Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Ruxolitinib

Proprietary Product Name: Jakavi

Sponsor: Novartis Pty Ltd

First round CER: 1 October 2012
Second round CER: 25 March 2013

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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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

Abbreviation	Meaning
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
Cmax	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
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

Abbreviation	Meaning
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
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

Abbreviation	Meaning
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
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

Abbreviation	Meaning
SMQ	Standard MedDRA query
SOC	System organ class
STAT	Signal transducer and activator of transcription
Tmax	Time of maximum observed concentration
TNF	Tumor necrosis factor
TPO	Thrombopoietin
WBC	White blood cell
WHO	World Health Organization
µM	Micromolar

1. Clinical rationale

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.[1, 2]. 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 60 years of age. 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.[3] Primary myelofibrosis (PMF) is one of the classical Philadelphia-negative chronic myeloproliferative neoplasms (MPNs). 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.[4,5] 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.[6] The JAK2V617F mutation is present in around 45% to 68% of patients with PMF.[6]

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.[7] 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. He comments that splenomegaly may also respond to interferon-α but this agent is often poorly tolerated in patients with MF. He also notes 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 comments 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 notes that treatments for MF associated anaemia include blood transfusion, corticosteroids, anabolic steroids (usually danazol) and erythropoiesis-stimulating agents. He comments 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.[8]

The local expert states that corticosteroids, antihistamines and analgesics are the mainstay of treatment for constitutional symptoms of sweats, anorexia, bone pain and pruritus. He notes that pruritus may also respond well to cytoreductive treatment with interferon or less often to hydroxyurea. He further comments that radiotherapy is the mainstay of treatment for localised extramedullary haematopoiesis and that hepatomegaly may respond to cytoreduction with hydroxyurea. The local expert notes 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, he comments 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.

2. Contents of the clinical dossier

2.1. 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.

2.2. 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.

2.3. 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.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

3.1.1. 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 1-4 below).

Table 1: 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
#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

Study	Objectives	Doses	Duration	N*	Subjects
#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	Bioavailability – relative) IR and SR tablets	R - IR, SR1, SR2 – 25 mg (tablets)	sd (x3)	9	Healthy

Table 2: 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	Health RI

Table 3: 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) – methotrexate on ruxolitinib and vice versa	R – 25 mg (tablet); M – 7.5 to 30 mg	sd (x2)	18	RA

Table 4: 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

In the clinical pharmacology studies, venous blood was collected to measure plasma concentrations of ruxolitinib (and metabolites in specific studies) for PK and PD analyses. Plasma samples for ruxolitinib and metabolites were analysed by a validated liquid chromatographic tandem mass spectrometry assay (LC-MS/MS).

In general, blood sampling for PK analysis was undertaken predose and then postdose for 36 or 48 h in the single and multiple dose studies involving healthy volunteers, subjects with renal impairment and subjects with hepatic impairment. In these studies, sampling times to 36 to 48 h post dose was longer than 5 half-lives (that is, 3 x 5 = 15 hours) and sufficient to adequately describe the ruxolitinib plasma concentration time profile. However, in patients with MF (Study #251), blood sampling for PK analysis was only undertaken to 9 h postdose, which was about 3 half-lives and was just adequate for description of the terminal elimination phase.

For single dose studies, PK parameters evaluated included peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), area under plasma concentration time response curve from time 0 to time t or infinity(AUC_{0-t} or $AUC_{0-\infty}$,), half life ($t_{1/2}$) λ_z, oral clearance (CL/F), apparent volume of distribution (Vz/F), and for multiple dose studies, PK parameters evaluated include C_{max}, T_{max}, trough plasma concentration (C_{min}), $AUC_{0-\tau}$, $t_{1/2}$, Terminal Elimination Rate Constant (λ_z), CL/F, V_z/F, urinary excretion (A_e), renal clearance (CLr), and fe. Standard non-compartmental (model-independent) pharmacokinetic methods were used to calculate and analyse PK parameters and all methods were adequately described in the submitted study reports.

3.2. Population pharmacokinetic analyses

The submission included three population pharmacokinetic (Population-PK) analyses (see Table 5, below). The pivotal Population-PK analysis is considered to be the analysis in patients with MF reported in INCYTE-DMB-11.04.1. This report included PK data from the Phase I/II dose-escalation Study #251, and the two key Phase III Studies #351 and #352. The model development dataset included ruxolitinib pooled data from Study #251 and the blinded portion of Study #351, and consisted of 2187 ruxolitinib plasma samples from 272 subjects. The external model validation dataset included data from Study #352 consisting 1067 ruxolitinib plasma samples from 142 subjects.

The Population-PK analysis from the Phase I/II Study #251 was reported in INCB 18424-251. This was a preliminary Population-PK analysis and has not been evaluated as all relevant data appear to have been included in the pivotal Population-PK analysis (NCYTE-DMB-11.04.1). The results of the population-pK analysis of oral clearance (CL/F) and plasma terminal-phase half-life ($t_{1/2}$) in healthy subjects were reported in INCYTE-DMB-11.02.1. Healthy subjects in this analysis came from 9 Phase I studies (#131, #132, #133, #134, #135, #137, #138, #139, and #142). The number of safety profiles included 290 (that is, the number of PK profiles equals the number of subjects in all studies except for Study #131, Part 1, where most subjects received two levels of dose). The CL/F and $t_{1/2}$ data from the Population-PK analysis in healthy subjects have been included in the relevant sections of the body of the CER.

Table 5: 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.

3.3. 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 this CER.

The clinical data also included reports of bioanalytical and analytical methods for human studies validating the assay methods used to measure plasma concentrations of ruxolitinib and its metabolites, and characterising the pharmacodynamic (PD) assay for cytokine-induced STAT3 phosphorylation (STAT3p) in human whole blood.

3.4. Summary of pharmacokinetics

3.4.1. Absorption

From the Phase I mass-balance study (#134) it can be inferred that absorption of ruxolitinib is nearly complete (> 95%) following oral administration. In this study, single-dose radiolabelled ^{14}C-ruxolitinib 25 mg was administered as an oral solution to 6 healthy male volunteers after an overnight fast. The mean± standard deviation (SD) total recovery of the administered radioactivity was 95.53±4.93%, with 73.61±10.18% and 21.92±5.95% being recovered from the urine and feces, respectively.

In healthy subjects, the T_{max} following administration of single oral doses of ruxolitinib 25 mg fasted was rapid with mean values ranging from 0.75 to 1.3 hours. Similarly, in patients with MF ruxolitinib was also absorbed rapidly typically attaining peak plasma concentrations within 0.3 to 2 hours, after single and multiple dose tablet administration. Representative PK parameters for ruxolitinib in healthy subjects following single 25 mg doses of different formulations in the fasted state are summarised below in Table 6.

Table 6: Comparison of ruxolitinib PK parameters after a single 25 mg oral dose using powder in capsule, solution, tablet and capsule formulations; healthy volunteers (HV).

Study	Dose 25 mg fasting	N	C_{max} (nM)	t_{max} (h)	$AUC_{0\text{-}inf}$ (nM.h)	$t_{1/2}$ (h)
#131	Powder in capsule	6 HV	1090± 607	2.4 ± 2.0	4330±1470	3.1 ±0.7
#131	Tablet	12 HV	865±201	1.3± 0.9	3424 ± 893	2.8 ±0.8
#134	Solution	6 HV	1093±651	0.63±0.21	3200±1361	2.3 ±0.4
#139	Tablet (IR)	9 HV	1100±332	0.94 ±0.46	4360±2020	2.8 ±0.7
#138	Tablet	47 HV	1510±400	0.96 ±0.50	5320±1680	2.6 ±0.9
#137	Tablet	8 HV	1500±693	0.75 ± 0.46	3860±1640	2.8 ±0.7
#142	Tablet	8 HV	1150±332	0.94 ± 0.42	4330±1040	3.8 ±0.9

In a population-PK analysis in MF patients, ruxolitinib plasma concentrations were adequately described by a two compartment model with first order absorption. In this analysis, the estimated population mean absorption half-life was approximately 0.168 h (~10 minutes) following an estimated population mean typical 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).

In Caco-2 monolayers, ruxolitinib exhibited a high apparent permeability coefficient (Papp) of 21.5 x 10^{-6} cm/sec, which was greater than that of the high permeability model drug metoprolol, suggesting a potential for high oral absorption. Transport experiments with different concentrations of ruxolitinib (1, 10, 50, and 100 µM) resulted in similar Papp values (28.6, 20.0, 21.5, and 17.9 x 10^{-6} cm/s, respectively) indicating the absence of saturable absorption (INCYTE-DMB-08.147).

3.4.2. Bioavailability

3.4.2.1. Absolute bioavailability

The submission included no absolute bioavailability study. The sponsor provided a justification for not providing an absolute bioavailability study contained within its "justification for biowaiver from EMA[a]" seeking an exemption from providing *in-vivo* bioavailability studies for the 5, 15, and 20 mg ruxolitinib IR tablets. The justification is based on ruxolitinib being a BCS class 1 drug (that is, high solubility, high permeability). In particular, the sponsor states that near complete oral absorption (≥ 95%) was observed in the ^{14}C-ruxolitinb mass balance study (#134). In addition, the sponsor comments that, in healthy subjects, the pharmacokinetics of ruxolitinib were linear after single and multiple dose administration and after multiple dose administration (every 12 h) there was minimal accumulation (10%). Furthermore, a high-fat breakfast did not alter the pharmacokinetics of ruxolitinib to a "clinically relevant extent". The sponsor also stated that there was no clinical evidence to suggest site-specific absorption or transporter interactions. In addition, dissolution of the 5 mg tablet used in the Phase III program was rapid (≥ 85% in 30 minutes) and dissolution of the expected commercial formulations (5, 15, and 20 mg tablets) was also rapid.

[a] European Medicines Agency

Comment: The clinical aspects of the sponsor's justification for not providing an absolute bioavailability study are satisfactory. *In vitro*, ruxolitinib has high aqueous solubility over the pH range 1.0 to 8.0 (> 25 mg/250 mL), high permeability (21.5 x 10-6 cm/s across Caco-2 cell monolayers), and demonstrates rapid dissolution at three pH conditions (0.1N hydrochloric acid (HCl), pH 4.5 acetate buffer, and pH 6.8 phosphate buffer.

3.4.2.2. Bioavailability relative to an oral solution or micronised suspension

There was no study formally comparing the bioavailability of ruxolitinib tablets with oral solutions or micronised suspensions. However, the submission did include one mass-balance study using an oral suspension of ^{14}C-ruxolitinib 25 mg (#134) and the single-dose pharmacokinetics of ruxolitinib from this study and studies involving tablet formulations were similar to the IR tablet formulation (see Table 6, above).

3.4.2.3. Bioequivalence of clinical trial and market formulations

The submission included no bioequivalence study comparing clinical trial and market formulations.

3.4.2.4. Bioequivalence of different dosage forms and strengths

1. Different strengths 5, 15, and 20 mg of the tablet dosage forms

The submission included no bioequivalence study comparing the 5, 15, and 20 mg ruxolitinib IR tablets proposed for registration. The sponsor submitted a justification for not providing such a study based on ruxolitinib being a BCS class 1 drug. In addition to the issues discussed above relating to the sponsor's justification for not submitting an absolute bioavailability study, the sponsor argued that in the "unlikely event that a formulation would not be bioequivalent, the risk to patients is low". The sponsor commented that if the recommended target dose is 15 mg once every 12 h (q12h) then the intersubject variability in ruxolitinib exposure of 30% observed in healthy subjects could be within the "range equivalent to a 10-20 mg dose". The sponsor also noted that in the extreme example of a formulation being 70% of the reference dose (presumably 15 mg q12h) then this would be equivalent to an initial starting dose of 10 mg q12h with an exposure range equivalent to a 7 mg to 13 mg dose. The sponsor states that in this case the reduced dosage would not present a safety risk to the patient but it is not known whether this would translate to a loss of efficacy.

Comment: The clinical aspects of the sponsor's justification for not providing a bioequivalence study comparing the 5, 10, and 20 mg ruxolitinib IR tablets are satisfactory.

2. Different dosage forms immediate release (IR) and sustained release (SR)

The submission included one, open-label, single-centre, two-cohort study designed to compare the bioavailability of single-dose ruxolitinib IR and SR (SR-1 and SR-2) 25 mg tablet formulations (Study #139). This study has not been formally evaluated as the SR tablet is not being proposed for registration. However, PK data from this study relating to the IR formulation have been included in relevant sections this CER.

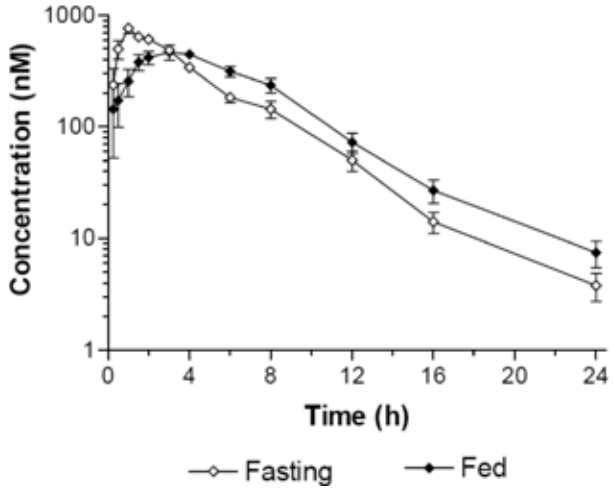
3.4.2.5. Influence of food

The effect of food on the bioavailability of ruxolitinib was evaluated in Phase I Study #131. In Part 2 of this study, ruxolitinib 25 mg tablets were administered as a single dose either following an overnight fast or immediately following a high-fat, high-calorie meal in a cross-over study in 12 healthy subjects. The results of the study are summarised in below in Table 7, and the mean±standard error (SE) plasma concentration-time curves are provided below in Figure 1.

Table 7: Study #131 – Ruxolitinib PK parameters fasting and fed following a single-dose 25 mg tablet to healthy volunteers (n=12).

Treatment	n	C_{max} (nM)	t_{max} (h)	$t_{½}$ (h)	AUC_{0-t} (nM*h)	$AUC_{0-\infty}$ (nM*h)	CL/F (L/h)
Fasted	12	865 ± 201 845	1.3 ± 0.9 1.1	2.8 ± 0.8 2.7	3407 ± 885 3301	3424 ± 893 3318	25.4 ± 6.7 24.6
High-fat, High calorie meal	12	672 ± 227 640	2.7 ± 1.6 2.2	3.1 ± 0.9 2.9	3575 ± 1029 3442	3598 ± 1033 3465	24.5 ± 7.2 23.5
Geometric mean relative bioavailability and 90% confidence Intervals (reference = fasted)							
		75.7% 62.7, 91.3%	- -	- -	104% 96.5, 113%	104% 96.8, 113%	- -
Values are mean ± SD and geometric mean							

Figure 1: Ruxolitinib plasma concentrations (mean±SE) in healthy subjects (n=12) following single-dose 25 mg fasting and fed.



Comment: Exposure to ruxolitinib in the fed and fasted state based on the C_{max} was not bioequivalent as the 90% CI of the relevant geometric ratio was not enclosed entirely within the standard bioequivalence interval of 80% to 125%. Food reduced the geometric mean C_{max} by 24.3% relative to fasting, and delayed the mean t_{max} by 1.6 hours. Exposure based on AUC_{0-inf} was bioequivalent following fed and fasting administration as the 90% CI for the relevant ratio was enclosed entirely within the standard bioequivalence interval of 80% to 125%. Neither the half-life nor clearance of ruxolitinib differed significantly following fed and fasted administration. Overall, the reduced ruxolitinib C_{max} fed relative to fasting is unlikely to be clinically significant. The data from this study suggests that ruxolitinib can be administered with or without food.

3.4.2.6. Dose proportionality

Dose proportionality following single doses of ruxolitinib was investigated in Study #131. In Part 1 of this study, a powder-in-capsule formulation was administered orally in the fasted state to healthy subjects at ascending single doses of 5 mg to 200 mg in a randomised cross-over design (see Table 8, below). The mean C_{max} and AUC_{0-inf} values increased approximately linearly proportional to dose over the range 5 mg to 200 mg. The power-function regression analysis produced dose-proportionality equations of $C_{max} = 38.8 \cdot Dose^{0.992}$ (p=0.837 for β=1) and $AUC_{0-inf} = 174 \cdot Dose^{0.974}$ (p=0.409 for β=1). The exponent, β, of the power function (or equivalently the slope of the log-transformed equation) was not statistically significantly different from 1 for C_{max} or AUC_{0-inf}; 0.992 (90% CI: 0.925, 1.06) and 0.974 (90% CI: 0.921, 1.03), respectively.

Table 8: Study #131 – Ruxolitinib PK parameters (mean ± SD, and geometric mean) following single doses as powder in capsule to healthy subjects.

Cohort	Dose (mg)	n	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (nM*h)	Cl/F (L/h)	Vz/F (L)
1 & 2	5	12	205 ± 72.8 195	1.7 ± 0.69 1.5	2.8 ± 1.1 2.6	862 ± 273 823	20.7 ± 6.45 19.8	83.0 ± 40.1 74.9
1	10	6	382 ± 114 368	2.1 ± 1.2 1.7	3.6 ± 1.5 3.4	1790 ± 395 1750	19.0 ± 3.87 18.6	95.0 ± 34.5 90.7
2	25	6	1090 ± 607 934	2.4 ± 2.0 1.8	3.1 ± 0.67 3.0	4330 ± 1470 4110	21.0 ± 7.92 19.9	87.7 ± 20.7 85.7
1	50	6	1760 ± 515 1700	1.2 ± 0.68 1.0	2.7 ± 0.56 2.7	7160 ± 1950 6930	24.4 ± 7.09 23.5	96.9 ± 41.8 90.5
2	100	6	4570 ± 1360 4390	1.6 ± 0.80 1.4	2.7 ± 0.51 2.7	16900 ± 4710 16400	20.6 ± 5.69 19.9	78.7 ± 13.8 77.7
1	200	6	7100 ± 1350 7010	1.9 ± 1.3 1.6	5.0 ± 2.0 4.7	30700 ± 2640 30600	21.4 ± 1.77 21.3	155 ± 64.6 146

Comment: Dose proportionality following single-dose administration of ruxolitinib as powder in capsule over the dose range 5 mg to 200 mg has been satisfactorily established.

3.4.2.7. Bioavailability during multiple-dosing

Bioavailability during multiple-dosing was investigated in Study #132. In this Phase I, multiple-dose, dose-escalation study, the pharmacokinetics of ruxolitinib were assessed following once-daily (qd) or twice-daily (bd) 10-day dosing regimens in healthy subjects using the powder-in-capsule formulation used in Part 1 of Study #131. There were no significant changes in observed pharmacokinetic parameters on Day 10 compared with Day 1 for all regimens and the exposure parameters (C_{max} and AUC) suggest that there is no marked accumulation of ruxolitinib between Day 1 and Day 10 of dosing. The single-dose and steady state PK parameters for ruxolitinib are summarised below in Tables 9 and 10, respectively.

Table 9: Study #132 – Ruxolitinib first dose PKs (mean±SD; geometric mean).

Regimen	n	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)	C_{last} (nM) [a]	AUC_{0-t} (nM·h)	CL/F (L/h)	Vz/F (L)
15 mg BID	8	613 ±161 597	1.4 ±0.3 1.4	2.7 ±0.8 2.6	38.4 ±31.1 29.1	2420 ±743 2320	20.6 ±6.10 19.8	76.5 ±20.0 74.2
25 mg BID	18	1210 ±422 1120	1.2 ±0.3 1.2	2.8 ±1.0 2.6	50.8 ±36.7 41.3	3960 ±1250 3790	21.1 ±6.08 20.3	83.1 ±33.5 77.3
50 mg BID	9	2230 ±884 2070	1.6 ±1.0 1.4	3.1 ±1.3 2.9	156 ±128 82.1	8390 ±2940 7900	20.7 ±8.98 19.1	83.8 ±23.2 81.1
50 mg QD	9	2560 ±1020 2410	1.1 ±0.3 1.1	3.2 ±0.8 3.1	15.9 ±27.6 7.5	8580 ±4390 7880	22.0 ±7.72 20.6	96.0 ±32.4 91.9
100 mg QD	9	4530 ±1480 4300	1.3 ±0.3 1.3	3.3 ±0.6 3.3	30.6 ±29.9 20.3	15600 ±4570 15000	22.5 ±7.22 21.6	105 ±22.3 103

[a] C_{last} corresponds to C_{12h} for twice-daily dosing or C_{24h} for once-daily dosing. [b] Prior to statistical comparisons, dose-dependent parameters (C_{max}, C_{last}, and AUC) were normalized to a common dose.

Table 10: Study #132 – Ruxolitinib steady state PKs (mean±SD; geometric mean).

Regimen	n	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)	C_{min} (nM)	$AUC_{0\text{-}tau}$ (nM·h)	CL/F (L/h)	Vz/F (L)
15 mg BID	8	681 ±223 649	1.7 ±0.6 1.7	2.9 ±0.8 2.8	37.2 ±19.6 31.5	2716 ±770 2610	19.6 ±6.47 18.7	82.2 ±34.8 76.7
25 mg BID	18	1200 ±306 1160	1.6 ±1.1 1.4	3.1 ±1.0 2.9	54.6 ±37.1 45.1	4535 ±1412 4330	19.7 ±5.91 18.8	82.3 ±19.7 79.7
50 mg BID	6	2710 ±972 2570	1.2 ±0.4 1.2	3.2 ±0.8 3.1	111 ±85.9 80.1	8513 ±2660 8170	20.8 ±6.44 20.0	89.7 ±13.4 88.9
50 mg QD	9	2360 ±649 2290	1.2 ±0.5 1.1	2.9 ±0.8 2.8	6.6 ±9.5 n/a	7764 ±2138 7470	22.9 ±7.68 21.9	90.2 ±21.4 87.9
100 mg QD	9	4890 ±1060 4780	1.3 ±0.2 1.3	3.9 ±0.7 3.8	25.9 ±23.5 16.8	17135 ±4628 16600	20.4 ±5.97 19.7	111 ±31.2 108

Serial trough plasma ruxolitinib concentrations indicate that steady state was reached by the morning of Day 2 for all regimens, which is consistent with the short plasma terminal half-life of about 3 h (see Table 13, below).

Table 11: Study #132 – Ruxolitinib trough plasma concentrations (mean±SD; geometric mean).

