Thrombocytopenic patients (platelet count < 100 x 10^9/L) were not included in the trials. The sponsor proposes allowing the use of ruxolitinib at a lower starting dose of ≤ 5 mg bd in patients with platelet count 50-100 x 10^9/L provided hepatic function is normal and renal function is no worse than mildly impaired. Preliminary data from two ongoing trials were presented. The safety of ruxolitinib in thrombocytopenic patients was unclear.

The evaluator recommended a lower ruxolitinib starting dose in patients with moderate to severe renal impairment as in the USA whereas the sponsor requests the lower starting dose only in severe renal impairment. A conservative approach is advisable in view of the limited data and considerable variability in ruxolitinib exposure (see *Pharmacokinetics*).

Ruxolitinib is not specific for mutant JAK2 and in particular JAK2 V617F, the major abnormality in PMF, PPV-MF and PET-MF. It also inhibits wild-type JAK2 and JAK1. It was not clear from the subgroup analyses if ruxolitinib reduced spleen volume to a similar extent regardless of JAK2 V617F mutation or myelofibrosis subtype.

Summary of issues

1. Appropriateness of primary efficacy endpoint in the ruxolitinib trials.
2. Appropriateness of treating intermediate-risk level-1 and low risk patients with ruxolitinib.
3. Initiating ruxolitinib in patients with platelet count < 100 x 10^9/L and recommended starting dose.
4. Starting dose of ruxolitinib in patients with moderate to severe renal impairment.

Advice from ACPM sought

The Committee was requested to provide advice on the following specific issues:

1. The Committee's opinion of the primary efficacy endpoint, ≥ 35% reduction in spleen volume, as a valid and reliable measure of clinical benefit? What is the Committee's opinion of the support from the secondary endpoints?
2. Only high risk and intermediate-2 risk patients were included in the trials. Based on the preliminary data from ASH 2012, what is the Committee's opinion on broadening the indication to include treatment of disease-related splenomegaly or symptoms regardless of risk category?
3. Thrombocytopenic patients (platelet count < 100 x 10^9/L) were not included in the trials. Based on the preliminary data from ASH 2012, what is the Committee's opinion of allowing ruxolitinib at a lower starting dose of ≤ 5 mg bd in patients with platelet count 50-100 x 10^9/L provided hepatic function is normal and renal function is no worse than mildly impaired?
4. What starting dose of ruxolitinib would the Committee recommend in patients with moderate to severe renal impairment?
5. The benefit-risk balance of ruxolitinib in the proposed indication?

The Committee was also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Pre ACPM preliminary assessment

The Delegate considered that the application for Jakavi (ruxolitinib) should be approved for registration subject to finalisation of the product information.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered these products to have an overall positive benefit–risk profile for the indication as proposed;

> *Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis*

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed PI/CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Jakavi tablets containing ruxolitinib 5 mg, 10 mg and 20mg, indicated for:

> *Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis*

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au