	Day 2	Day 3	Day 5	Day 7	Day 9	Day 10		
Regimen	0 h	0 h	0 h	0 h	0 h	0 h	12 h	24 h
15 mg BID	61.0 ±35.7 52.9	60.5 ±38.4 51.4	76.9 ±40.0 68.5	63.0 ±34.8 55.4	60.8 ±39.0 51.4	64.4± 31.4 57.9	37.6 ±19.3 32.0	--
25 mg BID	118 ±107 84.5	107 ±80.3 81.7	92.8 ±67.8 73.2	71.4 ±61.5 NA	35.5 ±34.4 18.6	87.8 ±59.6 72.7	59.3 ±38.0 50.6	--
50 mg BID	263 ±181 218	220 ±182 174	231 ±137 188	210 ±140 163	244 ±163 192	181 ±102 153	148 ±114 101	--
50 mg QD	15.9 ±27.6 7.5	14.4 ±24.5 6.3	11.9 ±21.0 5.4	11.6 ±16.0 6.7	12.3 ±19.1 NA	6.9 ±9.5 NA	--	8.0 ±11 NA
100 mg QD	30.6 ±29.9 20.3	32.9 ±22.7 24.6	31.4 ±27.6 19.2	34.1 ±30.0 21.8	30.0 ±18.0 22.2	33.2 ±37.2 19.4	--	33.8 ±29.2 21.4

Mean ruxolitinib C_{max} and AUC increased approximately linearly proportional to dose for both the three bd regimens and the two qd regimens. For the three bd regimens at steady state, the power-function regression analysis produced dose-proportionality equations for C_{max} = $29.2 \cdot Dose^{1.14}$ (p=0.286 for β=1) and $AUC_{0\text{-}12h} = 203 \cdot Dose^{0.947}$ (p=0.703 for β=1), which indicates that the steady-state C_{max} and $AUC_{0\text{-}12h}$ increased approximately linearly proportional to the dose over the range of 15 mg to 50 mg bd.

3.5. Distribution

3.5.1. Volume of distribution

The mean steady state apparent volume of distribution (V_z/F) ranged from 82 to 111 L in healthy subjects (Study #132) from 53 to 65 L (Study #251) in patients with MF.

3.5.2. Plasma protein binding

The unbound fraction of ruxolitinib in human serum *in vitro* was 2.6% at 10 µM and 3.6% at 3.0 µM, and in human plasma was 3.3% at 10 µM (INCYTE-DMB-07.11.1). In a separate *in vitro* study, the mean fraction unbound of 1 µM ruxolitinib was 14.8, 7.9, 5.3, 3.8 and 2.9% at 10, 20, 30, 40 and 50 mg/mL of human serum albumin (HAS), respectively (INCYTE-DMB-10.05.1). An inverse linear relationship was observed between the fraction unbound of ruxolitinib and the concentration of HSA, (r^2=0.85). Overall, the data suggest that binding to HSA at concentrations expected in healthy subjects (40 to 50 mg/mL) is about 96% to 97%. The authors of INCYTE-DMB-10.05.1 comment that pathological conditions resulting in a 30% to 50% decrease in HSA are likely to result in a no more than 2 fold increase in unbound ruxolitinib which is unlikely to be clinically significant.

3.5.3. Erythrocyte distribution

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).

3.6. Metabolism

3.6.1. *In vivo* (humans)

Metabolic clearance is the primary route of elimination of ruxolitinib. Metabolic profiling was undertaken in mass-balance Study #134 in healthy males (n=6). After a single oral dose of ^{14}C-ruluxotinib 25 mg, ruxolitinib (parent compound) was the predominant peak present in plasma representing 74%, 66% and 58% of the total radioactivity at 1, 2 and 6 h post-dose, respectively (average from intra-subject samples was 63%). The largest metabolite peak was M18, which represented 7.3%, 9.1% and 14% of the total radioactivity at 1, 2 and 6 h post-dose (average from intra-subject samples was 12%). Eight other peaks were observed in plasma, each averaging <5% of the ruxolitinib related radioactivity (based on the intra-subject samples).

Based on average concentrations (ng equivalents/g) for the six subjects in the mass balance study, the M18 plasma concentration was 18% that of the ruxolitinib concentration and was the only metabolite with a concentration > 10% that of ruxolitinib. Based on the $AUC_{0\text{-}24h}$, two metabolites (M18 and M16) had values > 10% of ruxolitinib (30% and 14%, respectively), with $AUC_{0\text{-}24h}$ values for all other observed metabolites being <10% of the $AUC_{0\text{-}24}$ for ruxolitinib.

In urine, the two largest peaks were M27, a 3-hydroxylation of the cyclopentyl moiety, and M11, a 3-ketone on the cyclopentyl moiety, each representing approximately 19% to 25% of the radioactivity by HPLC and 15% to 16% of the administered dose between 0-48 h. The metabolites M7 and M8, both 3-hydroxylations of the cyclopentyl moiety, and M49 (hydroxylation and ketone on the pyrrolidine) each contributed 11% to 18% of radioactivity and 8.0% to 11% of the dose. All other peaks, consisting of mono- and di-hydroxylations as well as *O*-glucuronides, represented less than 13% of the radioactivity and less than 5% of the administered dose.

In feces, M8 was the largest ruxolitinib-related component representing approximately 22%, 24% and 29% of the radioactivity by HPLC in the samples at 24-48, 48-72, and 72-96 h post-dose, respectively, and accounting for approximately 2% of the administered dose at each time interval. Metabolites M7, M27 and M49 were also significant fecal metabolites, each representing 10% to 16% of the total radioactivity and approximately 2.3% to 4.6% of the administered dose between 24 and 96 h postdose. Other peaks in feces consisted of ruxolitinib as well as mono- and di-hydroxylated metabolites identified as M43, M45, M16, M31, and M18, each of which represented less than 10% of the radioactivity and less than 2% of the administered dose.

Comment: The results indicate that the parent compound (ruxolitinib) is the predominant circulating moiety in humans and the major circulating metabolite is M18. M18 was the only metabolite with both a plasma concentration and $AUC_{0\text{-}24h}$ value > 10% that of ruxolitinib (18% and 30%, respectively). Overall, oxidation is the major Phase I metabolic pathway for ruxolitinib, primarily resulting in hydroxylated and ketone metabolites and the hydroxylated metabolites can undergo conjugation (for example, glucuronidation). Less than 1% of administered dose of ruxolitinib was excreted unchanged in the urine and feces.

3.6.2. *In vitro* (humans)

The *in vitro* metabolism of ruxolitinib in humans was investigated using human recombinant CYP enzymes and human liver microsomes. Recombinant enzyme preparations of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 metabolized ruxolitinib (1 μm) with 86%, 60%, 53%,

82% and 2% of the initial concentration of ruxolitinib remaining after 30 minute incubations (60 minutes for CYP2C9), respectively (INCYTE-DMB-07.02.1). To determine the relative contribution of these CYP isozymes to the metabolism of ruxolitinib in humans, ruxolitinib was incubated with human liver microsomes in the presence and absence of selective chemical inhibitors of CYP1A2, CYP2C9, CYP2C19,CYP2D6 and CYP3A4 (INCYTE-DMB-07.02.1; INCYTE-DMB-09.93.1). In INCYTE–DMB-0.93.1, in the absence of any CYP inhibitor approximately 35% of parent compound remained after 30 minutes incubation. When ketoconazole (a potent CYP3A4 inhibitor) was co-incubated with ruxolitinib, 74% of the parent compound remained, while co-incubations with selective inhibitors of CYP1A2, CYP2C9, CYP2C19 and CYP2D6, resulted in 38%, 40%, 35% and 42% of the parent compound remaining, respectively.

Comment: The sponsor states that the CYP3A4 is the predominant CYP enzyme responsible for the metabolism of ruxolitinib. This conclusion appears to be reasonable based on the results from the relevant *in vitro* studies.

3.7. Excretion

3.7.1. Routes and mechanisms of excretion

The mass-balance study (#134) showed that, following a single oral dose of 25 mg of ^{14}C-ruxolitinib to 6 healthy males, recovery of the administered radioactivity was 95.53±4.93%, with 73.61±10.18% and 21.92±5.95% being recovered in urine and feces, respectively (see Table 12, below). 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 where recovery was 50%. The results indicate that urinary elimination was the major route of excretion for ruxolitinib derived radioactivity. Less than 1% of the ruxolitinib derived radioactivity recovered in the urine and feces was parent drug.

Table 12: Study #134 – Excretion of radioactivity in the urine and feces; healthy subjects (n=6).

Time collection interval (h)	Mean % Dose recovered (N=6)		
	Urine	Feces	Total
0 – 24	69.9	0.5	70.4
0 – 48	73.0	9.9	82.9
0 – 72	73.4	16.1	89.5
0 – 96[a]	73.5	18.8	92.3
0 – 192[a]	73.6	21.9	95.5

[a]: Samples collected up to 144 h for four subjects, 168 h for one subject and 192 h for one subject.

In Study #131, on average 0.11% (range: 0.03 to 0.39%) of an oral dose of ruxolitinib (100 mg qd) was recovered in urine as unchanged ruxolitinib over a 1 steady-steady state dosing interval in healthy subjects (n=9). The urine concentration was assayed using a non-validated HPLC/MS/MS method. Given the low urinary recovery of the parent compound, a Good Laboratory Practices (GLP) assay for determination of ruxolitinib concentrations in urine samples was not developed.

3.7.2. Clearance

The apparent oral clearance (CL/F) of ruxolitinib in healthy adult subjects was calculated from 9 Phase I studies. The mean±SD CL/F was 19.2±6.94 L/h, based on data from 290 subjects. There was a two-fold range in mean CL/F cross the studies from 14.1 L/hr to 28.2 L/hr. The sponsor speculates that as ruxolitinib is a BCS Class 1 drug with greater than 95% oral absorption it is likely that the variability in oral clearance reflects variability in metabolic clearance. The sponsor refers to published data indicating that a high degree of variability in CYP3A4 catalytic activity has been reported[9], suggesting that the observed variability in the oral clearance of ruxolitinib may be related to the intrinsic variability in CYP3A4 expression and activity given that the drug is predominantly metabolised by this CYP enzyme.

In healthy volunteers, oral clearance of ruxolitinib was approximately 10% lower in females than in males (Study #138) but this marginal difference is not expected to be clinically significant. 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 apparent clearance compared with female subjects (22.1 and 17.1 L/h, respectively), although this was within the variability of CL/F for the total population (39.1% CV).

3.7.3. Half-life

The terminal phase elimination half-life of ruxolitinib in healthy adult subjects was calculated from 9 Phase I studies. The mean±SD terminal half-life was 3.1±1.0 hour, based on data from 290 subjects, and ranged across the studies from 2.3 to 4.0 hours. The approximate two-fold range in half-life across the studies is consistent with the range observed for apparent oral clearance. Data in healthy volunteers from Study #138 indicates that gender has no significant effect on mean half-life (2.6 h in both males and females). In the Population-PK analysis in patients with MF, the apparent terminal elimination half-life was estimated to be approximately 3.76 h for males and 4.07 h for females.

3.7.4. Intra- and inter-individual variability of ruxolitinib pharmacokinetics

In the single dose study in healthy subjects (#131), ruxolitinib PK parameters exhibited intersubject variability (CV%) ranging from 19.0% (following 200 mg) to 55.9% (following 25 mg) for C_{max}, and from 8.59% (following 200 mg) to 34.0% (following 25 mg) for $AUC_{0\text{-}inf}$. In the multiple dose study in healthy volunteers (#132), steady-state ruxolitinib pharmacokinetic parameters exhibited intersubject variability (CV%) ranging from 21.7% to 35.8% for C_{max}, and from 27.0% to 31.3% for $AUC_{0\text{-}t}$. In patients with MF from Study #251, steady-state pharmacokinetic parameters exhibited intersubject variability ranging from 2.2% to 44.1% for C_{max} and from 20% to 57% for $AUC_{0\text{-}\tau}$, showing that steady-state intersubject variability in patients with MF was greater than in healthy subjects. The Population-PK analysis in patients with MF [showed intersubject variability (CV%) of 39.1%. for the apparent oral clearance (INCYTE-DMB-11.04.1).

3.7.5. Pharmacokinetics and pharmacodynamic activity of the metabolites

In INCYTE-DMB-10.55.1, the pharmacokinetics of eight mono-oxygenated metabolites of ruxolitinib were determined using plasma concentration data from four Phase I clinical studies in healthy subjects (#133, #135, #138, #142). The metabolite data from the renal impairment study (#142), the hepatic impairment study (#137) and the rifampin-ruxolitinib interaction study (#135) are summarised separately later in the relevant sections of this CER. The metabolite data from healthy subjects from Study #138 are summarised immediately below.

Study #138 was the largest ruxolitinib Phase I clinical pharmacology study in healthy subjects. In this study, 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. Three minor metabolites, M7, M8 and M11 were present in plasma with concentrations of approximately 5-9% of the parent and another three metabolites, M9, M14 and M16 each represented about 2% of the parent drug in plasma. The total amount of all eight metabolites in plasma was 65% of the parent drug systemic exposure, based on $AUC_{0\text{-}inf}$ values.

In a human whole blood assay measuring IL-6 induced STAT3 phosphorylation (pSTAT3), all metabolites were shown to be pharmacologically active with weaker activity (approximately 2 to 5 fold) relative to the parent compound (INCYTE-IN VITRO-09.11.1). After taking into consideration the on-target pharmacologic potency for the metabolites relative to the parent drug (that is, 50% inhibitory concentration (IC_{50}) of pSTAT3 inhibition in whole blood), the total pharmacodynamic contribution from all the metabolites was estimated to be about 18% of parent drug (INCYTE-DMB-10.55.1).

3.8. Pharmacokinetics in the target population (MF)

3.8.1. Study #251 – non-compartmental analysis (NCA)

Study #251 was a Phase I/II, open-label study exploring the safety, tolerability, and efficacy of ruxolitinib, administered orally to patients with PMF, PPV-MF, and PET-MF. The study consisted of 3 parts evaluating a total of eight dose regimens:

- Part 1: dose escalation and expansion, bd dosing, evaluating two dose levels of 25 mg bd and 50 mg bd;
- Part 2: alternative dosing schedules (A, B and C) evaluating five dose regimens of 10 mg bd, 25 mg bd, 25 mg qd, 50 mg qd and 100 mg qd; and
- Part 3: three independent patient groups (Group I, II and III) evaluating six dose regimens of 10 mg bd, 15 mg bd, 25 mg bd, 50 mg qd, 100 mg qd and 200 mg qd.

A total of 154 subjects were enrolled, 32 subjects were in Part 1, 29 subjects were in Part 2 and 93 subjects were in Part 3.

In Part 1 of the study, blood samples for PK analysis were collected predose and then at 0.5, 1, 1.5, 2, 4, 6, and 9 h postdose on Days 1 and 15 of Cycle 1, and predose on Day 1 of Cycles 2 and 3. In Part 2, blood samples for PK analysis were collected predose and then at 0.5, 1, 1.5, 2, 4, 6, and 9 h post-dose on Day 15 of Cycle 1 and predose on Day 1 of Cycles 2 and 3. In Part 3, blood samples for PK analysis were collected predose and then at 2 h after administration of the morning dose on Day 15 of Cycle 1 and Day 1 of Cycle 2.

Plasma concentration data from rich sample collection during Cycle 1 for subjects in Part 1 and 2 were used for non-compartmental analysis, while all plasma concentration data were used for Population-PK analysis. The steady-state pharmacokinetics (Cycle 1, Day 15) derived from non-compartmental analysis are summarised below in Table 13.

Table 13: Study INCB 18424-251 – Ruxolitinib steady-state pharmacokinetics (mean±SD and geometric mean), Cycle 1, Day 15; non-compartmental analysis.

Part[a]	Regimen	n	C_{max} (nM)	t_{max} (h)	C_{min} (nM)	$t_{1/2}$ (h)	$AUC_{0-\tau}$ (nM*h)	AUC_{0-t} (nM*h)	Cl/F (L/h)	V_z/F (L)
1A	25 mg bid	27	1481 ± 575 1374	0.83 ± 0.45 0.74	47± 54 --	1.94 ± 0.50 1.88	4363 ± 2066 3949	4148 ± 1885 3778	22.7 ± 10.1 20.7	60 ± 23 56
1B	50 mg bid	5	3460 ± 1305 3255	0.87 ± 0.58 0.71	173 ± 273 47	1.99 ± 0.82 1.86	9832 ± 5631 8547	9075 ± 4584 8085	22.2 ± 14.3 19.1	56 ± 30 51
2A	25 mg qd	6	1417 ± 150 1410	0.84 ± 0.38 0.78	0 ± 0 --	1.60 ± 0.36 1.57	3567 ± 777 3494	3291 ± 604 3243	23.9 ± 5,5 23.4	53 ± 6.7 53
2A	50 mg qd	1	3380	1.00	16	3.14	15211	11042	10.7	49
2A	100 mg qd	3	4607 ± 101 4606	1.00 ± 0.50 0.91	37 ± 55 13	1.95 ± 0.64 1.88	17020 ± 3351 16808	15138 ± 1415 15094	19.7 ± 3.65 19.4	53 ± 7.4 53
2B	10 mg bid	12	518 ± 229 486	1.04 ± 0.54 0.92	18± 19 11	1.80 ± 0.41 1.77	1514 ± 756 1380	1444 ± 710 1321	25.6 ± 10.1 23.7	65 ± 27 60
2C	25 mg bid	7	1650 ± 506 1578	0.79 ± 0.49 0.68	85± 102 43	1.96 ± 0.59 1.90	4939 ± 2566 4463	4444 ± 1918 4120	19.9 ± 8.1 18.3	53 ± 16 50

For the 3 bd and the 3 qd regimens at steady state, the power-function regression analysis produced dose-proportionality equations for $C_{max} = 32.3 \cdot Dose^{1.17}$ (p=0.1243 for β=1) for bd and $C_{max} = 87.9 \cdot Dose^{0.87}$ (p=0.0709 for β=1) for qd. These results indicate that the steady-state C_{max} increased approximately linearly proportional to the dose over the range of 10 mg to 50 mg bd and 25 mg to 100 mg qd, and the exponent, β, of the power function (or equivalently the slope of the log-transformed equation) was not statistically significantly different from 1 for C_{max}.

The mean $AUC_{0-\tau}$ increased approximately linearly proportional to dose from 10 mg to 100 mg. The power-function regression analysis produced dose-proportionality equations for $AUC_{0-\tau}=103.5 \cdot Dose^{1.13}$ (p=0.1925 for β=1), which indicates that the steady-state $AUC_{0-\tau}$ increased approximately linearly proportional to the dose over the range of 10 mg bd to 100 mg qd, and the exponent, β, of the power function (or equivalently the slope of the log-transformed equation) was not statistically significantly different from 1 for $AUC_{0-\tau}$.

Steady-state ruxolitinib PK parameters exhibited moderate inter-subject variability, ranging from 2.2% to 44.1% for C_{max} and from 20% to 57% for $AUC_{0-\tau}$.

Comment: The ruxolitinib plasma concentration time curves in patients with MF showed that plasma concentrations declined in a monophasic or biphasic fashion. Non-compartmental analysis indicates that following fasting, oral, first-dose or multiple-dose administration of ruxolitinib tablets, ruxolitinib was absorbed rapidly, typically attaining peak plasma concentrations within 0.3 to 2 h after administration in all subjects. The bd and qd regimens were linearly proportional over the administered dose ranges as assessed by the C_{max} and the $AUC_{0-\tau}$. Intersubject variability in the both the C_{max} and the $AUC_{0-\tau}$ were moderate.

In general, pharmacokinetics were comparable in healthy subjects and patients with MF despite a significant difference in mean ages. In healthy subjects, the mean±SD oral apparent clearance (CL/F) was 19.2±6.94 L/h, based on data from 290 subjects in 9 Phase I studies, and there was two-fold range in mean CL/F across the studies of 14.1 to 28.2 L/hr. The mean CL/F values for the dosing regimens in patients with MF (Study #251) were all within the range of means for this parameter in healthy subjects, apart from the 50 mg qd regimen which included only 1 patient. In patients with MF (Study #251), the mean CL/F ranged from 19.9 to 25.7 L/h across the dose regimens (excluding 50 mg qd). In healthy subjects, the mean±SD terminal half-life was 3.1±1.0 hour, based on data from 290 subjects in 9 Phase I studies, and ranged across the studies from 2.3 to 4.0 hours. The mean terminal half-life range in patients with MF (Study #251) was shorter (approximately 1.6 to 2.0 hours) than that observed in healthy subjects (approximately 3 hours) and probably reflect the shorter sampling time in patients with MF (9 hours) compared with healthy subjects (at least 24 hours).

3.8.2. INCYTE-DMB-11.04.1 - Population pharmacokinetic analysis

3.8.2.1. Methods

The submission included a Population-PK analysis in patients with MF (PMF, PPV-MF, or PET-MF) based on data from Studies #251, #351, and #352, using Nonlinear Mixed Effects Modeling (NONMEM®) Version 7.1.0 (INCYTE-DMB.11.04.1). Study #251 was a Phase I/II, open-label, dose-escalation study and Studies #351 and #352 were the key, Phase III, randomised, controlled studies. All subjects from the ruxolitinib treatment arms who had at least two plasma ruxolitinib plasma concentrations with a documented sampling time and time of preceding dose were considered for inclusion in the analysis. Full-profile PK sampling was done in Parts 1 and 2 of Study #251, and sparse sampling was done in Part 3 of Study #251 and in Studies #351 and #352 (see Table 14, below).

Table 14: INCYTE-DMB-11.04.1 – Sampling strategies.

Study	PK Sampling Times
251	Part 1: predose and 0.5, 1, 1.5, 2, 4, 6, and 9 h post-dose on Days 1 and 15 of Cycle 1 predose on Day 1 of Cycles 2 and 3 Part 2: predose and 0.5, 1, 1.5, 2, 4, 6, and 9 h post-dose on Day 15 of Cycle 1 predose on Day 1 of Cycles 2 and 3 Part 3: predose and 2 h after administration of morning dose on Day 15 of Cycle 1 and Day 1 of Cycles 2 and 3
351	Weeks 4 and 12: predose, 1 ±0.25 h, 2 ±0.25 h, and between 4 and 12 h post-dose Weeks 8, 16, 24, 36, 48, 60, 72, then every 24 wk after Week 72: random samples
352	Weeks 4 and 12: predose, between 0 and 2 h, and between 2 and 4 h post-dose Weeks 8, 16, 24, 36, 48, 60, and 72; then every 24 wk after Week 72: random samples

The model development dataset included ruxolitinib concentration data from Study #251 pooled with concentration data from the blinded portion of Study #351. This dataset contained 2187 ruxolitinib concentrations from 272 subjects. The analysis population was approximately

56% male, primarily White (92%), and ranged in age from 39 to 87 years. The median body weight (WT) and body mass index (BMI) were 72.75 kg and 24.7 kg/m^2, respectively. The median value of the calculated creatinine clearance (ClCr) was 68.5 mL/min, indicating that the population, on average, had a mild decrease in glomerular filtration rate. The median value of aspartate aminotransferase (AST) was 30 U/L, indicative of mild elevations in this liver enzyme within the analysis population. Serum albumin (ALB) levels were generally within the normal range (median = 42 g/L).

The external model validation dataset included ruxolitinib plasma concentration data from Study #352. This dataset contained 1067 ruxolitinib concentrations from 142 subjects. The validation population was approximately 44% male, primarily white (80%) and ranged in age from 35 to 83 years. Median body weight and BMI were 68.6 kg (range: 48 to 109 kg) and 23.6 kg/m^2 (range: 15.1 to 37.3 kg/m$_2$), respectively. Median values of ClCr, AST, and serum ALB were 79.5 mL/min, 23.5 U/L, and 45 g/L, respectively.

Ruxolitinib tablets (5 mg or 25 mg) were administered as oral doses in an outpatient setting. Most starting doses were 10 mg to 25 mg bd and most maximum doses were 20 mg to 25 mg bd. In addition, 25, 50, and 100 mg qd were also tested in Study #251 (1 subject received a dose of 200 mg qd). Dose modification was allowed based on subject response.

3.8.2.2. Results

The final Population-PK model was a 2-compartment disposition model with first-order absorption, absorption lag time (ALAG), and linear elimination. The final PK model was parameterized in terms of k_a, $ALAG_1$, CL/F, Vc/F, Q/F, and Vp/F (see Table 15 below).

Table 15: INCYTE-DMB-11.04.1 – Final Population-PK parameter estimates.

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV[a])	
	Population Mean	%SEM[b]	Final Estimate	%SEM
k_a[c] (h^{-1})	4.12	14.3	75.0	43.7
$ALAG_1$[d] (h)	0.0545	5.96	NE[e]	NE
CL/F[f] (L/hr) for Males	22.1	3.40	39.1	9.22
CL/F (L/hr) for Females	17.7	3.50		
V_c/F[g] for subject with body weight of 72.9 kg (L)	58.6	2.80	28.0	12.7
V_p/F[h] (L)	11.2	18.6	102	36.6
Q/F[i] (L/hr)	2.53	20.3	NE	NE
RV[j] (%CV)	35.5	6.19	NA[k]	NA
Minimum Value of the Objective Function = 22819.031				

[a] %CV = percent coefficient of variation; [b] %SEM = percent standard error of the mean; [c] ka = first-order absorption rate constant; [d] ALAG1 = absorption lag time; [e] NE = not estimated; [f] CL/F = apparent oral clearance; [g] Vc/F = apparent volume of distribution for the central compartment; [h] Vp/F = apparent volume of distribution for the tissue (peripheral) compartment; [i] Q/F = apparent intercompartmental clearance; [j] RV = residual variability; [k] NA = not applicable

Comment: The Population-PK analysis was extensively documented and reporting of the results met the relevant TGA adopted EU guidelines (CHMP/EWP/185990/06). All model parameters were estimated with good precision (≤ 20.3% standard error of the mean (SEM) and ≤ 43.7% SEM for fixed and random effect parameters, respectively). Absorption of ruxolitinib was rapid, with a short absorption lag time of approximately 3 minutes and an estimated absorption half-life of approximately 10 minutes. The estimated interindividual variability (IIV) in the first-order absorption rate constant (k_a = 4.12 h^{-1}) was 75.0 % coefficient of variance (CV). The sponsor commented that the large IIV in k_a was

anticipated, not only because of the typically high IIV inherent in the absorption process but also partly due to the lack of sufficient data to fully inform the absorption process because of the sparse sampling strategy.

Covariate analysis was performed to identify factors predictive of variability in ruxolitinib pharmacokinetics. Only gender was found to be a statistically significant predictor of oral apparent clearance (CL/F), with males having an approximately 25% higher CL/F compared with females (22.1 L/h versus 17.7 L/h, respectively). The unexplained IIV in CL/F was 39.1 %CV. Body weight was the only statistically significant predictor of apparent central volume of distribution (Vc/F), and was described by a linear function, which predicts a Vc/F of 56.3 L for a typical 70 kg individual with an unexplained IIV of 28.0% and an approximate 8 L increase in Vc/F for every 10 kg increase in body weight. However, although both gender and body weight were found to be statistically significant covariates, the geometric mean AUC_{ss} ratios for both gender (male versus female) and body weight (≤ 72.9 versus > 72.9 kg) were maintained within the bounds of 0.5 to 2 at both the 15 mg bd and 20 mg bd dosage regimens. An approximate 2 fold increase or 50% decrease in the population mean value of steady state AUC (AUC_{ss}) was chosen empirically to define clinical relevance. If the AUC_{ss} ratio was contained within the bounds 0.5 to 2.0 then the magnitude of the covariate effect was considered to be relatively insignificant.

The apparent volume of distribution for the tissue (peripheral) compartment (Vp/F) at steady-state was 11.2 L for a typical subject, with IIV of 102.0 %CV. The sponsor commented that the large IIV in the Vp/F is, in part, a reflection of the variable disposition patterns observed across the analysis population, with profiles exhibiting a mix of both mono-exponential and bi-exponential declines in plasma concentrations following C_{max}.

Based on formal covariate analysis, no notable differences in the population pharmacokinetics of ruxolitinib were observed between subjects with varying degrees of hepatic or renal dysfunction. Based on the current data and analysis methods, there is no statistically significant influence of the concomitant administration of CYP3A4 inducers, CYP3A4 inhibitors, warfarin, digoxin, or prednisone on the pharmacokinetics of ruxolitinib. None of the concomitant medications that were explored or any of the laboratory indices of kidney and liver function were found to be significant descriptors of IIV in PK parameters.

The predicted typical value of the apparent terminal elimination half-life using the parameter estimates from the final population model was 3.76 h and 4.07 h for male and female subjects, respectively, weighing 72.9 kg. The study data did not allow for a conclusive assessment of dose proportionality.

3.9. Pharmacokinetics in other special populations

3.9.1. Pharmacokinetics in subjects with impaired hepatic function

The submission included one study (#137) comparing the pharmacokinetics of ruxolitinib in subjects with hepatic dysfunction based on Child-Pugh (CP) classification (mild [CP-A], moderate [CP-B], and severe [CP-C]) with healthy subjects. Ruxolitinib (single 25 mg tablet) was administered to all subjects (fasting). The results are summarised below in Table 16.

Table 16: Study #137 – Hepatic impairment, ruxolitinib PK parameters following single 25 mg dose.

Group	n	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (nM·h)	$AUC_{0-\infty}$ (nM·h)	CL/F (L/h)	V_z/F (L)
A (normal function)	8	1500 ± 693 1350	0.75 ± 0.46 0.66	2.8 ± 0.7 2.7	3850 ± 1630 3510	3840 ± 1620 3520	25.6 ± 12.7 23.2	95.2 ± 28.0 91.5
B (mild dysfunction)	8	1300 ± 408 1240	1.4 ± 0.4 1.3	4.6 ± 1.4 4.5	7430 ± 3940 6550	7480 ± 4000 6590	14.2 ± 8.24 12.4	85.5 ± 36.4 80.0
C (moderate dysfunction)	8	1100 ± 390 1050	1.0 ± 0.5 0.87	4.1 ± 1.1 3.9	4670 ± 1490 4490	4690 ± 1500 4510	18.7 ± 4.97 18.1	104 ± 15.3 103
D (severe dysfunction)	8	1240 ± 496 1150	1.3 ± 0.5 1.2	5.0 ± 1.6 4.9	6220 ± 2720 5800	6250 ± 2720 5830	14.9 ± 5.45 14.0	104 ± 40.9 98.2
P-values from a one-factor ANOVA of log-transformed data								
		0.645	0.0718	0.0017	0.0372	0.0362	0.0362	0.411
Geometric mean relative bioavailability and 90% confidence intervals (Reference = Group A)								
B (mild dysfunction)	8	0.92 0.66 - 1.29			1.87 1.29 - 2.71	1.87 1.29 - 2.71		
C (moderate dysfunction)	8	0.78 0.56 - 1.10			1.28 0.88 - 1.86	1.28 0.88 - 1.85		
D (severe dysfunction)	8	0.85 0.60 - 1.19			1.65 1.14 - 2.40	1.65 1.14 - 2.40		

Note(s): Parameter values are mean ± standard deviation and geometric mean. ANOVA = analysis of variance.

Comment: In subjects with mild, moderate, and severe hepatic impairment, exposure to ruxolitinib, based on the AUC_{0-inf} increased by 87%, 28%, and 65%, respectively, relative to subjects with normal hepatic function. C_{max} values were lower in subjects with hepatic impairment (8% to 22%), relative to subjects with normal hepatic function. Apparent oral clearance (CL/F) notably decreased in subjects with hepatic impairment compared with subjects with normal hepatic impairment, while the half-life ($t_{1/2}$) notably increased.

In this study the "no effect" boundary for hepatic impairment for the C_{max} and AUC was pre-specified as 80% to 125% for the relevant ratios (impairment [test]: normal [reference]). The 90% CIs for all relevant C_{max} and AUC ratios were outside the pre-specified "no effect" boundary. In particular, the upper 90% CIs for the AUC_{0-inf} ratios (impaired/normal) were 2.71, 1.85, and 2.40 for subjects with mild, moderate and severe hepatic impairment, suggesting that the ruxolitinib dose should be reduced by 50% for all patients with hepatic impairment.

The study also included a PD analysis in which the effects of hepatic impairment were assessed on markers of JAK-STAT activation (including *ex vivo* IL-6 stimulated pSTAT3). In subjects with normal hepatic function (Group A) and with mild (Group B) or moderate (Group C) hepatic dysfunction, ruxolitinib demonstrated time-dependent inhibition of cytokine pSTAT3 with maximal inhibition (approximately 70%) occurring at 1 h after administration and pSTAT3 levels returning to baseline levels by 24 h in all subjects examined. No significant differences in PDs were observed among groups A, B and C. In subjects with severe hepatic dysfunction (Group D), the maximum inhibition of pSTAT3 observed at 1 h was similar to that observed in the other 3 groups. However, there appeared to be a prolongation of PD activity in subjects with severe hepatic dysfunction so that 30% to 40% inhibition of pSTAT3 was still observed 24 h post-dose and pSTAT3 levels did not return to baseline until 36 to 48 h post-dose.

PK/PD analysis from INCYTE-DMB-10.55.1 (ruxolitinib and metabolites in subjects from Study #137) showed that the pharmacological activity (IC_{50}) adjusted AUC of ruxolitinib plus the metabolites, expressed as a percent of parent AUC, was 116%, 110%, 110%, and 112% for patients with normal hepatic function, mild hepatic impairment, moderate hepatic impairment and severe hepatic impairment respectively. The results suggest that the contribution of the metabolites to the PD activity of ruxolitinib in subjects with hepatic impairment (10% to 12%) is marginally lower than that in subjects with normal hepatic function (16%). Based on the combined PK and PD data from Study #137, the sponsor concludes that a lower starting dose of ruxolitinib may be required for patients with hepatic dysfunction with subsequent dose adjustments guided by the safety and efficacy in individual patients. The proposed PI

recommends that the ruxolitinib starting dose should be reduced by approximately 50% in patients with hepatic impairment. This recommendation is considered to be acceptable.

3.9.2. Pharmacokinetics in subjects with impaired renal function

The submission included one study (#142) comparing the pharmacokinetics of ruxolitinib in subjects with renal impairment with healthy subjects with normal renal function. Ruxolitinib (single 25 mg tablet) was administered to all subjects (fasting). The study included 6 treatment cohorts: Cohort 1: healthy subjects with normal renal function (CLcr > 80 mL/min); Cohort 2: subjects with mild renal dysfunction (CLcr 50 to 80 mL/min); Cohort 3: subjects with moderate renal dysfunction (CLcr 30 to 49 mL/min); Cohort 4: subjects with severe renal dysfunction (CLcr less than 30 mL/min); Cohort 5: subjects with End stage renal disease (ESRD) receiving haemodialysis (dosing post-dialysis); and Cohort 6: subjects with ESRD receiving haemodialysis (dosing pre-dialysis). The results are summarised below in Table 17.

Table 17: Study #142. Renal impairment, ruxolitinib PK parameters following single 25 mg dose.

Cohort	n	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (nM·h)	$AUC_{0-\infty}$ (nM·h)	CL/F (L/h)	V_d/F (L)
1 (normal)	8	1150 ± 332 1110	0.94 ± 0.42 0.85	3.8 ± 0.87 3.7	4300 ± 1030 4210	4330 ± 1040 4230	19.7 ± 4.02 19.3	106 ± 24.6 103
2 (mild)	8	1300 ± 494 1240	1.1 ± 0.52 0.99	3.9 ± 0.96 3.8	4780 ± 1030 4650	4790 ± 1030 4670	18.0 ± 5.62 17.5	99.0 ± 28.0 95.5
3 (moderate)	8	1320 ± 291 1290	0.75 ± 0.46 0.66	3.7 ± 0.94 3.6	5270 ± 1230 5140	5290 ± 1240 5160	16.2 ± 4.08 15.8	84.5 ± 19.6 82.4
4 (severe)	8	929 ± 309 882	1.0 ± 0.46 0.90	3.7 ± 0.71 3.6	4530 ± 1290 4350	4540 ± 1290 4360	19.6 ± 6.87 18.7	101 ± 25.5 98.4
5 (ESRD, dialysis predose)	4	1060 ± 78.7 1060	1.0 ± 0.41 0.93	3.6 ± 0.81 3.6	3900 ± 377 3890	3930 ± 370 3920	20.9 ± 1.84 20.8	108 ± 17.2 107
6 (ESRD, dialysis postdose)	4	1050 ± 230 1040	1.0 ± 0.41 0.93	2.8 ± 0.68 2.8	3510 ± 604 3470	3530 ± 612 3480	23.8 ± 4.97 23.4	94.1 ± 8.67 93.8
P-values from a one-factor ANOVA of log-transformed data								
Cohorts 1-5		0.075	0.571	0.992	0.367	0.375	0.375	0.381
Cohorts 1-6		0.102	0.681	0.412	0.155	0.158	0.158	0.465
Geometric mean relative bioavailability and 90% confidence intervals (Reference = Cohort 1)								
2 (mild)	8	111% 89 - 140%			111% 90 - 136%	110% 90 - 136%		
3 (moderate)	8	116% 92 - 146%			122% 99 - 150%	122% 99 - 150%		
4 (severe)	8	79% 63 - 99%			103% 84 - 127%	103% 84 - 127%		
5 (ESRD, dialysis predose)	4	95% 72 - 125%			92% 72 - 119%	93% 72 - 119%		
6 (ESRD, dialysis postdose)	4	93% 70 - 123%			82% 64 - 106%	82% 64 - 106%		

Note(s): Parameter values are mean ± standard deviation and geometric mean. ESRD = end-stage renal disease; ANOVA = analysis of variance.

Comment: Exposure to ruxolitinib based on the AUC_{0-inf} was 10%, 22% and 3% higher in patients with mild, moderate and severe renal impairment, respectively, relative to healthy subjects with normal renal function, while exposure was 7% and 18% lower in patients with ESRD dialysis pre-dose and ESRD post-dose, respectively. Exposure to ruxolitinib based on the C_{max} was 11% and 16% higher in patients with mild and moderate renal impairment, respectively, relative to healthy subjects with normal renal function, while exposure was 21%, 5%, and 93% lower in patients with severe renal impairment, ESRD dialysis pre-dose, and ESRD dialysis post-dose, respectively.

In this study, the pre-defined "no effect" boundary for the C_{max} was 70% to 143%, and for the AUC_{0-inf} was 80% to 125%. The 90% CI for the C_{max} ratios were within or just without (moderate impairment) the pre-specified "no effect" boundary for all relevant values, while the 90% CI for the AUC_{0-inf} ratios were outside (upper bound) the pre-specified "no effect" boundary for mild, moderate and severe renal impairment. Therefore, in accordance with the relevant FDA Guidance for Industry, the sponsor explored the correlation between ruxolitinib systemic exposure (C_{max} and AUC_{0-inf}) and renal function (modified diet in renal disease [MDRD] glomerular filtration rate [GFR] or urine CLcr) using a linear regression model for the 32 study

subjects in Cohorts 1 through 4. The results suggested that there was no statistically significant linear relationship between ruxolitinib plasma exposures and corresponding renal function as the p-value for the model fit was well above 0.05 in each case. The range of (MDRD) GFR and urine CLcr values were 7.1 to 113 mL/min and 14 to 165 mL/min, respectively. The sponsor commented that the absence of an effect of renal function on ruxolitinib pharmacokinetics was also evident in the essentially flat slopes of the regression equations, or by inspection of the scatter plots of systemic exposure parameters against MDRD-GFR and against urine CLcr. Oral apparent clearance (CL/F) did not notably differ across the 6 treatment cohorts nor did the half-life or the apparent volume of distribution.

Haemodialysis appeared to have negligible effects on ruxolitinib clearance, when assessed by either examining the ruxolitinib arterial-venous concentration difference or by determining the amount of ruxolitinib recovered in dialysate fluid (< 0.02% of the oral dose). The results from both methods suggest that ruxolitinib is minimally dialyzed and the contribution of dialysis to ruxolitinib clearance is negligible in ESRD subjects. The sponsor commented that this conclusion was expected based on the minor contribution (1% or less) of renal excretion to the total oral clearance of ruxolitinib, as well as the very large unbound volume of distribution of ruxolitinib (approximately 3000 L, fu = 3.3%) as compared to the total volume of plasma volume dialysed (approximately 50 L) during a 4 h dialysis procedure.

The study also included a PD analysis. In Cohorts 1 through 4, ruxolitinib demonstrated concentration-dependent inhibition of cytokine-induced pSTAT3, mirroring the PK time course with maximal inhibition (approximately 70 %) occurring 1 h after administration, and cytokine-induced pSTAT3 levels returning to control levels by 24 h in all subjects examined. No significant differences in PDs were observed among subjects with mild, moderate, or severe renal disease compared with healthy subjects. In subjects with ESRD who received ruxolitinib post-dialysis there appeared to be a prolongation of PD activity with 50% to 60% inhibition of pSTAT3 maintained from 8 to 48 h after dosing, which was significantly longer compared with other cohorts. Cytokine-induced pSTAT3 levels returned to 70% of control (corresponding to 30% inhibition) approximately 4 h after these subjects underwent additional haemodialysis 48 h post-dose.

PK/PD analysis from INCYTE-DMB-10.55.1 (ruxolitinib and metabolites in subjects from Study #142) analysis showed that the pharmacological activity (IC_{50}) adjusted AUC of ruxolitinib plus the 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 results indicate that in subjects with ESRD the metabolites and the parent compound both contribute to a similar extent to the pharmacological activity of ruxolitinib. The results also indicate that in subjects with severe renal function the metabolites have approximately 50% of the pharmacological activity of the parent compound.

Based on the totality of the PK and PD data in subjects with renal impairment the sponsor recommends that no dose adjustment is required in patients with mild renal impairment. However, in patients with moderate and severe renal impairment, an approximately 50% dose reduction is recommended for the starting dose, with additional dose modifications made based on careful monitoring of safety and efficacy. Furthermore, the sponsor's recommended starting dose for patients with ESRD on dialysis is 15 mg for patients with platelet count between 100-200 x 10^9/L and 20 mg for patients with a platelet count of > 200 x 10^9/L, with subsequent dose adjustments made with careful monitoring of safety and efficacy. The sponsor's dosage recommendations were considered to be acceptable.

3.9.3. Pharmacokinetics according to age

There were no non-compartmental PK analyses based on age in either healthy subjects or patients with MF. In the Population-PK analysis in patients with MF (INCYTE-DMB-11.04.1), the

median age in the 272 patients in the pooled model development data was 65 years (range: 39, 83) and in the 142 patients in the model validation data was 67 years (range: 35, 83). In this analysis, age had no statistically significant effect on the pharmacokinetics of ruxolitinib.

3.9.4. Pharmacokinetics according to gender

The submission included an evaluation of the effects of gender on the pharmacokinetics of ruxolitinib from Study #138, the Thorough QTc study that enrolled similar numbers of male and female patients. The results from this comparison are summarised below in Table 18.

Table 18: Study #138 - Ruxolitinib PKs in male and female healthy subjects following fasting ruxolitinib 25 mg.

Gender	No. of Subjects	CL/F (L/h)	$t_{1/2}$ (h)
Female	23	15.9 ± 4.99	2.6 ± 0.65
		15.2	2.6
Male	24	17.6 ± 4.98	2.6 ± 1.1
		16.9	2.5

PK parameters are reported as mean ± SD and geometric mean

Comment: The Phase I (NCA) data from Study #138 showed that CL/F in females was approximately 10% lower compared with males, while the $t_{1/2}$ values were identical. In the Population-PK analysis in patients with MF (INCYTE-DMB-11.04.1), gender was found to be a statistically significant predictor of CL/F, with the CL/F in females being about 20% lower than in males (17.7 L/h versus 22.1 L/h, respectively).

3.9.5. Pharmacokinetics according to race

The submission included an assessment of the effect of race and ethnicity on the pharmacokinetics of ruxolitinib across all Phase I clinical trials in healthy subjects. The mean apparent oral clearance (CL/F) in Black subjects (n=75) was approximately 14% lower than in White subjects (n=195); 17.6±6.4 versus 20.2±7.0 L/h, respectively), while the half-life ($t_{1/2}$) was about 24% higher (3.6±1.1 versus 2.9±1.0 hours, respectively). Subject numbers in Asians (n=9), American Indians (n=6) and Hispanics (n=4) are considered to be too small to allow meaningful conclusions to be drawn about comparative pharmacokinetics in these racial and ethnic groups.

3.10. Pharmacokinetic interactions

3.10.1. Pharmacokinetic interactions demonstrated in human studies

3.10.1.1. Interaction ruxolitinib with ketoconazole and erythromycin

The submission included a single-dose ruxolitinib and multiple dose ketoconazole (potent CYP3A4 inhibitor) and erythromycin (moderate CYP3A4 inhibitor) interaction study in healthy subjects to assess the effects of the drug-drug combinations on the pharmacokinetics and pharmacodynamics of ruxolitinib. The study included two cohorts who received the following treatments in succession: Day 1 – ruxolitinib 10 mg (2 x 5 mg tablets) as a single dose; Days 2 to 4, 200 mg ketoconazole bd (Cohort 1) or 500 mg erythromycin bd (Cohort 2); Day 5 ruxolitinib 10 mg (2 x 5 mg tablets) with ketoconazole 200 mg bd (Cohort 1) or erythromycin 500 mg bd (Cohort 2). The results for ruxolitinib combined with ketoconazole are summarised below in Table 19 and for ruxolitinib combined with erythromycin in Table 20. The study did not collect data on the pharmacokinetics of the metabolites of ruxolitinib.

Table 19: Study #133 – Ruxolitinib PKs following ruxolitinib 10 mg with and without ketoconazole.

Treatment	n	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (nM·h)	$AUC_{0-\infty}$ (nM·h)	CL/F (L/h)	Vz/F (L)
INCB018424 alone	16	667 ±187 644	0.84 ±0.35 0.78	3.7 ±1.1 3.5	2770 ±1160 2560	2830 ±1220 2600	13.6 ±5.53 12.6	65.8 ±16.0 63.7
INCB018424 + ketoconazole	16	880 ±210 856	1.2 ±0.48 1.1	6.0 ±2.5 5.6	4910 ±1980 4590	5480 ±2740 4970	7.13 ±2.70 6.57	54.1 ±13.1 52.7
P-values from a crossover ANOVA of log-transformed data								
Treatment		0.0006	0.0398	<0.0001	<0.0001	<0.0001	<0.0001	0.0066
Geometric mean relative bioavailability and 90% confidence intervals (reference = INCB018424 alone)								
		133% 118 - 149%	--	--	179% 163 - 197%	191% 172 - 212%	--	--

Note(s): Values are mean ± standard deviation and geometric mean. ANOVA = analysis of variance.

Table 20: Study #133 – Ruxolitinib PKs following ruxolitinib 10 mg with and without erythromycin.

Treatment	n	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (nM·h)	$AUC_{0-\infty}$ (nM·h)	CL/F (L/h)	Vz/F (L)
INCB018424 alone	14	584 ±160 562	1.3 ±0.4 1.3	4.3 ±1.4 4.1	2180 ±518 2130	2240 ±572 2180	15.5 ±3.99 15.0	92.9 ±28.8 89.1
INCB018424 + erythromycin	14	630 ±174 609	1.1 ±0.4 1.1	4.7 ±1.3 4.5	2760 ±755 2670	2860 ±790 2760	12.2± 3.15 11.8	79.5 ±20.0 76.7
P-values from a crossover ANOVA of log-transformed data								
Treatment		0.316	0.301	0.256	0.0003	0.0002	0.0002	0.0836
Geometric mean relative bioavailability and 90% confidence intervals (reference = INCB018424 alone)								
		108% 94.5 - 125%	--	--	126% 116 - 136%	127% 117 - 138%	--	--

Note(s): Values are mean ± standard deviation and geometric mean. ANOVA = analysis of variance.

Comment: Co-administration of multiple-dose ketoconazole 200 mg bd significantly decreased the apparent oral clearance (CL/F) of single doe ruxolitinib 10 mg by approximately 48%, resulting in increases in geometric mean ruxolitinib C_{max} and $AUC_{0\text{-}inf}$ of 31% and 91%, respectively. The 90% CIs for the geometric mean ratios of both the C_{max} and the $AUC_{0\text{-}inf}$ were well outside the 85% to 125% standard bioequivalence interval. The PD results were consistent with the PK results and showed that, compared with ruxolitinib alone, combination treatment with ketoconazole increased the ruxolitinib PD effect by about 2 fold based on the PD $AUC_{0\text{-}t}$ (p=0.0004). The geometric mean ratio of PD $AUC_{0\text{-}t}$ between ruxolitinib plus ketoconazole and ruxolitinib alone was 1.98 (90% CI: 1.52, 2.58). Furthermore, inhibition of cytokine-induced pSTAT3 was 70% to 80% greater and duration of inhibition was 1 to 8 h longer when ketoconazole was co-administered with ruxolitinib compared with ruxolitinib alone. The results provide evidence of a clinically important PK interaction between ruxolitinib and ketoconazole and indicate that ruxolitinib dose should be reduced by 50% when the drug is co-administered with ketoconazole or other potent CYP3A4 inhibitors.

Co-administration of multiple-dose erythromycin 500 mg bd decreased the apparent oral clearance (CL/F) of ruxolitinib by approximately 21%, resulting in increases in ruxolitinib geometric mean C_{max} and $AUC_{0\text{-}inf}$ by 8% and 27%, respectively. The 90% CI for the $AUC_{0\text{-}inf}$ ratio (117%, 138%) was outside the standard bioequivalence limits of 80% to 125%, while the 90% CI for the C_{max} ratio (94.5%, 125%) was just within the limits. The PD results showed that, compared with ruxolitinib alone, combination treatment with erythromycin decreased the ruxolitinib PD effect by about 20% as indicated by the PD $AUC_{0\text{-}t}$ (p=0.010). The geometric mean ratio of PD $AUC_{0\text{-}t}$ between ruxolitinib plus erythromycin and ruxolitinib alone was 0.80 (90% CI: 0.70, 0.92). The results suggest that there is unlikely to be a clinically significant PK interaction between ruxolitinib and erythromycin or other moderate inhibitors of CYP3A4 inhibitors. However, the dose of the ruxolitinib used in this study (10 mg single dose) was lower than that being recommended for approval (initially 15 mg or 20 mg bd). Consequently, caution

is required when ruxolitinib is co-administered with moderate CYP3A4 inhibitors. Furthermore, there are no data on the effects of the co-administration of ruxolitinib and erythromycin on the metabolites of ruxolitinib which is a further reason for caution when ruxolitinib is co-administered with moderate CYP3A4 inhibitors.

3.10.1.2. Interaction with rifampin

The submission included a single-dose ruxolitinib and multiple-dose rifampin (potent CYP3A4 inducer) and multiple-dose rifabutin (moderate CYP3A4 inducer) interaction study in healthy subjects to assess the effects of the drug-drug combinations on the pharmacokinetics and pharmacodynamics of ruxolitinib. In Cohort 1, ruxolitinib 50 mg (2x 25 mg) was administered alone on Day 1, rifampin 600 mg once daily was administered alone on Days 3 to 12, and ruxolitinib 500 mg and rifampin 600 mg were co-administered on Day 13. In Cohort 2, the effect of co-administration of ruxolitinib 50 mg with rifabutin 300 mg once daily using a comparable treatment regimen to Cohort 1 was to be undertaken only if data from Cohort 1 showed an inducer effect of rifampin on ruxolitinib pharmacokinetics. However, based on the data from Cohort 1 the sponsor elected to cancel Cohort 2. The results of the PK interaction between ruxolitinib and rifampin are summarised below in Table 21.

Table 21: Study #135 – Ruxolitinib PKs following ruxolitinib with and without rifampin.

Treatment	n	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (nM·h)	$AUC_{0-\infty}$ (nM·h)	CL/F (L/h)
INCB018424 alone (Day 1)	12	3760 ±1080 3620	1.1 ±0.5 1.0	3.3 ±0.8 3.2	12600 ±3760 12100	12800 ±3870 12200	14.1 ±5.05 13.4
INCB018424 + rifampin (Day 13)	10	2020 ±1040 1810	0.90 ±0.4 0.8	1.7 ±0.6 1.6	4490 ±2920 3710	4510 ±2940 3720	51.9 ±28.3 43.8
INCB018424 alone (repeat, Day 34)	8	2830 ±987 2680	1.2 ±0.7 1.0	3.2 ±0.9 3.1	10100 ±3370 9560	10100 ±3440 9610	18.0 ±6.71 17.0
P-values from a crossover ANOVA of log-transformed data [a]							
Treatment		0.0012	0.218	<0.0001	<0.0001	<0.0001	<0.0001
Geometric mean relative bioavailability and 90% confidence intervals [a]							
		47.9% 35.8 - 64.1%	--	--	29.4% 21.4 - 40.4%	29.2% 21.3 - 40.0%	--

Note: INCB01824 = ruxolitinib. Note(s): Values are mean ± standard deviation and geometric mean. ANOVA = analysis of variance. [a] ANOVA, relative bioavailability, and 90% confidence intervals were calculated based on data from the 10 subjects who completed the study through Day 13; the reference is ruxolitinib alone administered on Day 1.

Comment: Rifampin (600 mg qd for 10 days) significantly decreased ruxolitinib geometric mean C_{max} and AUC_{0-inf} by 52% and 71%, respectively. 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). When the C_{max} and AUC_{0-inf} on Day 34 were evaluated (after rifampin washout), the ruxolitinib geometric mean C_{max} and AUC_{0-inf} were approximately 32% and 61% lower on Day 13 (co-administered ruxolitinib and rifampin) relative to Day 34 (ruxolitinib alone). The results indicate that rifampin increases the metabolism of ruxolitinib by inducing CYP3A4 and this effect is still present 3 weeks after discontinuation of rifampin.

The PD results showed that following fasting, single-dose ruxolitinib 50 mg, cytokine-induced pSTAT3 was inhibited with maximal inhibition (80% to 90%) occurring at 1 h after administration with pSTAT3 levels returning to control levels by 24 h in all subjects examined. Compared with ruxolitinib alone, pre-treatment with rifampin caused a non-significant 10% decrease in ruxolitinib PD effect based on the PD AUC_{0-t} (p=0.33). The geometric mean ratio of the PD AUC_{0-t} between ruxolitinib plus rifampin and ruxolitinib alone was 90% (90% CI: 75%, 108%). The observed decrease in the PD effect of ruxolitinib when co-administered with rifampin was much less than predicted from the PK effect where a marked reduction in ruxolitinib exposure was observed following co-administration with rifampin.

The sponsor provided two potential explanations for the discrepancy between the observed PK results and the PD response when ruxolitinib was co-administered with rifampin. First, at a dose of 50 mg of ruxolitinib, the average plasma concentration (calculated as average $AUC_{0\text{-}t/24h}$) of ruxolitinib over the 24 h period post-dose (421 nM on Day 34) was greater than the IC_{50} value (234 nM) for pSTAT3. The pSTAT3 inhibition versus ruxolitinib plasma concentration relationship is described by a sigmoidal curve and data from a 50 mg dose is expected to fall on the non-linear portion of the sigmoidal curve meaning that changes in plasma concentration of ruxolitinib will not necessarily result in proportional changes in pSTAT3 inhibition. Second, an increased contribution to the PD activity from active metabolites may be expected following metabolic induction with rifampin. The total AUC values of ruxolitinib metabolites, on average, were nearly unchanged but the relative abundance of the metabolites (expressed as percent of ruxolitinib AUC) increased by more than 2 fold. Accordingly, the metabolite contribution to PD activity relative to the parent is estimated to increase from 15% to 36% following CYP3A4 induction by rifampin, thus partially off-setting the loss of PD activity of the parent drug.

The PK parameters for ruxolitinib metabolites following ruxolitinib alone (Day 34) and co-administered with rifampin (Day 13) from INCYTE-DMB-10.55.1 were summarised in a table in the study report. The Day 34 PK metabolite data for ruxolitinib alone were used for reference to the PD data instead of the Day 1 PK metabolite data as part of the PD samples collected on Day 1 were lost in transportation. It is considered that sponsor's explanation for the observed discrepancy between the PK and PD results are plausible.

In summary, the sponsor concludes that rifampin significantly reduced ruxolitinib plasma exposure but corresponding PD activity was relatively unchanged. Consequently, based on these results and to be conservative with respect to safety, the sponsor recommends no change in the initial dose of ruxolitinib when the drug is co-administered with rifampin or other CYP3A4 inducers. The sponsor's recommendation was considered to be acceptable.

3.10.1.3. Interaction with methotrexate

The submission included one, controlled, single-dose, two-way study designed to assess the potential PK interaction between methotrexate and ruxolitinib in subjects with rheumatoid arthritis (Study #136). The study included 18 patients with rheumatoid arthritis who had been receiving weekly methotrexate at a dose of 7.5 mg to 30 mg for at least 4 weeks prior to screening. On Day 1, methotrexate was administered alone at each subject's established dose level of ≥ 7.5 mg and ≤ 30 mg; on Day 7, ruxolitinib 50 mg (2 x 25 mg tablets) was administered; and on Day 8, methotrexate was co-administered with ruxolitinib 50 mg (2 x 25 mg tablets). Both drugs were administered after an overnight fast.

Methotrexate co-administration increased the geometric mean ruxolitinib C_{max} by 8.4% (Ratio = 108.4% [90% CI: 96.6, 121.2]) and the $AUC_{0\text{-}inf}$ by 8.7% (Ratio = 108.7% [90% CI: 98.8, 119.5). However, the results for the C_{max} and the $AUC_{0\text{-}inf}$ met the bioequivalence criteria as the 90% CI for both ratios were enclosed completely within the 80% to 125% bioequivalence interval. There were no marked differences in ruxolitinib oral apparent clearance or half-life following administration of ruxolitinib with and without methotrexate. The C_{max} and $AUC_{0\text{-}inf}$ of methotrexate and 7-0H-methotrexate (metabolite) were bioequivalent when methotrexate (normalised to a dose of 10 mg) was administered with and without ruxolitinib.

Comment: There is no evidence of a clinically important PK drug-drug interaction between ruxolitinib and methotrexate in subjects with rheumatoid arthritis. Based on the PK results, the dosing regimens of ruxolitinib and methotrexate need not be altered when these two drugs are co-administered. The planned PK assessment of methotrexate based on urinary excretion of the drug was not undertaken as no interaction was observed between methotrexate and ruxolitinib based on plasma PK parameters.

3.10.2. Clinical implications of *in vitro* findings

3.10.2.1. CYP enzyme inhibition

The potential of ruxolitinib to inhibit human CYP enzyme activities was examined with human recombinant CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (INCYTE-DMB-07.13.1), and CYP2B6 and CYP2C8 (INCYTE-DMB-09.24.1), using high-throughput fluorescent substrates and in human liver microsomes (INCYTE-DMB-09.71.1) and standard probe substrates (INCYTEDMB-09.87.1). *In vitro*, ruxolitinib was not a potent inhibitor of recombinant or microsomal CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 with IC_{50} values > 25 μM. Although ruxolitinib inhibited recombinant CYP3A4 activity using the fluorescent probe substrate screening assay (IC_{50} of 8.8 μM), ruxolitinib did not inhibit human liver microsomal CYP3A4 using two preferred probe substrates, midazolam and testosterone, with minimal inhibition at the highest concentration tested (IC_{50} values >25 μM). In addition, microsomal CYP3A4 enzyme activity was not inhibited when ruxolitinib was pre-incubated with NADPH, indicating ruxolitinib is not a mechanism-based inhibitor of CYP3A4 (INCYTE-DMB-09.92.1).

The potential of M18, a major metabolite of ruxolitinib, to inhibit CYP activity in human liver microsomes was also investigated using selective probe substrates (INCYTE-DMB-11.07.1). Following a single oral administration of 25 mg ruxolitinib to healthy human subjects, M18 was the only plasma metabolite representing >10% of the circulating drug-related material (17% based on AUC). The study demonstrated that M18 is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at therapeutically relevant concentrations with IC_{50} values > 3 μM. Since the mean steady-state plasma C_{max} of M18 in humans using a 25 mg bd dosing regimen is expected to be approximately 0.20 μM, the ratio of C_{max}/IC_{50} for the CYPs tested is < 0.1, suggesting the potential for M18 to cause clinical drug interactions via inhibition of the tested CYP enzymes is low.

Comment: The clinical steady state plasma C_{max} value of ruxolitinib following 25 mg bd (the highest proposed therapeutic dose) is 1.2 μM (total drug). The ratio of C_{max}/IC_{50} for ruxolitinib for each of the CYP enzymes tested was < 0.1, suggesting that the potential for ruxolitinib to cause clinical drug interactions via inhibition of these CYP isozymes is low.[10] Based on these data the sponsor stated that an *in vivo* evaluation with a sensitive CYP substrate was not considered necessary. The sponsor's conclusion was considered to be acceptable.

3.10.2.2. CYP enzyme induction

The potential for ruxolitinib to induce CYP3A4 was studied *in vitro* using the human pregnane X receptor (hPXR) assay (INCYTE-DMB-07-05.1). The *in vitro* data suggested that ruxolitinib may induce CYP3A4 at concentrations of approximately 10 μM or greater. The potential for ruxolitinib to induce CYP1A2 and CYP2B6 was investigated using three preparations of cultured human hepatocytes consisting of two lots cryopreserved human hepatocytes and one preparation of freshly isolated human hepatocytes (INCYTE-DMB-11.06.1). The *in vitro* data showed that at concentrations up to 10 μM was not inducer of CYP1A2 or CYP2B6 activity.

Comment: The *in vitro* data showed that ruxolitinib may induce CYP3A4 activity at concentrations of 10 μM or greater, while ruxolitinib at concentrations up to 10 μM was not an inducer of CYP1A2 or CYP2B6 activity. Consequently, clinically significant induction of CYP3A4, CYP1A2, and CYP2B6 is unlikely, given that the clinical steady state plasma C_{max} value of ruxolitinib following 25 mg bd (the highest proposed therapeutic dose) is 1.2 μM (total drug).

3.10.2.3. Interaction with drug transporters

Ruxolitinib crosses Caco-2 cell monolayers through a passive mechanism and is not a substrate for transporters including P-gp. In INCYTE-DMB-09.86.1, the bi-directional apical (A) to basolateral (B) transport of digoxin, a P-gp substrate, was determined across Caco-2 cell

monolayers in the presence of various concentrations of ruxolitinib. The bi-directional B-A/A-B transport ratio of digoxin (5 μM) decreased in the presence of ruxolitinib in a concentration-dependent manner, suggesting that ruxolitinib is a P-gp inhibitor with inhibition IC_{50} of digoxin transport of 21 μM. The clinical steady state plasma C_{max} value of ruxolitinib following 25 mg bd (the highest proposed therapeutic dose) is 1.2 μM (total drug), giving a C_{max}/IC_{50} ratio of < 0.1. Based on this ratio, it is unlikely that ruxolitinib at therapeutic concentrations will inhibit the P-gp mediated transport of drugs that are P-gp substrates.

To determine if the M18 metabolite of ruxolitinib is a P-gp inhibitor, the transport of ^{3}H-digoxin (1 μM) was assessed in the presence of different concentrations of M18 (0 to 3 μM) using MDR1 overexpressing cells (DMPK-R1100122, DMPK-R1100123, DMPK-R1100124, DMPK-R110125). No inhibition of digoxin uptake was observed by M18 at any of the concentrations tested. Since the mean plasma C_{max} for M18 in humans after an oral 25 mg dose of ruxolitinib is 0.14 μM (INCYTEDMB-10.55.1), it is unlikely that M18 at therapeutic concentrations will inhibit the transport of drugs that are substrates of these transporters.

Ruxolitinib and M18 were also tested *in vitro* for inhibitory potential against a panel of human drug transporters (BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3) using individual cell lines that overexpress these transporters (DMPK-R1100122, DMPKR1100123, DMPK-R1100124, DMPK-R110125). Ruxolitinib was not a potent inhibitor of any of these transporters with IC_{50} values ranging from 6.5 μM for OAT3 to 48 μM for BCRP, while M18 did not inhibit any of these transporters at the highest concentration tested (3 μM). The sponsor notes that the C_{max}/IC_{50} ratios for ruxolitinib and M18 based on unbound C_{max} at the highest dose (0.04 μM for ruxolitinib at 25 mg bd with M18 lower than parent), are less than 0.1 for BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1 and OAT3. These results suggest that both ruxolitinib and M18 are unlikely to inhibit the transport of drugs which are substrates for these transporters. The sponsor refers to the criteria from the draft European Medicines Agency (EMA) Guideline on the Investigation of Drug Interactions (April 2010) which uses the unbound C_{max} at the highest therapeutic dose for testing BCRP, OATP, OCT and OAT *in vivo* inhibitor interactions,

Comment: The draft EMA Guideline on the Investigation of Drug Interactions (CPMP/CHMP/125211/2010) referred to by the sponsor have now been adopted by the CHMP (21 June 2012)[b] and come into effect on 1 January 2013. The guidelines had not yet been adopted by the TGA at the time of preparing this CER.

3.11. 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 pharmacokinetics of ruxolitinib were 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 BSC category 1 compound (that is, high solubility, high permeability). The sponsor argues that ruxolitinib is a BSC drug based on its aqueous solubility (over a pH range from 1.0 to 8.0),

[b]<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf>

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 (~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 di-hydroxylated 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 (~ 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 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±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-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% 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% 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.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

The following pharmacodynamic data were submitted and have been evaluated:

- effect of ruxolitinib in health subjects on the QTcF[c] interval in a "Thorough QT/QTc study" complying with the relevant TGA adopted ICH E14 guidelines[d] (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)

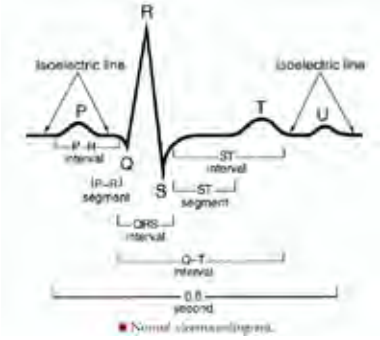
4.2. Thorough QTc study #138

The submission included a Phase I, single-centre (USA), randomised, 4-way cross-over study evaluating the effects of single-doses of placebo, 25 mg ruxolitinib, 200 mg ruxolitinib, and 400 mg moxifloxacin on the heart-rate corrected QT interval in healthy adult volunteers. The study was double-blind with regard to ruxolitinib and placebo and open-label for moxifloxacin. The primary objective of the study was to confirm a lack of effect of ruxolitinib on the heart rate corrected QT interval. The secondary objectives were to determine the safety and tolerability of ruxolitinib and to determine the plasma pharmacokinetics of the drug. The study was conducted in accordance with the TGA adopted ICH E14 guidance for the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.[d]

4.2.1. Subjects and treatment

Fifty subjects (25 men and 25 women) were enrolled and 47 subjects completed all 4 treatments and were analysed for QT change. The mean age of the 50 enrolled patients was 33 years (range: 18, 55), and the majority were white (n=40, 80%), with the remainder being Asian (n=5, 10%) or "other" (n=5, 10%). The inclusion and exclusion criteria were designed to select healthy subjects without medical conditions that could affect the validity of the study. The study excluded subjects with significant cardiovascular disease and subjects with a history of unstable angina or uncontrolled hypertension. Single doses of the study drugs were administered to each subject according to the randomisation scheme in 1 of 8 treatment sequences, and doses were administered orally after at least a 10 h fast from food and a 1 h fast from water. Treatment periods were separated by a 1 week wash-out.

[c]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.



[d] 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>

4.2.2. ECG assessments

All electrocardiogram (ECGs) were performed following 10 minutes of rest, and triplicate ECG readings from 12-lead Holter monitors were spaced by 1-2 minutes. In the baseline phase, an ECG was performed on Day -1, and triplicate ECG readings were obtained from 12-lead Holter monitors at 90, 60, and 30 minutes prior to dosing on Day 1. In the treatment phase, subjects were treated on Days 1, 8, 15 and 22 in a cross-over manner. Triplicate 12-lead ECG readings were obtained from 12-lead Holter monitors at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 h post-dose. Blood samples for PK analysis were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 h post-dose. In the follow-up phase, subjects returned for laboratory evaluations, physical examination and ECGs at 14 days after the last dose of study medication.

4.2.3. Statistical methods

The primary hypothesis was that the largest time-matched difference in change from the Day 1 pre-dose baseline QTcF between each ruxolitinib dose and placebo was 10 ms (that is, H_0: r max = 10 versus the alternative hypothesis H_A: r max < 10 msec). The primary endpoint was the baseline and placebo adjusted QTcF (r r QTcF). The primary analysis was performed using a repeated measures mixed effects linear model that included fixed effects of treatment sequence, study treatment, study period, ECG time point and study drug-by-ECG time point interaction. All 4 treatments were included in the analysis, although only the 2 ruxolitinib doses and placebo were used for testing the primary hypothesis. All inferences were based on the least square means estimated from this model. For each time point, the mean difference between each ruxolitinib dose and placebo was calculated, along with a 1-sided 95% upper confidence bound on the difference. An analysis to test for a differential effect of each ruxolitinib dose on QTcF intervals between men and women was also performed.

4.2.4. Results

The results for the primary analysis showed that largest mean difference from placebo in baseline-corrected QTcF for the 25 mg dose of ruxolitinib was 1.69 ms at 2 h after administration, and the largest upper bound 95% CI was 5.15 ms at the same time point. The largest observed mean difference from placebo for the 200 mg dose of ruxolitinib was 3.28 ms at 12 h after administration, and the largest upper bound of the 95% CI was 6.62 ms at the same time point. Therefore, the primary hypothesis was rejected and the study was deemed negative for QT interval prolongation.

Assay sensitivity was assessed by placing a 1-sided lower 99% confidence bound on the mean differences between moxifloxacin and placebo at 1, 2, 3, 4, and 6 h post-dose. The mean difference in QTcF between moxifloxacin and placebo was 10 to 11 ms at 1, 2 and 3 h post-dose and 7.2 to 9.2 ms at 4 and 6 hours. The largest mean difference in QTcF post-dose between moxifloxacin and placebo was 10.7 ms at 1 hour and the largest 99% lower confidence bound on the mean difference was 6.2 ms at the 1 h post-dose time point. These results demonstrated that the assay had sensitivity.

QTcF intervals (one or more) > 450 ms were observed in 3 subjects treated with ruxolitinib 200 mg, 2 subjects treated with ruxolitinib 25 mg and 2 subjects treated with placebo. No subjects had a QTcF interval > 480 ms at any evaluated time point.

QTcF increases > 30 ms from Day 1 pre-dose baseline were observed in 1 subject treated with placebo (single increase) and no subjects treated with ruxolitinib. No subjects had QTcF increases > 60 ms from the Day 1 pre-dose baseline at any evaluated time point.

Only small increases in heart rate over placebo were seen, maximally 3.7 (95% CI: 1.4, 6.0) beats per minute (bpm) in the ruxolitinib 200 mg treatment arm compared with placebo at 1.5 hours. No subjects met the criteria for increase in the QRS interval (that is, > 110 ms that was also a 25% increase over the Day 1 pre-dose baseline) or the PR interval (that is, >200 ms that was also a 25% increase over the Day 1 pre-dose baseline).

A linear regression analysis demonstrated no statistically significant relationship between the placebo-subtracted differences in changes from the Day 1 pre-dose baseline in QTcF intervals and $\log_{10}$ ruxolitinib plasma concentration.

Comment: The study showed no evidence that ruxolitinib is associated with clinically significant prolongation of the QTcF interval. For both ruxolitinib 25 mg and 200 mg, the mean difference from placebo in baseline-corrected QTcF did not exceed 5 ms at any evaluated time point, and the upper bound of the 95% CI for the mean differences did not exceed 10 ms at any evaluated time point. Examination of the tabulated summary of subjects with new ECG changes and the adverse event findings observed in the study give rise to no concerns relating to the cardiac safety of ruxolitinib. However, it should be noted that the subjects in this study were healthy young adults without pre-existing cardiovascular disease.

4.3. Pharmacodynamic biomarkers

4.3.1. Overview

MF is characterised by a clonal stem cell proliferation that results in the release of haematopoietic stem cells into the blood, extramedullary haematopoiesis, and organomegaly and is associated with production of elevated levels of inflammatory and proangiogenic cytokines. Pharmacodynamic biomarkers were evaluated in the Phase I/II dose-escalation study (#251), the pivotal Phase III study (#351), and the supportive Phase III study (#352). The submission included a separate report evaluating 90 pharmacodynamics biomarkers in subjects with MF from Study #251 (INCYTE-IN-VITRO-10.06.2). Based on the results of Study #251, a selected panel of 20 plasma proteins were explored in Studies #351 and #352. The results from #351 are summarised below and the results from Study #352 have been examined and are considered to be consistent with those from Study #351). The results of the preliminary report have also been examined (INCYTE-IN-VITRO-10.06.2) The results from Study #352 and report INCYTE-IN-VITRO-10.06.2 have not been included in the CER.

4.3.2. Pivotal Study #351 – results

The primary data analysis consisted of an evaluation of 20 selected analytes, including: IL-1β, IL-6, IL-8, IL-1RA, TNFα, TNFRII, MCP-1, MIP-1β, ICAM-1, VCAM-1, CD40, β-2-microglobulin, CRP, EGF, VEGF, FGF-basic, PAI-I, myeloperoxidase, erythropoietin, and leptin. Data were not analysed until after the database was frozen and locked. Samples were analysed by a blinded independent laboratory using a bead based immunoassay platform for the determination of the plasma levels of approximately 89 protein analytes. There were no statistically significant differences between baseline values in patients in the ruxolitinib and placebo groups. However, compared with healthy controls, baseline values were notably elevated in MF patients for biomarkers that are classically associated with inflammation, including CD40, CRP, ICAM-1, IL-1ra, IL-6, IL-8, MCP-1, MIP-1β, TNF-α, TNFRII, and VCAM-1.

Many of the plasma markers associated with an inflammatory response demonstrated a rapid and significant change in MF patients treated with ruxolitinib (that is, CD40, CRP, ICAM-1, IL-1ra, MCP-1, MIP-1β, TNF-α, TNFRII and VCAM-1). In contrast, none of these markers showed significant changes from baseline in the placebo group after 4 weeks or 24 weeks of treatment. The most marked treatment difference between the two groups related to CRP with an 86% median decrease being observed at 4 weeks in the ruxolitinib group compared with a slight increase in the placebo group. Consistent with this observation, the levels of a number of cytokines, cytokine antagonists and cytokine receptors were also lower following 4 weeks treatment with ruxolitinib, with the reductions being maintained at 24 weeks. However, not all plasma inflammatory markers changed with ruxolitinib treatment (for example the chemokines IL-8 and MCP-1 did not change significantly).

Vascular endothelial growth factor (VEGF), secreted from stromal cells, may be responsible for endothelial cell proliferation and pathological angiogenesis observed in a number of malignancies. VEGF showed a decrease of approximately 20% by Week 4 in the ruxolitinib group and this decreased was sustained through to Week 24, and was significantly different from placebo. Erythropoietin (EPO) receptor activation signals through JAK2 and EPO levels were significantly elevated by 2 to 4 fold in the ruxolitinib group at Weeks 4 and 24, while the no significant changes were observed in the placebo group. Plasma leptin has been shown to be a measure of the amount of body fat and most individuals with MF present with a state of catabolic excess. Median leptin levels were more than 2 fold higher than baseline in the ruxolitinib group at week 4 and 3-fold higher at Week 24. In contrast, median leptin levels in the placebo group showed a slight decrease over the 24 weeks of observation. Myeloperoxidase (MPO) and β-2-microglobulin (β2M) represent markers of malignant cell burden. Both were substantially elevated at baseline and levels were lower at Week 4 in the ruxolitinib group and this decrease was maintained to Week 24. In contrast, the median levels of these two biomarkers in the placebo group either did not change (MPO) or increased (β-2M) over the 24 weeks of observation.

4.3.3. IL-6 stimulated SAT3 phosphorylation (pSTAT3)

The STAT3 transcription factor is directly phosphorylated by JAKs in response to stimulation by cytokines such as interleukin-6 (IL-6) and can be used as a pharmacodynamic (PD) marker for JAK inhibition. Therefore, an assay was developed to measure IL-6 stimulated STAT3 phosphorylation (pSTAT3) in human whole blood and IC_{50} (inhibitory concentration at 50% inhibition) values for ruxolitinib inhibition. Report INCYTE-IN VITRO-11.01.1 compared IC_{50} values for IL-6 stimulated pSTAT3 from healthy adult volunteers across multiple ruxolitinib Phase I clinical pharmacology studies (#131, #132, #135, #137 and #142). Data from these studies showed that IL-6 stimulated pSTAT3 was inhibited by ruxolitinib with an IC_{50} value ranging from ~229 nM to ~349 nM. There was no evidence of a gender effect on ruxolitinib inhibition of IL-6 stimulated pSTAT3 based on IC_{50} values in males (~229 nM) and females (~287 nM) (Studies #131, #132).

In patients with MF (Studies #251 and #351), both the basal and IL-6 stimulated levels of pSTAT3 in the pre-dose sample were elevated compared with levels previously observed in healthy subjects, demonstrating that the JAK/STAT pathway was constitutively activated in the peripheral blood of patients with MF enrolled in Studies #251 and #351. The sponsor suggested that the differences were most likely due to elevated cytokines levels or the presence of the activating JAKV617F mutation in patients with MF, which might account for the lower IC_{50} (140 nM) observed in patients with MF compared with healthy subjects (~229 nM to ~349 nM). However, no data were submitted to test the sponsor's explanation. Elevations in pSTAT3 noted at baseline in subjects with MF (Studies #251) returned to levels seen in healthy subjects after 2-4 weeks treatment with ruxolitinib.

In patients with MF (Study #251), there was a clear dose-dependent relationship between ruxolitinib and inhibition of IL-6 stimulated pSTAT3. Maximal inhibition ranged from an average of 34% at 10 mg bd to 99% at 100 mg qd. For all doses studied, maximal inhibition was observed at 2 h after administration (the earliest time point measured) consistent with the plasma ruxolitinib T_{max} at 1 h. The IL-6 stimulated pSTAT inhibition at the 6 h and 9-12 h time points were lower than at the 2 h time point, consistent with the lower plasma concentrations at the later time points. In Study #351, the mean inhibition of IL-6 stimulated pSTAT3 observed at 2 h post-dose on Day 1 in patients with MF was 55.1% in the ruxolitinib treated group (n=72) versus -7.5% for placebo (n=72), demonstrating significant inhibition of the JAK-STAT pathway by ruxolitinib. As previously discussed, the total pharmacodynamic contribution from all ruxolitinib metabolites based on IC_{50} values for pSTAT3 inhibition was estimated to be about 18% of parent drug (INCYTE-DMB-10.55.1).

4.4. PK/PD study in patients with MF (INCYTE-DMB-11.05.1)

4.4.1. Overview

The submission included a PK/PD analysis in patients with MF using data from Studies #251, #351, and #352, using Nonlinear Mixed Effects Modeling software (NONMEM®; V7.1.0). The analysis was complex and was reported in extensive detail in the provided Final Incyte Corporation Pharmaceutical Development Report dated 11 May 2011 (INCYTE-DMB-11.05.1). Indirect response models were utilised to characterise the efficacy outcomes of spleen volume and total symptom score and the safety outcomes of platelet count, haemoglobin level, and absolute neutrophil count. The indirect response models assume that the effects produced by ruxolitinib are reversible but that there is a lag time for maximal change in the respective PD endpoints. Ruxolitinib exposures in were average daily steady-state plasma concentrations ($C_{ss(ave)}$) expressed in nanomolar (nM) units. The $C_{ss(ave}$ was calculated for each subject as the average daily dose (nM/day) divided by the individual Bayes estimate of apparent clearance (CL/F), expressed in L/day, derived from the Population-PK model. For analysis of the total symptom score derived from the MFSAF, the $C_{ss(ave)}$ was computed from 4 week intervals prior to each PD measurement. For analysis of platelet counts, haemoglobin levels and absolute neutrophil counts, the $C_{ss(ave)}$ was computed from the intervals between two consecutive visits when a PD measurement was taken.

Comment: While there are no specific TGA adopted guidelines on the reporting of PK/PD analyses, it is considered that the sponsor's presentation and reporting of the analyses are consistent with the principles for the reporting of population pharmacokinetic analyses described in the relevant TGA adopted EMA guideline CHMP/EWP/185990/06.

4.4.2. PK/PD – spleen volume reduction from baseline at week 24 (efficacy)

The final population PK/PD model used to describe spleen volume response at Week 24 was an indirect response model that characterised the effect of ruxolitinib through an inhibitory E_{max} model. In addition to E_{max}, the model was parameterised in terms of maximum decrease in spleen volume due to ruxolitinib exposure (I_{max}) and exposure producing 50% of maximal reduction in response (IC_{50}). In addition, the model included a placebo effect (E_{plc}) on spleen volume reduction by incorporating a fixed effect additive shift from baseline spleen volume. The dataset at Week 24 contained 228 spleen volume measurements (16 from Study #251 and 212 from Study #351). The $C_{ss(ave)}$ for this analysis was computed from 14 day time intervals prior to each PD measurement. The parameter estimates from the final PK/PD model are summarised below in Table 22.

Table 22: INCYTE-DMB-11.05.1 - Parameter estimates and standard errors from final inhibitory E_{max} PK/PD model for spleen volume at Week 24.

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV[a])	
	Population Mean	%SEM[b]	Final Estimate	%SEM
E_{plc}[c] (cm^3)	86.4	30.3	NE[d]	NE
I_{max}[e] for subject with baseline spleen volume of 2450.3 (cm^3)	1,780	17.0	31.8	26.7
IC_{50}[f] (nM)	193	37.1	NE	NE
RV[g] (%CV)	16.6	15.2	NA[h]	NA

[a] %CV = percent coefficient of variation; [b] %SEM = percent standard error of the mean; [c] Eplc = placebo effect; [d] NE = not estimated; [e] I_{max} = maximum reduction in spleen volume at Week 24 (cm^3); [f] IC_{50} = $C_{ss(ave)}$ producing 50% of maximal inhibition in spleen volume formation (nM); [g] RV = residual variability; [h] NA = not applicable

Comment: The PK/PD model estimated the typical maximum reduction in spleen volume (I_{max}) at Week 24 to be 1,780 cm^3 for a subject with a median baseline spleen volume of 2,450.3 cm^3, reflecting an approximate 73% maximum reduction in spleen volume at Week 24. The mean estimated IC_{50} for the estimated maximal reduction at Week 24 was 193 nM. The model also estimated that an average ruxolitinib concentration of approximately 218 nM is needed to produce a clinically relevant 35% reduction in spleen volume from baseline at Week 24. The report also included a PK/PD model for the change in spleen volume over time. In this model, the covariates of gender and JAK2V617F mutation status were the only statistically significant predictors of IC_{50}. Typical IC_{50} values for $C_{ss(ave)}$ were estimated at 414 nM and 206 nM for males who are negative and positive for the JAK2V617F mutation, respectively, and 244.3 nM and 121.5 nM for females who are negative and positive for the JAK2V617F mutation, respectively. IC_{50} values were about 41% lower in females compared with males.

4.4.3. PK/PD – total symptom score (efficacy)

The PK/PD model for the time course in MFSAF total symptom scores (TSS) characterised the effect of ruxolitinib through an inhibitory E_{max} model applied to the TSS equilibration rate constant (k_{out}) describing the input (or production) of TSS. The maximum decrease in TSS due to ruxolitinib exposure was described by I_{max} and exposure producing 50% of maximal reduction in response was described by IC_{50}. Due to the restricted range in possible TSS (from 0 to 60), a logit transformation was implemented to appropriately constrain model predictions between 0 and 60. The dataset for the analysis contained 1,566 scores from 242 subjects enrolled in Study #351. The $C_{ss(ave)}$ was computed from 4-week intervals prior to each PD measurement. The parameter estimates from the final PK/PD model are summarised below in Table 23.

Table 23: INCYTE-DMB-11.05.1 - Parameter estimates and standard errors from final indirect response PK/PD model for the MFSAF total symptom score.

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV[a])	
	Population Mean	%SEM[b]	Final Estimate	%SEM
E_{plc}[c] for subjects with ≤ 1 blood transfusion more than 8 weeks prior to screening visit (intercept term)	0.0808	48.1	0.815 SD[d]	17.2
E_{plc} for subjects with >1 blood transfusion more than 8 weeks prior to screening visit (intercept term)	0.490	28.0		
k_{out}[e] (hr^{-1})	0.0200	10.4	87.3	16.0
I_{max}[f]	3.23	11.0	78.7	27.4
IC_{50}[g] (nM)	233	9.79	NE[h]	NE
Gamma (γ)	1.08	20.3	92.4	57.1
Effect of baseline total symptom score on E_{plc} (power term)	-0.460	12.3	NA[i]	NA
Additive RV[j] (SD)	1.14	40.3	NA	NA
Proportional RV (%CV)	12.5	32.7	NA	NA

[a] %CV = percent coefficient of variation; [b] %SEM = percent standard error of the mean; [c] Eplc = placebo effect; [d] NE = not estimated; [e] k_{out} = first-order total symptom score equilibration rate constant; [f] I_{max} = maximum inhibition in total symptom score; [g] IC_{50} = $C_{ss(ave)}$ producing 50% of maximal inhibition in total symptom score production (nM); [h] RV = residual variability; [i] NA = not applicable; [j] RV = residual variability

Comment: The population mean estimates of I_{max} and IC_{50} were 3.23 (that is, maximum reduction in total symptom raw score of 57.7) and 233 nM, respectively,

indicating a substantial reduction in total symptom score at average ruxolitinib plasma concentrations achieved with ≥ 10 mg bd dosing regimens. Simulations based on the final model parameter estimates, not adjusted for placebo effect, demonstrated a substantial reduction in TSS by Week 24 for average ruxolitinib concentrations as low as 100 nM. The simulations demonstrated a dose-response relationship for reductions in TSS, with similar responses being observed for doses of 10 mg bd to 25 mg bd. No covariates were found to be statistically significant predictors of I_{max} or γ, a sigmoidicity factor (Hill co-efficient) included to better describe the steepness of the exposure response relationship. However, baseline total symptom score and blood transfusion status (eight weeks prior to screening) were each statistically significant predictors of the placebo effect (E_{plc}). The E_{plc} decreases with increasing baseline total symptom score, and decreases to a greater extent in subjects with > 1 prior blood transfusion in the 8 weeks prior to the screening visit compared with subjects with ≤ 1 blood transfusion in the corresponding time period.

4.4.4. PK/PD – platelet count (safety)

Three separate semi-mechanistic PK/PD models developed using three different subsets from the study population were constructed to characterise the time course of platelet counts in response to ruxolitinib exposure. The final model used the PP (per protocol) subset that included 5,135 platelet count measurements from 225 subjects and including subjects regardless of dose changes and blood transfusion prior to enrollment. The PP was the largest of the three subsets, and the results from this analysis are the only ones described in this CER.

In the PP subset, the drug effect in the final indirect response PK/PD model was characterised via an inhibitory E_{max} function applied to the zero-order platelet count formation rate constant (k_{in}). The maximum fractional inhibition of platelet count formation due to ruxolitinib exposure was described by I_{max}, and ruxolitinib exposure producing 50% of maximal inhibition of platelet count formation was described by IC_{50}. Ruxolitinib exposure was $C_{ss(ave)}$ for the time period between successive clinic visits in which PD measurements were taken. A placebo effect parameter was not incorporated into the structural PK/PD model. No covariates were found to be statistically significant predictors of platelet response. The parameter estimates from the final PK/PD model in the PP are summarised below in Table 24.

Table 24: INCYTE-DMB-11.05.1 - Parameter estimates and standard errors from the final PK/PD indirect response model for platelet count; PP population.

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV[a])	
	Population Mean	%SEM[b]	Final Estimate	%SEM
Baseline Platelet Count (10^9/L)	276	4.46	57.3	7.56
k_{out}[c] (hr^{-1})	0.00149	8.86	115	12.4
I_{max}[d]	1.00	FIXED	NE[e]	NE
IC_{50}[f] (nM)	205	8.49	102	17.8
Covariance between IIV in k_{out} and IIV in IC_{50}[g]	0.700	19.7	NA[h]	NA
RV[i] (SD[j], log_e units)	0.239	5.95	NA	NA

[a] %CV = percent coefficient of variation; [b] %SEM = percent standard error of the mean; [c] k_{out} = first-order platelet count removal rate constant; [d] I_{max} = maximum fractional inhibition of platelet count formation; [f] IC_{50} = $C_{ss(ave)}$ producing 50% of maximal inhibition platelet count formation (nM); [g] RV = residual variability; [h] SD = standard deviation; [i] NA = not applicable.

Comment: In the final PK/PD model (PP population) the estimated mean population baseline platelet count was 276 x 10^9/L, which was less than the observed mean of 310 x 10^9/L. The typical first order-out platelet count removal rate constant

(k_{out}) was estimated to be 0.00149 hr^{-1} resulting in a zero-order platelet count formation rate constant (k_{in}) of 0.411 x 10^9/L/hr and a platelet half-life of approximately 19 days for a typical subject. The IC_{50} was estimated to be 205 nM. The I_{max} parameter was fixed to a value of 1 to facilitate better estimation of other drug effect parameters, regardless of physiologic feasibility. Inter-individual variability was high for all parameters. Simulated exposure-response relationships at Week 24 showed that higher steady state ruxolitinib plasma concentrations were associated with lower platelet counts. The simulations also showed that platelet counts remained above 100 x 10^9/L at Week 24 with all five bd dosing regimens (5, 10, 15, 20, 25 mg bd), and above 50 x 10^9/L at Week 24 for patients with the lowest baseline counts of 100 x 10^9/L treated with 15 mg bd. The sponsor considers that the simulations lend support to the proposed strategy of stepwise dose reductions for the management of thrombocytopenia. Further, the sponsor considers that the simulations support two different starting doses (15 mg bd and 20 mg bd) based on baseline platelet counts to insure that a typical patient stays at or above the threshold count of 50 x 10^9/L.

4.4.5. PK/PD – absolute neutrophil count (safety)

The PK/PD indirect response model was structured to reflect the inhibitory effect of ruxolitinib on the production of circulating neutrophils in the PP population. The model was parameterised in terms of k_{in} describing the production of neutrophils and k_{out} describing the loss of or removal of neutrophils. The system was assumed to be at steady-state at baseline, where the baseline neutrophil count is represented by k_{in}/k_{out}. The drug effect was characterised via an inhibitory E_{max} function applied to k_{in}, with the maximum decrease in neutrophil count due to ruxolitinib exposure being described by I_{max} and ruxolitinib exposure producing 50% of maximal reduction in response being described by IC_{50}. The dataset contained 4,235 ANC measurements from 216 subjects. Ruxolitinib exposure was $C_{ss(ave)}$ for the time period between successive clinic visits in which PD measurements were taken. Subjects receiving placebo were excluded from the analysis population. The parameter estimates from the final PK/PD model are summarised below in Table 25.

Table 25: INCYTE-DMB-11.05.1 - Parameter estimates and standard errors from the final PK/PD indirect response model for ANC; PP population.

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV[a])	
	Population Mean	%SEM[b]	Final Estimate	%SEM
I_{max}[c]	1.00	FIXED	NE[d]	NE
IC_{50}[e] for JAK2V617F negative (nM)	810	24.9	86.0%	19.9
IC_{50} for JAK2V617F positive (nM)	301	0.00588		
IC_{50} for JAK2V617F unknown (nM)	303	24.2		
Baseline Absolute Neutrophil Count effect on IC_{50} (power)	-0.567	13.8		
MTT[f] (hr)	403	1.83	109%	18.3
Baseline	1.00	FIXED	24.2%	18.6
RV[g] (%CV)	29.5	5.58	NA[h]	NA

[a] %CV = percent coefficient of variation; [b] %SEM = percent standard error of the mean; [c] I_{max} = maximum reduction in ANC. d NE = not estimated; [e] IC_{50} = $C_{ss(ave)}$ producing 50% of maximal inhibition in ANC (nM); [f] MTT – mean transit time; [g] RV = residual variability; [h] NA = not applicable.

Comment: The typical first-order neutrophil removal rate (k_{out}) was estimated to be 0.00248 hr^{-1}, resulting in a zero-order neutrophil proliferation rate (k_{in}) of

0.0256 x 10^9/L/hr for a typical subject with baseline ANC of 10.3 x 10^9/L, and equating to a mean neutrophil half-life of approximately 11.6 days. The maximum inhibitory effect on neutrophil production (I_{max}) was fixed to a value of 1.0 to facilitate better estimation of other drug effect parameters, regardless of physiologic feasibility. Covariate analysis identified baseline ANC and JAK2V617F mutation status to be statistically significant predictors of the IC_{50} for ANC. The typical IC_{50} estimates for ruxolitinib $C_{ss(ave)}$ were 301 nM and 810 nM for subjects with median baseline ANC values of 10.3 x 10^9/L who are positive or negative for the JAK2V617F mutation, respectively, and 303 nM for subjects with unknown mutation status. No other covariates were found to be statistically significant predictors of baseline ANC, MTT, or IC_{50}. Marked intersubject variability was noted for the IC_{50} with the CV% being 86% irrespective of JAK2V617F mutation status.

Higher baseline ANC values were associated with lower IC_{50} estimates, while subjects with negative status for the JAK2V617F mutation were predicted to have IC_{50} values more than twice as high as those with positive status for the mutation. Therefore, the highest IC_{50} values (1220 nM) would be predicted for subjects with low baseline ANC (5 x 10^9/L) and negative status for the JAK2V617F mutation, while subjects with the median baseline ANC (50 x 10^9/L) and positive status would be predicted to have IC_{50} estimates of 301 nM and 123 nM, respectively. These estimates are indicative of wide variability in the expected neutrophil response over the range of ruxolitinib exposures expected with 15 mg bd doses.

4.4.6. PK/PD - haemoglobin concentration (safety)

In the PK/PD modelling of exposure and haemoglobin concentration better estimate of observed RBC life span were obtained from the blood transfusion independent (BTI) subset of the population rather than the per-protocol (PP) subset. Consequently, the data from the PP subset were considered to be unreliable. The PK/PD analysis in the BTI subset (which represents an analysis population not confounded by recent or current blood transfusions) provided better data from which to estimate ruxolitinib related effects on haemoglobin concentration. However, the population mean estimate of MTT of 63.3 days derived from the BTI subset still under predicted the expected RBC life span but not to the same degree as the PP population. The BTI subset included 2,074 haemoglobin measurements from 87 subjects.

The PK/PD model in the BTI subset was structured to reflect the inhibitory effects of ruxolitinib on the formation of progenitor reticulocytes (PRC) resulting in inhibition of red blood cell proliferation. Ruxolitinib inhibits the zero-order formation rate (k_{in}) of PRC (representing the influx of the youngest reticulocyte precursors from the bone marrow into the systemic circulation). The drug effect is characterised by an inhibitory E_{max} model, with the maximum decrease in PRC formation described by I_{max}, and ruxolitinib exposure producing 50% of maximal response described by IC_{50}. The ruxolitinib $C_{ss(ave)}$ was the average daily steady-state plasma concentration for the time period between successive clinic visits in which PD measurements were taken. Utilisation of a hypothetical progenitor compartment and four transit compartments, three to reflect the maturation process and one to represent mature red blood cells (RBCs), was sufficient to adequately characterise haemoglobin response to ruxolitinib exposure. A placebo effect parameter was not incorporated into the structural PK/PD model. The parameter estimates from the final PK/PD model in the BTI subset is summarised below in Table 26.

Table 26: Parameter estimates and standard errors from the final indirect response PK/PD life-span model with feedback mechanism for haemoglobin levels; BTI subset.

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV[a])	
	Population Mean	%SEM[b]	Final Estimate	%SEM
Baseline Hemoglobin Concentration (g/L)	122	1.65	14.1	13.1
MPT[c] (hr)	451	15.1	NE[d]	NE
MTT[e] (hr)	1,520	23.7	NE	NE
I_{max}[f]	1.00	FIXED	NE	NE
IC_{50}[g] (nM)	615	28.9	81.7	31.0
Gamma[h] (γ)	2.18	37.6	NE	NE
Covariance between IIV in Baseline Hemoglobin Concentration and IIV[a] in IC_{50}[j]	-0.0478	36.2	NA	NA
RV[k] (SD[j], log_e units)	0.0714	11.5	NA[m]	NA

[a] %CV = percent coefficient of variation; [b] %SEM = percent standard error of the mean; [c] MPT = mean transit time for precursor cells; [d] NE = not estimated; [e] MTT = mean transit time for red blood cell aging process; [f] I_{max} = maximum fractional inhibition of hemoglobin formation; [g] IC_{50} = $C_{ss(ave)}$ producing 50% of maximal inhibition in hemoglobin formation (nM); [h] Gamma = power term for feedback mechanism; [i] RV = residual variability; [j] SD = standard deviation; [k] NA = not applicable

Comment: The population mean estimates in the BTI population were 615 nM for the IC_{50} and 2.18 for the power term for the feedback mechanism on PRC formation (γ). The feedback mechanism on the PRC formation rate was included in the model to account for the rebound in haemoglobin concentration over time following the predicted nadir. The feedback is a function of the baseline haemoglobin concentrations relative to the total predicted haemoglobin concentrations, in which the progenitor formation rate is proportionally augmented as haemoglobin levels become lower. The estimated mean population baseline haemoglobin concentration in the BTI population was 122 x 10^9/L. The population mean estimates of MPT and MTT were 18.8 days and 63.3 days, respectively, resulting in a zero-order progenitor proliferation rate (k_{prc}) of 0.0022 g/L/hr and first-order haemoglobin transfer rate (k_{tr}) of 0.0026 hr^{-1} for a typical subject. The I_{max} parameter was fixed to a value of 1 to facilitate better estimation of other drug effect parameters, regardless of physiologic feasibility. No covariates were found to be statistically significant predictors of baseline haemoglobin concentration or IC_{50}.

Simulations for the dose–response relationship at Week 24 demonstrated that higher steady state ruxolitinib concentrations were associated with greater reductions in haemoglobin concentration. The simulated time-course data predict a nadir in haemoglobin concentration at approximately 10 to 12 weeks after initiation of treatment followed by a slow increase in concentration. The time-course simulations show a relatively linear exposure-response relationship within the range of expected average ruxolitinib concentrations dosing regimens (5, 10, 15, 20, 25 mg bd), and demonstrated incremental reductions in haemoglobin concentration with 5 mg bd dose increases.

4.5. 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).

5. 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 PET-MF (see Table 27, 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 27: 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[e] questionnaire and the modified MFSAF[f], 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.

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

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, 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 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.

6. Clinical efficacy

6.1. 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, #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 28.

Table 28: 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=148 BAT: N=73 56 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.

6.2. Study #351- pivotal efficacy study for the proposed indication

6.2.1. Design, objectives, locations and dates

Study #351 is an ongoing, Phase III, multi-national, multi-centred, randomised, double-blind, placebo-controlled clinical trial of the efficacy and safety of ruxolitinib for the treatment of primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF). The study is identified by the acronym COMFORT-1 (Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment 1) and has been published.[13]

The **primary objectives** were to evaluate the efficacy, safety, and tolerability of ruxolitinib given twice daily (bd) compared with placebo, in patients with PMF, PPV-MF, or PET-MF. The s**econdary objectives** were to evaluate the effect of ruxolitinib on patient reports of MF symptoms, and to evaluate the population pharmacokinetics of ruxolitinib.

The study is being undertaken in 68 sites in the USA, 6 sites in Canada and 15 sites in Australia. It was initiated on 24 August 2009 and was on-going at the time of the data cut-off date of 2 November 2010. The final CSR was dated 27 April 2011. The principal investigator is located in the Anderson Cancer Center, Houston, Texas, USA. The study was sponsored by the Incyte Corporation (USA). The study protocol and all amendments were reviewed by Independent Ethics Committees (IEC) or Institutional Review Boards (IRB) for each study centre and the study was conducted according to the ethical principles of the Declaration of Helsinki as described in ICH E6, and/or local laws, whichever provided the greatest level of protection for the study participants. All patients provided informed consent.

Comment: The data cut-off date for the CSR was 2 November 2010 (last patient visit). However, two additional addenda to the CSR were included in the submission. In addendum 1 (dated 4 May 2011), additional MRI data provided longer follow-up

regarding the duration of response through to the cut-off date of 28 January 2011. In addendum 2 (dated 31 October 2011), updated overall survival data were provided through to the cut-off date of 1 March 2011. Data from both of these addenda have been evaluated and included in the relevant sections of this CER.

6.2.1.1. Inclusion and exclusion criteria

The study population included men and women, aged 18 years or older, who had been diagnosed with myelofibrosis (PMF, PPV-MF, or PET-MF) according to 2008 World Health Organization (WHO) criteria (Table 29) and were naive to JAK inhibitor therapy.

Table 29. The 2008 World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia and primary myelofibrosis; source Tefferi and Vardiman, 2008.

	Polycythemia vera[a]	*Essential thrombocythemia*[a]	*Primary myelofibrosis*[a]
Major criteria	1 Hgb > 18.5 g dl^{-1} (men) > 16.5 g dl^{-1} (women) or Hgb or Hct > 99th percentile of reference range for age, sex or altitude of residence or Hgb > 17 g dl^{-1} (men), or > 15 g dl^{-1} (women) if associated with a sustained increase of ⩾2 g dl^{-1} from baseline that cannot be attributed to correction of iron deficiency or Elevated red cell mass > 25% above mean normal predicted value	1 Platelet count ⩾450 × 10^{9} l^{-1}	1 Megakaryocyte proliferation and atypia[b] accompanied by either reticulin and/or collagen fibrosis, or In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (i.e. pre-fibrotic PMF).
	2 Presence of *JAK2V617F* or similar mutation	2 Megakaryocyte proliferation with large and mature morphology. No or little granulocyte or erythroid Proliferation.	2 Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm
		3 Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm	3 Demonstration of *JAK2V617F* or other clonal marker or no evidence of reactive marrow fibrosis
		4 Demonstration of *JAK2V617F* or other clonal marker or no evidence of reactive thrombocytosis	
Minor criteria	1 BM trilineage myeloproliferation 2 Subnormal serum Epo level 3 EEC growth		1 Leukoerythroblastosis 2 Increased serum LDH 3 Anemia 4 Palpable splenomegaly

Abbreviations: CML, chronic myelogenous leukemia; EEC, endogenous erythroid colony; Epo, erythropoietin; Hct, hematocrit; Hgb, hemoglobin; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; WHO, World Health Organization.
[a]Diagnosis of polycythemia vera (PV) requires meeting either both major criteria and one minor criterion or the first major criterion and 2 minor criteria. Diagnosis of essential thrombocythemia requires meeting all four major criteria. Diagnosis of primary myelofibrosis (PMF) requires meeting all three major criteria and two minor criteria.
[b]Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.

Risk categorization was based on the IWG scoring system.[14] This system identifies 4 risk groups based on the presence or absence of 5 baseline prognostic predictors of shortened survival. The 5 baseline prognostic predictors are: (1) age > 65 years; (2) presence of constitutional symptoms; (3) haemoglobin concentration < 10 g/dL; (4) leukocyte count > 25 x 10^9/L; and (5) circulating blast cells ≥ 1%. The 4 risk groups are low risk (no prognostic predictors), intermediate risk-1 (1 prognostic predictor), intermediate risk-2 (2 prognostic factors), and high risk (≥ 3 prognostic predictors).

Comment: The diagnostic criteria for MF are acceptable. The sponsor stated that data from the ongoing exploratory dose escalation study (#251) showed that there was little difference "in the manifestations or prognosis" of the subsets of MF (that is, PMF, PPV-MF, or PET-MF), and that the patients generally responded to treatment with ruxolitinib independently of these subsets and of JAK2 mutational status. The sponsor also stated that study population was "*further qualified in response to feedback from the FDA for the final SPA [Special Protocol*

Assessment]-approved protocol to include only subjects in whom changes in splenomegaly could be assessed and were likely to be clinically meaningful, and for whom active treatment was indicated on the basis of various other measures of disease burden including IWG risk category and significant symptoms".

6.2.1.2. Study phases

The protocol (amendment #3) specified 4 phases: (1) screening phase of up to 35 days; (2) baseline phase of 7 days; (3) on-treatment phase during which participation may continue for subjects receiving benefit on study drug or open label ruxolitinib until the later of marketing approval (presumably FDA) or when the last randomised subject remaining in the study has completed Week 144 (36 months); and (4) follow-up phase of 28±7 days after the last dose of study drug or open-label ruxolitinib. Efforts were made to follow-up discontinued subjects every 6 months in order to determine if leukemic transformation or death had occurred.

6.2.1.3. Study treatments

6.2.1.3.1. Starting dose

Patients were centrally randomised through an Interactive Voice Response System (IVRS) to receive ruxolitinib or matching placebo tablets with a 1:1 ratio. The starting dose was determined by baseline platelet count and could be taken without regard to meals approximately 12 h apart. Patients with baseline platelet counts > 200 x 10^9/L began 20 mg bd (4 x 5 mg tablets bd), and patients with baseline platelet counts of 100 to 200 x 10^9/L, inclusive, began 15 mg bd (3 x 5 mg tablets bd).

6.2.1.3.2. Dose increase for inadequate efficacy

After the first 4 weeks of therapy the dose could be increased by 5 mg bd for patients who demonstrated inadequate efficacy, and who met the following 3 conditions: (1) inadequate efficacy demonstrated by palpable spleen length below the left costal margin that had been reduced by less than 40% at the week 4 visit relative to baseline; (2) platelet count at Week 4 of 150 x10^9/L and platelet count had never been below 150 x 10^9/L at a prior laboratory evaluation since baseline; and (3) absolute neutrophil count levels had remained at or above 1 x 10^9/L since baseline. Patients who continued in the extension phase after Week 24 may have had their dose increased because of lack of efficacy, based on the clinical judgment of the investigator and provided specified haematological safety criteria were met.

6.2.1.3.3. Dose reductions for safety

Administration of ruxolitinib or placebo was interrupted if platelet counts fell below 50 x 10^9/L or if the ANC fell below 0.5 x 10^9/L, and doses were decreased for platelet counts less than 125 x 10^9/L (see Table 30, below). It was recommended that haematology parameters be obtained at least weekly for platelet counts < 100 x 10^9/L or an ANC < 1 x 10^9/L, and at least twice weekly for platelet counts < 50 x 10^9/L or an ANC < 0.5 x 10^9/L. Dosing could be restarted or increased following recovery of platelet and absolute neutrophil counts to specified mandatory levels (see Table 31, below).

Table 30: Study #351 – Dose reductions for reductions in platelet count.

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

Table 31: Dose restart or increases following recovery of platelet count or ANC.

Current Platelet Count (in thousands)	Dose Restart or Dose Increase Guidelines (NOTE: **maximum doses** are displayed. Doses must never be more than 5 mg BID BELOW a dose that previously resulted in platelet count < 100 K/μL)
< 50 K/μL	Continue hold
50 to < 75 K/μL	5 mg BID for at least 2 weeks; if stable, may increase to 10 mg BID
75 to < 100 K/μL	10 mg BID for at least 2 weeks; if stable, may increase to 15 mg BID
100 to < 125 K/μL	15 mg BID
≥ 125 K/μL	20 mg BID
Current ANC Level	Dose Restart or Dose Increase Guidelines (NOTE: maximum doses are displayed. Doses may never be more than 5 mg below a dose that previously resulted in ANC of < 500/μL)
< 500/μL	Continue hold
500 to < 750/μL	5 mg BID for at least 2 weeks; if stable, may increase to 10 mg BID
750 to < 1000/μL	10 mg BID for at least 2 weeks; if stable, may increase to 15 mg BID
≥ 1000/μL	15 mg BID for at least 2 weeks; if stable may increase to 20 mg BID
≥ 1500/μL	20 mg BID

NOTE: Whether the dose interruption occurred because of neutropenia, thrombocytopenia or both, when restarting, both the platelet count and ANC must be considered to determine the restart dose, with the lower calculated dose being used, and in any case the maximum dose must not exceed 5 mg bd LESS than the dose that resulted in ANC falling below 500/μL or platelets falling below 100,000/μL. Subjects who had platelet count falling below 100,000/μL or ANC falling below 500/μL while receiving a dose of 5 mg bd may resume a dose of 5 mg bd but never higher, once platelet count rises above 50,000/μL and ANC is above 500/μL.

6.2.1.3.4. Cross-over prior to primary endpoint analysis (before Week 24)

Patients with protocol-defined spleen growth were eligible for unblinding prior to the primary study endpoint being reached (early cross-over). If there was a ≥ 25% increase in spleen volume compared with baseline before Week 24, it must have been accompanied by specific worsening of symptoms (early satiety accompanied by weight loss or worsening pain requiring daily narcotic use). After Week 24, asymptomatic spleen growth alone was sufficient for early unblinding and potential cross-over. Patients found to have been randomised to placebo after early unblinding were eligible to cross-over immediately, provided haematology laboratory parameters were adequate. Patients found to have been randomised to ruxolitinib were withdrawn from the study because symptomatic increase in spleen size increase would indicate that the subject was not receiving benefit from therapy.

6.2.1.3.5. Cross-over after primary analysis (after week 24)

After the primary data analysis was completed, the study was unblinded and all patients who were randomised to placebo had the opportunity to cross-over and begin receiving open-label ruxolitinib, provided haematology parameters were adequate (that is, platelet count > 75 x 10^9/L and ANC > 0.5 x 10^9/L). Patients who had been randomised to ruxolitinib were withdrawn from the study or could continue and receive open-label ruxolitinib if, in the investigator's judgment, continuation with possible dose change provided the best option for the subject.

6.2.1.3.6. Concomitant CYP3A4 inhibitors

The protocol included specific instructions to reduce ruxolitinib dose by 50% for all doses above 5 mg qd when administered with potent CYP3A4 inhibitors.

6.2.1.3.7. Duration of treatment

Treatment could continue for subjects receiving benefit on study drug or open label ruxolitinib until the later of marketing approval (presumably FDA) or when the last randomised subject remaining in the study completed Week 144 (36 months).

6.2.1.3.8. Withdrawal from treatment or assessment

The withdrawal criteria included: subject withdrew consent; further participation would be injurious to the subject's health or well-being in the investigator's medical judgment; study terminated; pregnancy; splenic irradiation required; leukemic transformation (as evidenced by bone marrow blast counts ≥ 20%, or peripheral blast counts ≥ 20% lasting at least 8 weeks).

6.2.1.4. Efficacy endpoints

6.2.1.4.1. Primary efficacy endpoint

The primary efficacy endpoint was the proportion of patients who achieved a ≥ 35% reduction in spleen volume from baseline to Week 24 as measured by MRI (or CT if applicable). The spleen volume determined using a standardized imaging protocol and image analysis algorithm.

Comment: The primary efficacy endpoint was reduction in spleen volume rather than overall survival (OS), progression free survival (PFS) or disease free survival (DFS). The TGA adopted EMA guideline on the evaluation of anticancer medicinal products indicates that Phase III confirmatory oncology trials should provide evidence of clinical benefit, and that acceptable primary endpoints include OS and PFS/DFS, and where PSF/DFS is the selected primary endpoint OS should be reported as a secondary endpoint and *vice versa* (CPMP/EWA/205/95 Rev 3/Corr.).[g] Furthermore, the TGA adopted Appendix 2 to the parent cancer guideline, which relates to confirmatory studies in haematological malignancies, specifically indicates that in more severe cases of myelodysplastic syndrome the recommendations expressed in the parent guideline relating to OS, PFS and DFS apply. Appendix 2 suggests that, while PFS "in principle" is an "acceptable primary endpoint survival data are also needed in order to exclude with reasonable certainty detrimental effects on survival". In addition, Appendix 2 notes that symptom burden is of major concern in all stages of myelodysplastic syndromes and consequently "*QoL assessment in properly conducted double-blind studies are welcomed in trials aiming to establish a benefit in terms of survival and/or progression*". Based on the relevant TGA adopted guidelines, it is considered that PFS should have been selected as the primary efficacy endpoint in pivotal Study #351 and OS as the secondary efficacy endpoint.

While it is considered that the choice of reduction in spleen volume as the primary efficacy endpoint appears to be inconsistent with the relevant TGA adopted guidelines some support for this endpoint comes from consensus guidelines. The European Myelofibrosis Network (EUMNET) consider that consensus criteria for major or moderate clinico-haematological response in MF were changes in haemoglobin concentration, spleen size and constitutional symptoms, while changes in platelet count and white blood cell count were complimentary criteria and were of value for determining minor response.[15] The International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) defined three response categories, complete remission (CR), partial remission (PR) and clinical improvement (CI).[16] The consensus panel agreed that the CI response was applicable only to patients with moderate to severe cytopenia or splenomegaly.

The sponsor notes that the spleen is enlarged in approximately 90% of patients with MF, as assessed by palpation, and that both the EUMNET and the IWG-MRT have defined criteria for response based on changes in palpable spleen length. EUMNET considers a 50% reduction in spleen length to be a clinical response for palpable spleen lengths of 10 cm or less, or 30% decrease in patients with palpable spleen length of at least 10 cm.[15] The IWG-MRT consider a 50% decrease in length for spleens of 10 cm or more, or a spleen that is palpable at 5 cm becoming non-palpable, to be a clinical response.[16] Based on both guidelines, the sponsor

[g]<http://www.tga.gov.au/pdf/euguide/ewp020595enrev3.pdf>

considers that a reduction in palpable spleen length of 50% or more would be "clinically meaningful for all but the smallest of enlarged spleens". In this study the sponsor elected to use imaging (MRI/CT) to determine spleen size rather than palpation in order for an objective, unbiased assessment of size to be made. Comparison of MRI measurements of spleen volume and spleen assessment by palpation in a subset of 27 patients enrolled in Study #251 showed that a 50% reduction in palpable spleen length correlated with a reduction in spleen volume of 32%. Based on this finding, response to ruxolitinib treatment was defined as a ≥ 35% reduction in spleen volume assessed by MRI or CT. Patients who met this criterion were designated as responders.

In Study #351, imaging for determination of spleen volume was undertaken at baseline and then every 12 weeks up to 72 weeks, followed by every 24 weeks. Images were initially read by a local radiologist who was instructed not to provide a quantitative measure of spleen volume but could provide a qualitative assessment (for example, enlarged, smaller). The scans from individual subjects were then interpreted by a central reader who was blinded to initial treatment assignment.

Overall, it is considered that reduction in spleen volume is an acceptable measure of clinical improvement in MF but it is uncertain whether it will translate into improvement in overall survival or progression free survival. However, reduction in spleen volume is likely to result in improvement of symptoms associated with splenomegaly.

6.2.1.4.2. Secondary efficacy endpoints

- Duration of maintenance of a ≥ 35% reduction from baseline in spleen volume in patients initially randomised to receive ruxolitinib, defined as the longest duration of consecutive measurements of ≥ 35% reduction observed prior to the time of database freeze for patients who have at least one measured ≥ 35% reduction, and who either had at least one subsequent measurement or, who subsequently dropped out prior to another assessment.
- Proportion of patients who have ≥ 50% reduction in total symptom score from baseline to Week 24 as measured by the modified MFSAF v2.0 diary.
- Change in total symptom score from baseline to Week 24 as measured by the modified MFSAF v2.0 diary.
- Overall survival.

Comment: The secondary efficacy endpoints are acceptable. Symptoms of MF were assessed using a symptom diary (modified Myelofibrosis Symptom Assessment Form [MFSAF] v2.0 diary), developed by the sponsor (Incyte) with recommendations from the FDA. Patients were issued a hand-held device to record answers to queries regarding 7 symptoms of MF using numerical scale from 0 (indicating absence of symptoms) to 10 (worst imaginable). Symptoms assessed included night sweats, itching, abdominal discomfort, pain under ribs on left, feeling of fullness (early satiety), muscle/bone pain, and inactivity. However, the total symptom score for baseline and on-study time periods was calculated based on the 6 symptom scores excluding the score for inactivity, following advice from the FDA that inactivity is not a symptom of the disease. The modified MFSAF v2.0 diary was completed by patients each night for 25 weeks beginning at Day -7 (first day of Baseline) through to Week 24 visit.

6.2.1.4.3. Exploratory efficacy endpoints

There were a large number of exploratory assessments most of which were exploratory efficacy endpoints. Results for selected exploratory efficacy endpoints have been reviewed in this CER.

6.2.1.4.4. Randomisation and blinding methods

Patients were centrally randomised through an Interactive Voice Recognition System (IVRS) to receive ruxolitinib or matching placebo tablets with a 1:1 ratio; site staff contacted an IVRS to obtain individual patient study drug assignment. In this study, patients were not stratified on the basis of disease severity. Patients, investigators and the sponsor remained blinded to the initial treatment assignment until the database was frozen and the primary data analysis was complete. Individual patient unblinding may have occurred if worsening symptomatic or asymptomatic spleen growth qualified for early crossover or if needed for safety reasons. An independent Data Safety Monitoring Board (DSMB) was established for the purpose of periodically examining the unblinded safety data to ensure that the benefit/risk ratio remained acceptable for participating patients.

6.2.1.4.5. Analysis populations

The intent-to-treat (ITT) population included all randomised patients. Treatment groups for this population were defined according to treatment assignment at the time of randomisation on Day 1 regardless of the actual study medication taken during the study. This population was used for analyses of all efficacy data. The ITT population included all 309 randomised patients, 155 in the ruxolitinib group and 154 in the placebo group.

The per-protocol (PP) population included those patients in the ITT population who: (1) met all inclusion criteria and did not have any exclusion criteria; (2) took the correct study drug assigned at randomisation on Day 1 during the controlled period; (3) took at least 80% of the assigned study drug between the day 1 and Week 24 visit; and (4) did not take any protocol specified prohibited medications. The PP population included 133 patients in the ruxolitinib group and 123 patients in the placebo group (85.8% and 79.9% of the ITT populations, respectively).

The safety evaluable population included randomised patients who received at least 1 dose of study drug. Treatment groups for this population were defined according to the actual treatment received. The safety evaluable population included 100% (155/155) of patients randomised to ruxolitinib and 98.1% (151/154) of patients randomised to placebo.

The PK/PD evaluable population included patients who received at least 1 dose of study drug and provided at least 1 sample for plasma PK and PD assessments.

6.2.1.4.6. Sample size

The primary efficacy endpoint was analysed using a chi-square test. Based on the data from ongoing Study #251, it was assumed that at least 30% of the patients treated with ruxolitinib would achieve a > 35% reduction from baseline to Week 24 and that the placebo response rate would be no more than 10%. Under this assumption, a sample size of 240 patients (120 per group) would provide a 97% power to detect a treatment difference in the primary endpoint at two-sided alpha level of 0.05 using a chi-square test. This study was overpowered for the primary endpoint in order to provide additional amount of power for the secondary efficacy endpoints.

6.2.1.4.7. Statistical methods

Primary efficacy analysis

The primary efficacy analysis of the proportion of patients achieving a ≥ 35% reduction in spleen volume (MRI/CT) from baseline to Week 24 was calculated for the ITT population and a secondary analysis was undertaken in the PP population. The difference between the two proportions was calculated using a SAP specified Fisher's exact test rather than chi-square test (due to the low proportion of responders in the placebo group) and significance was specified at a 2-sided alpha of 0.05.

The study included a pre-specified sensitivity analysis of the proportion of patients achieving a ≥ 35% proportion in spleen volume from baseline to last observation using a logistic regression model with baseline spleen volume, sex, MF type, hydroxyurea usage in the 3 months prior to entering the study and treatment as the model effects. Treatment effect (active versus control) was assessed by odds ratio with 95% CI and p-value, after adjusting for the covariates. The study also included additional pre-specified sensitivity analyses of the change in spleen volume from baseline to last observation using both parametric and non-parametric statistical methods.

The study also included pre-specified subgroup analyses of the primary efficacy endpoint using the primary method of analysis for each subgroup comparison. In addition, a logistic regression model with sex, age, MF type, previous hydroxyurea use, baseline spleen volume, baseline spleen palpation size and treatment as the model effects was also undertaken to estimate treatment differences in the hazard ratio (active versus control) after controlling for all sub-group factors.

Secondary efficacy analyses

The SAP stated that the secondary efficacy endpoints were to be analysed only when the study had reached the efficacy objective in the primary endpoint. The secondary efficacy variables were to be tested following a fixed sequence-testing-procedure with each at the 0.05 alpha level. The testing order was: (1) the proportion of patients who have a ≥ 50% reduction from baseline to Week 24 in the total symptom score; (2) change from baseline to Week 24 in the total symptom score; and (3) overall survival. The defined hierarchical testing procedure controlled the overall type I error at the 0.05 alpha level for the primary and all secondary efficacy analyses.

Missing values

Missing values for the primary efficacy endpoint were not to be imputed and patients must have had baseline spleen volumes to have been included in the primary efficacy analysis. Patients with missing Week 24 spleen volumes were considered not to have achieved the specified ≥ 35% reduction. Patients who dropped out of the study due to lack of efficacy or treatment-related adverse events or made an early cross-over to active treatment (placebo patients only) prior to the Week 24 visit were all considered to have not achieved the specified ≥ 35% reduction.

Missing values for the secondary endpoint of total symptom score were not to be imputed and patients must have had a baseline total symptom score in order to have been included in the analysis. Patients with missing Week 24 total symptom scores were considered not to have achieved the specified ≥ 50% reduction. Patients who dropped out of the study due to lack of efficacy or treatment-related adverse events, or were unblinded prior to Week 24 for the early cross-over to active treatment were all to be considered not to have achieved the specified ≥ 50% reduction.

Interim analysis

No interim analyses with stopping boundaries were planned for early stopping due to efficacy or for sample size adjustment.

6.2.1.4.8. Participant flow

The disposition of the 304 patients in the safety evaluable population is summarised below in Table 32.

Table 32: Study #351 – Disposition of patients in the safety evaluable population.

Variable	Ruxolitinib (N = 155)	Placebo (N = 151)
Number (%) of subjects who were still in the study as of 02 November 2010[a]	134 (86.5)	78 (51.7)
Number (%) of subjects who crossed over		36 (23.8)
Number (%) of subjects withdrawn from the study	21 (13.5)	37 (24.5)
Primary reason for withdrawal from study for subjects who did not cross over:[b]		
Death[c]	9 (5.8)	9 (6.0)[d]
Adverse event[e]	8 (5.2)	8 (5.3)
Disease progression	3 (1.9)	12 (7.9)[d]
Consent withdrawn	1 (0.6)	5 (3.3)
Other	0	3 (2.0)

a This includes all patients that had not withdrawn, not crossed over to ruxolitinib, and were alive.
b No patients were withdrawn from the study prior to cross-over because of a protocol deviation, lost to follow-up, non-compliance with study medication, non-compliance with study procedures, or termination of the clinical study by the Sponsor.
c The disposition of patients whose date of death and date of withdrawal from the study were the same were automatically categorized as death per the programming rules.
d One of the 11 deaths in the placebo group occurred after the subject withdrew from the study but within the 28-day safety follow-up period; this subject withdrew from the study for disease progression as determined by the investigator.
e This represents patients whose primary reason for withdrawal from the study was adverse event.

Comment: The proportion of patients still in the study as of 2 November 2010 was notably higher in the ruxolitinib group than in the placebo group (86.5% versus 51.7%, respectively). The main reason for this imbalance relates to the number of patients who crossed-over from placebo to ruxolitinib. In the patients who did not cross-over, a greater proportion in the placebo group withdrew due to disease progression compared with patients in the placebo group while withdrawals due to adverse events occurred in a similar proportion of patients in both treatment groups.

6.2.1.4.9. Major protocol violations/deviations

No patients in either treatment group were excluded from the ITT population because of protocol violations. The PP population included 133 patients in the ruxolitinib group and 123 patients in the placebo group who were clinically assessed as having reasonably adhered to the protocol. There were a total of 53 unique protocol violations resulting in patients being excluded from the PP 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. In addition, data was lost for one patient following re- location of the study site.

Of the 14 patients (8, ruxolitinib versus 6, placebo) with violations of inclusion/criteria resulting in exclusion from the PP population: 7 were excluded because of insufficient documentation to fully demonstrate MF per the WHO criteria (4, ruxolitinib versus 3, placebo); 5 were excluded because they did not meet the IWG risk criteria for intermediate risk-2 or high risk (2, ruxolitinib versus 3, placebo); and 2 in the ruxolitinib group were excluded because of inadequate baseline ANC or platelet count.

Comment: Overall, there were 22 major protocol violations resulting in exclusion from the ruxolitinib group (that is, 14.2% of the randomised population) in the PP population compared with 31 in the placebo group (that is, 20.1% of the randomised population). While there was an imbalance in the proportion of patients with major protocol violations between the two randomised treatment

groups it is considered that this difference is unlikely to have significantly biased the efficacy analysis in the ITT population.

6.2.1.4.10. Baseline data

Baseline demographics. The median age of the patients was 68 years (range: 40, 86). Patients were relatively evenly balanced between the sexes (54%, male versus 46%, female).The majority of patients were White (89.6%) with most of the other patients being Black (4.2%) or Asian (2.9%). In general, the treatment groups were well balanced with regard to baseline demographic characteristics but differences were noted in the age group distribution with a higher proportion of patients in the ruxolitinib group than in the placebo group being > 65 years (66.2% versus 54.8%, respectively).

Baseline disease characteristics of the ITT population. PMF was the diagnosis in nearly half of the patients (49.8%), PPV-MF in 31.4% of patients and PET-MF in 18.4% of patients. Overall, the median duration of disease from initial diagnosis was 2.2 years, with a large range of from 0 to 33.2 years. There were 36 patients with an initial diagnosis of MF 10 years before entering the study. The majority of patients (61.2%) were designated high risk and 38.2% were designated intermediate risk-2. The median spleen volume was 2597.7 cm^3 in the ruxolitinib group and 2566.3 cm^3 in the placebo group. The sponsor notes that a normal spleen weighs ~150 g, is ~11 cm in craniocaudal length and has a volume of ~200 cm^3. The JAKV1674 mutation was present in 76.4% of patients, absent in 21.7% and unknown in 1.9%. Overall, the treatment groups were generally well balanced with regard to baseline disease characteristics with differences noted in disease subtype (more PMF in the placebo group than in the ruxolitinib group [54.5% versus 45.2%, respectively], and more PET-MF in the ruxolitinib group than in the placebo group [22.6% versus 14.3%, respectively], and ECOG Performance Status (higher proportion of patients in the ruxolitinib group with 0 or 1 than in the placebo group [88.7% versus 80.5%, respectively]).

Baseline laboratory assessments. In the total population, the median leukocyte count (18.2 x 10^9/L) was elevated above the upper limit of normal (ULN) (11.0 x 10^9/L), and the median ANC (14.4 x 10^9/L) was also elevated above the ULN (7.9 x 10^9/L). The median Hgb concentration was 105 g/L (range: 35, 173), which was below the lower limit of normal (LLN) for both men (130 g/L) and women (120 g/L). The median platelet count was 251.0 x 10^9/L (range: 81, 984). Overall, baseline laboratory assessments were similar for the ruxolitinib and placebo groups. The baseline abnormalities in laboratory assessments are consistent with the characteristics of MF. The protocol required an ANC > 1 x 10^9/L and a platelet count > 100 x 10^9/L; 1 patient randomised to ruxolitinib had an ANC < 1.0 x10^9/L and 1 patient randomised to ruxolitinib had a platelet count < 100 x 10^9/L.

Previous treatments or procedures in the ITT population included prior hydroxyurea use at any time in the past (67.1%, n=104, ruxolitinib versus 56.5%, n=87, placebo), splenic radiotherapy (0.6%, n=1, ruxolitinib versus 0%, placebo) and history of blood component transfusion (27.7%, n=43 versus 28.6%, n=44), including plasma, red blood cells or platelets.

The *general medical history* in the ITT population was similar in the two treatment groups with 99.7% (n=309) of all patients having a general medical history. In general, reported items were consistent with the clinical features of MF and were reasonably well balanced between the two treatment groups. Prior medical history items reported in ≥ 20% of patients in either treatment group (ruxolitinib versus placebo) were splenomegaly (88.4% versus 85.1%), fatigue (65.9% versus 58.4%), night sweats (55.5% versus 51.9%), anaemia (56.8% versus 46.8%), hypertension (43.2% versus 48.7%), weight decreased (43.9% versus 42.2%), early satiety (40.0% versus 29.29%) polycythemia vera (32.9% versus 31.8%), pruritus (32.3% versus 29.2%), peripheral oedema (26.5% versus 26.6%), hepatomegaly (25.8% versus 24.0%), essential thrombocythemia (23.9% versus 13.6%), insomnia (22.6% versus 14.3%), gastroesophageal reflux (21.9% versus 20.8%), abdominal pain (22.6% versus 18.2%),

leukocytosis (21.3% versus 15.6%), hypothyroidism (18.1% versus 20.1%), gout (18.1% versus 20.1%) and diarrhoea (16.8% versus 20.8%).

Prior medications for the treatment of MF in the ITT population was taken by 78.7% of patients in the ruxolitinib group and 72.7% of patients in the placebo group. The general pattern of prior medications for the treatment of MF was similar in the two treatment groups with the most commonly prior medications (≥ 10% in either treatment group, ruxolitinib versus placebo) being hydroxyurea (67.1% versus 56.5%), anagrelide or anagrelide HCL (19.4% versus 10.4%), and anti-anaemia medications (11.0% versus 11.9%).

Prior medications not specifically taken for the treatment of MF in the ITT population were used by nearly all patients in both the ruxolitinib group (97.4%) and the placebo group (96.8%). The most frequently reported prior medication not specifically taken for MF was acetylsalicylic acid used as an anti-thrombotic agent (43.9%, ruxolitinib versus 45.7%, placebo), while few patients reported acetylsalicylic acid use as an antipyretic (2 versus 4 in the ruxolitinib and placebo groups, respectively). Prior medications not specifically taken for the treatment of MF and reported in ≥ 10% in either treatment group (ruxolitinib versus placebo) were allopurinol (29.0% versus 29.9%), paracetamol (29.7% versus 34.4%), multivitamins (20.6% versus 10.4%), L-thyroxine ± sodium (17.4% versus 20.8%), omeprazole (14.2% versus 10.4%), glucosamine with methylsulfonylmethane (11.0% versus 10.4%), furosemide (11.0% versus 18.2%), hydrochlorothiazide (10.3% versus 6.5%), folic acid (10.3% versus 6.5%), lidocaine (9.7% versus 10.4%) and fish oil (9.7% versus 11.7%).

Concomitant medications in the ITT population prior to cross-over were used by 97.4% of patients in the ruxolitinib group and 100% of patients in the placebo group. Medications used by ≥ 5% patients in the ruxolitinib group compared with the placebo group were multivitamins (25.2% versus 13.9%), antidepressants (23.9% versus 18.5%), hypnotics and sedatives (21.9% versus 16.6%), quinolone antibacterials (18.7% versus 13.2%) and beta-lactam antibacterials penicillin (14.8% versus 5.3%). Medications used by ≥ 5% of patients in the placebo group compared with the ruxolitinib group were other analgesics and antipyretics (66.9% versus 58.7%), opioids (40.4% versus 25.8%), beta-blocking agents (35.1% versus 22.6%), loop diuretics (33.1% versus 23.9%), cough suppressants excluding combination with expectorants (33.1% versus 20.6%), lipid modifying agents (32.5% versus 27.1%), systemic antihistamines (29.8% versus 24.5%), potassium sparing agents (13.9% versus 6.5%), general anaesthetics (11.3% versus 5.8%) and blood glucose lowering drugs excluding insulin (9.9% versus 4.5%).

6.2.1.5. Results for the primary efficacy endpoint

The proportion of patients with a ≥ 35% reduction of spleen volume from baseline to Week 24 in the ITT population is summarised below in Table 33.

Table 33: Study #351 – Proportion of patients with ≥ 35% reduction in spleen volume from baseline to Week 24; ITT population.

	Ruxolitinib (n=155)	Placebo (n=154)
Evaluable patients	155	153
Patients achieving ≥ 35% reduction	41.9% (95% CI: 34.1, 50.1); n=65	0.7% (95% CI: 0.0, 3.6); n=1
Fisher's exact test p-value	< 0.0001	
Reasons for patients not achieving ≥35% reduction		

	Ruxolitinib (n=155)	Placebo (n=154)
Crossed Over to Ruxolitinib Prior to the Visit	0 (0.0%)	16 (10.4%)
Less than 35% Reduction	74 (47.7%)	105 (68.2%)
Discontinued Prior to the Visit	12 (7.7%)	25 (16.2%)
Missing Value at the Visit	4 (2.6%)	6 (3.9%)

Note: There were 153 evaluable patients in placebo group as one of the 154 randomised patients did not have a baseline MRI and, therefore, change from baseline could not be determined.

The logistic regression analysis showed that 40% of patients in the ruxolitinib group achieved a ≥ 35% reduction in spleen volume from baseline to last observation compared with 0.65% of patients in the placebo group, resulting in an odds ratio of 125.4 (90% CI: 16.8, 398.1) and $p < 0.0001$. A linear model with baseline, treatment and baseline by treatment interaction as the model effects showed that there was a statistically significant interaction at the pre-specified alpha level of 0.20 between baseline spleen volume and treatment (p=0.0712). To further explore the nature of the interaction an additional regression analysis was undertaken. This analysis showed that the change from baseline to Week 24 in spleen volume was larger for smaller baseline spleen volumes and smaller for larger baseline spleen volumes.

Of the 139 patients in the ruxolitinib group who had both baseline and Week 24 spleen volume evaluations all but 2 had some level of reduction in spleen volume at Week 24, with a median reduction of 33%. In contrast, of the 106 patients in the placebo group who had both baseline and Week 24 spleen volume evaluations the majority had increases in spleen volume, with a median increase of 8.5%.

Comment: In the ITT population, the reduction in spleen volume ≥ 35% from baseline to Week 24 was reported in 41.9% (95% CI: 34.1, 50.1) of patients in the ruxolitinib group and 0.7% (95% CI: 0.0, 3.6) of patients in the placebo group (ITT population). A statistically significant greater proportion of patients in the ruxolitinib group (41.9%) compared to the placebo group (0.7%) achieved a ≥ 35% reduction in spleen volume from baseline to Week 24 ($p<0.0001$, Fisher's exact test). The absolute difference between the two treatment arms was 41.28% (95% CI: 33.24%, 49.17%), evaluator's calculation for 95% CI for difference between two proportions using Newcombe-Wilson method without continuity correction.[17] The odds ratio for the proportion of patients with a reduction ≥ 35% was 134.4 (95% CI: 17.97, 1005). The sponsor drew attention to the clinical history of the 1 patient in the placebo group with a response. This patient died from disease progression 4 days after the Week 24 measurement and it was not determined whether the patient had a splenic infarct that may have accounted for the reduction in spleen size and rapid deterioration. Results of the sensitivity analysis in the PP population were similar to results of the primary analysis in the ITT population, with a significantly higher proportion of patients in the ruxolitinib group (42.9%) achieving a ≥ 35% reduction from baseline at Week 24 compared with the placebo group (0.8%), $p < 0.0001$.

6.2.1.6. Results secondary efficacy outcomes

(a) Duration of response

The duration of ≥ 35% reduction from baseline in spleen volume (estimated using the Kaplan-Meier method) in patients in the ruxolitinib group was a secondary endpoint. It was analysed in ruxolitinib treated patients 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 submission included an addendum to the original CSR providing an additional 3 months of duration of response data beyond that included in the original CSR. In the updated analysis, the median duration of response was 48.1 weeks (95% CI: 37.4, NE). Based on the Kaplan-Meier analysis, the probability that a subject would maintain a response decreased with increasing time on treatment (see Table 34, below).

Table 34: Study #351 (Addendum 1) - Kaplan-Meier analysis of duration of spleen volume response using; ITT population patients randomised to ruxolitinib.

Statistics	Ruxolitinib
Number (%) of Observed Events	23 (28.8)
Number (%) of Censored Events	57 (71.3)
Probability of response duration > 12 weeks (95% CI), weeks	0.91 (0.81,0.95)
Probability of response duration > 24 weeks (95% CI), weeks	0.75 (0.63,0.84)
Probability of response duration > 36 weeks (95% CI), weeks	0.65 (0.51,0.76)
Probability of response duration > 48 weeks (95% CI), weeks	0.60 (0.43,0.73)

The addendum also included an updated exploratory analysis of patients who achieved a ≥ 35% reduction from baseline, based on the study week that the response was achieved, showing the number of patients who maintained or lost their response between assessments (see Table 35, below). At Week 24, of the 61 patients who had ≥ 35% reduction at the prior assessment, 49 (80.3%) maintained the reduction; at Week 36, of the 65 patients who had ≥ 35% reduction at the prior assessment, 51(78.5%) maintained the reduction; at Week 48, of the 54 patients who had ≥ 35% reduction at the prior assessment, 26 (48.1%) maintained the reduction; and at Week 60 of the 28 patients who had ≥ 35% reduction at the prior assessment, 11 (39.3%) maintained the reduction. The data suggest greater loss of response at Weeks 48 and 60 compared with Weeks 24 and 36. However, the sponsor states that the decrease in the number of responders at Weeks 48 and 60 was due largely to patients being censored at these time-points (withdrew, had a missing value at the visit, or had not reached the visit), rather than because patients had lost their response. It is considered that the Week 48 and 60 data are too immature to allow meaningful conclusions about loss or maintenance of response to be made at these two time points in the exploratory analysis.

Table 35: Study #351 (addendum 1) - Disposition of patients who achieved a ≥ 35% reduction from baseline in spleen volume over time; ruxolitinib treated patients.

	Week 12	Week 24	Week 36	Week 48	Week 60
Newly achieved a ≥ 35% reduction	**61**	**16**	**3**	**2**	**1**
Had ≥ 35% reduction at prior visit:	**NA**	**61**	**65**	**54**	**28**
Continues to achieve ≥ 35% reduction	NA	49	51	26	11
No longer has ≥ 35% reduction	NA	8	12	1	1
Censored[a]	NA	4	2	25	16

[a] Censored subjects includes subjects who withdrew, had a missing value at the visit, or had not reached the visit.
Note: Subjects assessed at each visit are those with a ≥ 35% reduction from Baseline in spleen volume at that visit (newly achieved) or at the previous visit (continued to achieve).

Comment: The Kaplan-Meier analysis showed that the median duration of response in patients randomised to ruxolitinib was 48.1 weeks (95% CI: 37.4, NE). The analysis also showed that the probability of a subject maintaining a spleen volume reduction of ≥ 35% from baseline decreased over time.

(b) Proportion of patients who have ≥ 50% reduction in total symptom score from baseline to Week 24.

The proportion of patients who have ≥ 50% reduction in total symptom score from baseline to Week 24 as measured by the modified MFSAF v2.0 diary was a pre-specified secondary efficacy endpoint. In the ITT population, a statistically significantly larger proportion of patients in the ruxolitinib group achieved a ≥ 50% improvement from baseline in Week 24 total symptom score compared with the placebo group (45.9% [n=68/148] versus 5.3% [n=8/152], respectively, p < 0.0001, chi-square test).

Of the 129 patients in the ruxolitinib group who had both baseline and Week 24 total symptom scores the majority had some level of improvement in Week 24 total symptom score, with a median percent improvement of 56.2%. In contrast, of the 103 patients in the placebo group who had assessments at both baseline and Week 24 the majority of had increases in Week 24 total symptom score, with a median increase of 14.6%.

Comment: The proportion of patients with a ≥ 50% improvement in the total symptom score from baseline to Week 24 was key secondary efficacy endpoint as was the first to be statistically tested in the specified hierarchy if the primary efficacy endpoint was significant. A statistically significant larger proportion of patients in the ruxolitinib group achieved a ≥ 50% improvement from baseline to Week 24 in the total symptom score compared with the placebo group (45.9% and 5.3%, respectively, p < 0.0001, chi-square test).

(c) Change in total symptom score from baseline to Week 24.

The change in total symptom score from baseline to Week 24 as measured by the modified MFSAF v2.0 diary was a pre-specified secondary efficacy endpoint. The analysis included only patients who had non-missing change from baseline to Week 24 data. Data collected after the date of treatment cross-over was not included in the analysis. The mean±SD change in total symptom score from baseline to Week 24 was -8.6±10.0 in the ruxolitinib group (n=131) and +3.2±9.4 in the placebo group (n=105) and the difference was statistically significant (p<0.0001, Wilcoxon-rank sum test). The changes in mean score from baseline to Week 24 represents mean percent changes of -46% (improvement) in the ruxolitinib group and +42% (worsening) in the placebo group. The sponsor considers the observed differences between the two treatment groups in change in total symptom score from baseline to Week 24 to be of "marked clinical significance.

Changes from baseline to Week 24 collected in the modified MFSAF v2.0 diary were also assessed for the 6 individual symptoms contributing to the total symptom score and the inactivity symptom. In the ruxolitinib group, all 7 symptoms showed mean improvements from baseline to Week 24 from baseline, while in the placebo group all 7 symptoms showed mean worsening over the corresponding time interval. The differences between the two groups in mean scores were statistically significant for all 7 symptoms (p < 0.0001).

Comment: The change in total symptom score analysis was based on patients with non-missing baseline and Week 24 data. It is noted that 22 (14.2%) patients in the ruxolitinib arm and 49 (31.8%) patients in the ruxolitinib arm were excluded from the analysis presumably due to missing data at Week 24. However, the submission included an analysis of change from baseline to Week 24 in total symptom score using a LOCF method that included 147 patients in the ruxolitinib group and 148 patients in the placebo group. In this analysis, the mean±SD change from baseline to Week 24 total symptom score was -8.2±10.27 in the ruxolitinib group and +3.7±9.08 in the placebo group; p<0.0001, Wilcoxon rank-sum test. The results for the LOCF analysis were similar to results for the analysis based on patients with baseline and Week 24 data.

(d) Overall survival.

The submission included an addendum to the original CSR updating the overall survival data up to the data cut-off date of 1 March 2011. The overall survival analysis was defined for all patients in the ITT population (n=309) and was analysed according to the original randomisation group, regardless of whether the subject crossed over to ruxolitinib treatment prior to the analysis. The time origin for survival for each subject was the date of first treatment or, for patients without a treatment start date, date of randomisation. All deaths that occurred before, or on the date of data cut-off were included in the analysis. Patients were censored at date of data cut-off for those continuing in study, or at the later of either the date of withdrawal or the date of last follow-up for those who discontinued from the study before the date of data cut-off. The survival time was analysed using the Kaplan-Meier method and the hazard ratio of ruxolitinib compared with placebo was estimated using the Cox proportional hazard regression model.

The median follow-up through to 1 March 2011 was 51.9 weeks in the ruxolitinib group and 50.7 weeks in the placebo group. With a median follow-up of 51 weeks, the total number of deaths for the study was 37, 13 patients (8.4%) in the ruxolitinib group and 24 patients (15.6%) in the placebo group. The hazard ratio (ruxolitinib:placebo) was 0.499 (95% CI: 0.254, 0.980), p=0.0395.

Comment: The data showed that there is a statistically significant overall survival benefit for patients treated with ruxolitinib compared with placebo based on the HR. The HR showed that ruxolitinib reduced the risk of death by approximately 50% (95%CI: 25.4%, 98.0%). However, the study was not designed or powered for a robust statistical analysis of overall survival and no statistical adjustment was made for repeat OS testing. In addition, the data did not allow for calculation of median survival times for the two treatments due to the large proportion of censored patients. Consequently, the observed statistical significance for the HR should be considered to be nominal. The interpretation of the differences in overall survival between the two treatment groups at future time points are likely to be confounded due to the high probability of most patients in the placebo group switching to the ruxolitinib group.

6.2.1.7. Results for exploratory efficacy outcomes

(a) Subgroup analyses

The primary endpoint (proportion of patients who achieved a ≥ 35% reduction from baseline in spleen volume at Week 24) was assessed in a number of subgroups, the majority of which were pre-specified. There were no subgroup analyses in the placebo group as there was only 1 patient in this group who achieved the primary endpoint.

Comment: All the subgroup analyses should be considered to be exploratory. The study was not designed or powered to compare the primary efficacy endpoint in subgroups. The results for the subgroup analyses of the primary efficacy endpoint in the ruxolitinib groups showed: higher response in females versus males (59.2% versus 25.3%); higher response in patients aged ≤ 65 years versus > 65 years (45.7% versus 38.8%); higher response in non-whites versus whites (52.9% versus 40.6%); higher response in patients with spleen volume > median versus ≤ median (44.9% versus 39.0%); higher response in patients with baseline spleen length by palpation > 10 cm versus ≤ 10 cm (45.5% versus 28.1%); higher response in previous hydroxyurea users versus non-users (55.8% versus 35.0%); higher response in P-PV MF versus PMF versus P-ET MF (50.0% versus 38.6% versus 37.1%); higher response in USA versus non-USA patients (42.6% versus 40.0%); higher response in intermediate risk-2 versus high risk group (51.6% versus 35.6%); higher response in patients with JAK2V617F mutation-

positive versus mutation-negative (47.8% versus 27.5%); and higher response in patients starting on 20 mg bd versus 15 mg bd (53.0% versus 21.8%).

(b) Quality of Life (QoL)

The study included an exploratory analysis of effect of treatment on quality of life (QoL) assessed by the European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire (EORTC QLC-C30). The EORTC QLC-C30 is a 30-item self reporting questionnaire developed to assess the quality of life in cancer patients. It is grouped into 5 functional sub-scales (physical, role, emotional, cognitive and social), global health and QoL scale, and 9 symptom scales/items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The instrument captures status over the previous week for all scales/items, with the exception of the 5 functional scales which capture current status. The range of scores for all scales is from 0 to 100, and a 10 point difference is equivalent to 10% and is considered clinically meaningful. For functional and global health status/QOL scales, higher scores indicate better QoL and level of functioning, and for symptom scales, higher scores indicate greater level of symptoms or difficulties.

Comment: The results for the EORTC QLC-C30 at Week 24 showed clinically and statistically significant improvement in the global health status and functional subscales (physical, role, emotional, and social functioning) in the ruxolitinib group compared with the placebo group, with the exception of cognitive functioning which neither improved nor worsened.

6.2.2. Study #352 - supportive efficacy study for the proposed indication

6.2.2.1. Design, objectives, locations and dates

Study #352 is an ongoing, Phase III, multi-national, multi-centred, randomised, open-label clinical trial designed to compare the efficacy and safety of ruxolitinib with best available therapy (BAT) for the treatment of PMF, PPV-MF, or PET-MF. The study is identified by the acronym COMFORT-II and has been published.[18] The **primary objectives** were to compare the efficacy, safety, and tolerability of ruxolitinib given bd compared with BAT. The s**econdary objective** was to evaluate the population pharmacokinetics of ruxolitinib.

The study was undertaken at 56 sites in 9 European countries (Austria, Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden and the United Kingdom). It was initiated on 1 July 2009 (first subject visit) and the data cut-off date was 4 January 2011 (last subject visit). The CSR was dated 17 October 2011 (content final). The principal investigator was located at Guys and St. Thomas' Hospital, Department of Haematology, London, United Kingdom. The study was sponsored by Novartis/Incyte Corporation and Incyte Corporation transferred the responsibilities of the sponsor to Novartis on 15 March 2010. The study protocol and all amendments were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each centre. The study was conducted according to the ethical principles of the Declaration of Helsinki and all patients provided informed consent.

Comment: The study was open-label in design which exposes it to the well known biases associated with unblinded studies. However, the control in this study was BAT which makes the design unsuitable for blinding given the variability in treatments. The sponsor also stated that placebo could not be ethically used as a comparator because the Committee for Human Medicinal Products (CHMP) of the European Medicines Agency (EMA) advised that long-term (1 year) evidence of efficacy and safety should be assessed, and medical experts advised that a 1 year placebo control would not be feasible. The primary efficacy endpoint in this study was the proportion of patients achieving ≥ 35% reduction in spleen volume from baseline at Week 48 as measured by MRI (or CT for patients unable to undergo MRI) determined by an independent radiologist who was blinded to treatment assignment. The objective primary efficacy endpoint assessed by an

independent radiologist blinded to treatment mitigates the absence of patient and investigator blinding.

6.2.2.1.1. Inclusion and exclusion criteria

The study population included men and women, aged 18 years or older, who had been diagnosed with myelofibrosis (PMF, PPV-MF, or PET-MF) according to 2008 World Health Organization (WHO) criteria and who were not currently candidates for stem cell transplantation. Patients with MF requiring therapy must have been classified as high risk or intermediate risk level-2 based on IWG criteria. Patients were also required to have been on a stable therapeutic regimen at least 2 weeks before screening and no less than 4 weeks prior to baseline. In addition, patients were required to have had a palpable spleen measuring 5 cm or greater, a peripheral blast cell count < 10%, ECOG performance status of 0 to 3 and to have been naive to JAK inhibitor therapy. Patients were excluded if liver function, renal function, or bone marrow reserves were inadequate. The inclusion and exclusion criteria of Study #352 are acceptable and similar but not identical to those of Study #351.

6.2.2.1.2. Study phases

The study consisted of 5 phases: (1) screening phase which was not to exceed 28 days prior to study Day 1 (that is, day of randomisation); (2) baseline phase of up to 7 days duration; (3) randomised treatment phase from study Day 1 to either protocol-defined disease progression or study conclusion, whichever came first; (4) extension phase (including cross-over of control group patients) beginning with a Qualifying disease progression event and continuing until the subject is no longer receiving clinical benefit from ruxolitinib or until the study is concluded; and (5) follow-up phase occurring 28 to 37 weeks following the last dose of study drug or open label ruxolitinib. With the implementation of Protocol Amendment 3, subjects were followed every 3 months for survival, frequency of leukemia and start of new anti-neoplastic therapy for treatment of MF. The study withdrawal criteria have been examined and are considered to be satisfactory.

In the randomised treatment phase, disease progression was defined as meeting one of the following criteria: (1) increase in spleen volume of ≥ 25% from on-study nadir (the lowest of either baseline or smallest spleen volume measured on study); (2) splenic irradiation or splenectomy; (3) leukemic transformation defined as an increase in peripheral blood blast cells of ≥ 20% sustained for at least 8 weeks or as a bone marrow blast count of ≥ 20%; or (4) death. Patients who were diagnosed with leukaemic transformation or underwent splenic irradiation were withdrawn from the study. Patients who met disease progression criteria as evidenced by a ≥ 25% increase in spleen volume from the on-study nadir or splenectomy (termed Qualifying events) were eligible to enter the extension phase.

6.2.2.1.3. Study treatments

On study Day 1 of the randomised treatment phase, patients were randomised 2:1 to receive either ruxolitinib or BAT (selected by the investigator on a subject-by-subject basis). BAT could include a single agent or combination of agents for the treatment of the disease and its symptoms or no therapy. In the BAT group, 67.1% (n=49/73) of patients received BAT medication, while no BAT medication was recorded for 32.9% (n=24/79) of patients. The most commonly used BAT medications were anti-neoplastic agents (50.7%), consisting almost exclusively of hydroxyurea (46.6%), followed by glucocorticoids (16.4%). BAT could be changed at any time during the study except during the screening period. No experimental drugs were permitted to be administered with BAT during the study. It was recommended that patients in the BAT group were to either decrease the dose of BAT or switch to an alternative treatment approach if they: (1) could not maintain platelet counts ≥ 50 x 10^9/L and/or neutrophils ≥ 0.5 x 10^9/L; or (2) experienced another Grade 4 toxicity during the randomised treatment phase.

The ruxolitinib dosing regimens in the randomised treatment phase were consistent with those in Study #351. The starting dose was based on the baseline platelet count, and the maximum

dose was not to exceed 25 mg bd. Dose increase was allowed at week 4 in the randomised treatment phase in cases of inadequate efficacy by palpation of spleen size in subjects randomised to ruxolitinib. Dose increases beyond Week 4 in the randomised treatment phase were permitted for patients who demonstrated inadequate efficacy relating to increase in palpable spleen size relative to the on-study nadir palpable spleen size based on specified criteria.

In the extension phase, the ruxolitinib starting dose in patients who crossed-over from BAT was determined by the platelet count at the time of the cross-over. In the extension phase, the ruxolitinib dose could be increased in patients crossed-over from placebo and in patients originally randomised to ruxolitinib who continued with the drug in this phase.

The study mandated dose reductions or interruptions for decreases in platelet count and absolute neutrophil count and these criteria were the same as those for Study #351, as were the mandated dose restart or increase criteria.

6.2.2.2. Efficacy endpoints

6.2.2.2.1. Primary efficacy endpoint

The primary efficacy endpoint was the proportion of patients achieving ≥ 35% reduction in spleen volume from baseline at Week 48 as measured by MRI or CT (for patients unable to undergo MRI). CT scans were performed only if patients were not candidates for MRI or if an MRI facility was not readily available. MRI/CT scans were performed at baseline and then every 12 weeks. The MRI/CT scans were initially read by local radiologists who assessed them for quality and anatomic or vascular abnormalities. The scans were then sent to the central imaging laboratory for assessment by an independent central reviewer who was blinded to treatment assignment; scans from an individual patient were read by the same central radiology reviewer. The same imaging method (MRI/CT) was used for all visits for a given patient, unless a new contraindication to the use of MRI occurred. Results of spleen volume measurements were not provided to investigators unless the subject reached an endpoint of ≥ 25% increase in spleen volume relative to the on-study nadir (including baseline).

Comment: The ≥ 35% reduction in spleen volume was the same as that chosen for Study #351, but the primary analysis of reduction from baseline was assessed at Week 24 in Study #351 and Week 48 in Study #352.

6.2.2.2.2. Secondary efficacy endpoints

The key secondary efficacy endpoint was defined as the proportion of patients achieving a ≥ 35% reduction of spleen size as measured by MRI (or CT where applicable) from baseline at Week 24. Other secondary efficacy endpoints were the duration of maintenance of a ≥ 35% reduction from baseline in spleen volume, the time to achieve a first ≥ 35% reduction in spleen volume from baseline, progression free survival (PFS), leukemia free survival (LFS), overall survival (OS) and bone marrow histopathology.

Comment: The secondary efficacy endpoints are acceptable. No assessment of symptoms (such as MSAF diary) was specified as a secondary efficacy endpoint. However, study symptom and quality of life assessments were considered to be exploratory endpoints and were assessed by the EORTC quality of life questionnaire and the FACT-Lym scale. Clinical benefit outcomes of OS and PFS were both included in this study as secondary efficacy endpoints.

6.2.2.2.3. Exploratory efficacy assessments

The study included a number of exploratory assessments including exploratory efficacy endpoints. The results of the exploratory assessments from considered to be of relevance have been reviewed in the appropriate sections of this CER.

6.2.2.3. Randomisation and blinding methods

There was block randomisation with a block size of 6, stratified by prognostic category of intermediate risk-2 or high risk based on IWG criteria. The computed generated randomisation list was provided to a centralised, independent, Interactive Voice Recognition System (IVRS) provider. Patients were randomised 2:1 to ruxolitinib or BAT, respectively. The sponsor stated that a 2:1 randomisation ratio in favour of ruxolitinib was chosen in order to aid study recruitment and to allow more patients to be treated with the investigational agent since there is no clinically effective treatment for MF. The study was open-label. However, MRT/CT scans were assessed centrally by an independent radiologist blinded to treatment assignment.

6.2.2.4. Analysis populations

The Full analysis set (FAS) consisted of all patients who were randomised and stratified according to IWG prognostic criteria. Treatment groups for this population were defined according to the treatment assignment at the time of randomisation. Following the ITT principle, data were analysed according to the treatment assigned at randomisation. The FAS included a total of 219 patients, 146 in the ruxolitinib group and 73 in the BAT group.

The Per-protocol (PP) set consisted of all patients in the FAS without major protocol deviations. The PP set included a total of 202 patients, 137 in the ruxolitinib group and 65 in the BAT group.

The Safety set consisted of all subjects in the FAS who had taken at least 1 dose of study medication. Patients in the BAT group who were intended to receive no treatment (observation) were also included in the Safety set. Subjects were analysed according to treatment actually received. The Safety set included a total of 219 patients, 146 in the ruxolitinib group and 73 in the BAT group.

The PK analysis set consisted of patients who received at least 1 dose of ruxolitinib and provided at least 1 PK plasma sample. The PK analysis set included a total of 155 patients, 143 in the ruxolitinib group and 12 patients from the BAT group who had received ruxolitinib following cross-over.

6.2.2.4.1. Sample size

The sample size was based on the analysis of the primary efficacy variable. Assuming at least 35% of the active patients would achieve a 35% reduction from baseline to Week 48, and that the rate for the control patients would be no more than 10%, a sample size of 150 patients (100 active and 50 control) would provide at least 90% power to detect a treatment difference in the primary endpoint at a 2-sided alpha level of 0.05 using the Chi-square test.

In the current statistical analysis plan (SAP), this sample size of 150 patients would provide 81.6% power at two-sided level of 0.05 using the Cochran-Mantel-Haenszel (CMH) test under the following assumptions: ratio of patients with baseline prognostic category of intermediate risk-2 versus high risk was 1:1; response rate for intermediate risk-2 for active and control treatment groups was 40% and 15%, respectively, and for high risk was 30% and 5%, respectively. For the 219 patients enrolled, the power of the CMH test was 93.7%.

6.2.2.5. Statistical methods

6.2.2.5.1. Primary efficacy analysis

The primary efficacy endpoint was the proportion of patients achieving ≥ 35% reduction in spleen volume from baseline at Week 48 as measured by MRI (or CT if applicable). The primary efficacy variable was analysed using the FAS population, and the PP population was used for supportive sensitivity analyses of the primary end point. The null-hypothesis was that there is no difference in the proportions of patients achieving 35% reduction in spleen volume reduction from baseline to Week 48 and the alternative hypothesis is that the proportions are different. The proportion of patients who have 35% reduction in spleen volume at Week 48 was estimated with 95% CI (calculated as exact binomial CIs). The two proportions were compared

using the CMH test stratified by prognostic category (intermediate risk-2 or high risk). In the event that the proportion of one group was less than 4%, the exact CMH test was to be used. The baseline value was the last available assessment of spleen volume measured by MRI before or at the randomisation date. The last value was used in case of multiple values measured during the baseline visit. The Week 48 value was the spleen volume measured by MRI during the Week 48 visit (Days 308 to 364). The primary analysis was conducted when all enrolled patients had either completed Week 48 or were withdrawn from the study.

Missing values were not imputed. A patient was required to have a baseline spleen volume measurement to be included in the primary efficacy analysis. A subject with a missing Week 48 spleen volume measurement was considered as not having achieved the ≥ 35% reduction. Patients who dropped out of the study for any reason or who had a protocol-defined qualifying event of disease progression prior to Week 48 visit were considered as not having achieved the ≥ 35% reduction. If the Week 48 visit represented a disease progression event but the spleen volume reduction was ≥ 35%, the subject was counted as a responder for the primary endpoint.

The main sensitivity analysis was performed for the proportion of patients achieving ≥ 35% reduction in spleen volume from baseline at Week 48 using a logistic regression model with baseline spleen volume and treatment as the model effects and adjusted to baseline prognostic category. The odds ratio with a 95% CI of achieving ≥ 35% reduction in spleen volume was presented. Similar to Study #351, logistic regression analysis with baseline prognostic factors and treatment as model effects was undertaken, and linear models with baseline, treatment and baseline by treatment interaction as the model effects was explored to see if there was a significant baseline by treatment qualitative interaction in the percent change of spleen volume from baseline at Week 48. There were also pre-specified sub-group analyses of the primary efficacy endpoint.

6.2.2.5.2. Secondary efficacy analyses

- The key secondary variable was the proportion of patients achieving a ≥ 35% reduction of spleen volume as measured by MRI from baseline at Week 24, analysed as for the Week 24 primary efficacy endpoint.
- Duration of maintenance of spleen volume reduction was defined as the longest duration of consecutive measurements of ≥ 35% reduction observed prior to the time of database lock for patients who had at least one measured ≥ 35% reduction (Method 1). The censoring date was defined as the date of the last adequate assessment of the spleen volume. This endpoint was evaluated using the Kaplan-Meier estimate for each treatment group. The study also included two other methods of assessing duration of response (Methods 2 and 3). In Method 2, patients with ≥ 35% reduction from baseline at the last visit prior to the database freeze were included in the analysis with response duration of 1 day, loss of response was the date of observation of < 35% reduction from baseline that was also ≥ 25% increase from nadir. Method 3 was requested at a pre-submission meeting with the EMA rapporteur (Sweden) and consisted of a sensitivity analysis using a definition of duration of response similar to Method 2 with the start date defined as the first spleen volume measurement ≥ 35% reduction from baseline, but with the end date as the first measurement ≥ 25% increase over nadir, if the end date was not observed prior to database cut-off or start of the extension phase then the duration was censored at the last assessment.
- The time to achieve a ≥ 35% reduction in spleen volume from baseline was defined as the interval between randomisation and date of the first MRI showing ≥ 35% reduction from baseline in spleen volume.
- PFS was defined as the interval between randomisation and the occurrence of any one of the following events: (1) for a spleen volume increase, the progression date was the date of the first MRI showing a ≥ 25% increase in spleen volume from the on-study nadir (including baseline); (2) for leukemic transformation, the progression date was the date of the bone

marrow blast cell count of ≥ 20% obtained on bone marrow aspirate or the date of the first peripheral blast cell count of ≥ 20% that was subsequently confirmed to have been sustained for at least 8 weeks; and (3) for splenic irradiation, splenectomy, or death, the date of progression was the actual date of the event. PFS was summarised using Kaplan-Meier estimates for each treatment group. In addition, PFS was supplied with hazard ratios, and the corresponding 95% CIs were estimated using the Cox proportional hazards model stratified by baseline prognostic category. For treatment comparison of PFS, a stratified 2-sided log-rank test was used.

- LFS was defined as the interval between randomisation and the date of the bone marrow blast cell count of ≥ 20%, OR the date of the first peripheral blast cell count of ≥ 20% that was subsequently confirmed to have been sustained for at least 8 weeks, OR the date of death from any cause, whichever occurs first. LFS was assessed using the same methods as PFS.
- OS was defined as the interval between randomisation and death from any cause. The hazard ratio was estimated using the Cox proportional hazards model stratified by baseline prognostic category. For the comparison of OS between ruxolitinib and BAT, a stratified 2-sided log-rank test was used.
- Bone marrow histomorphology was noted as fibrosis density and was tabulated by fibrosis grade at baseline and post-baseline using descriptive statistics. Bone marrow fibrosis was measured according to the European consensus grading system using biopsy samples obtained at screening/baseline and specified study visits.[16] Bone marrow samples were collected, processed and assessed at the individual study sites using site specific procedures.

6.2.2.6. Level of significance and control of type 1 error

All tests were two-sided at the 0.05 level. The family-wise alpha level was controlled at 0.05 overall for two pre-specified comparisons (that is, primary efficacy endpoint and key secondary efficacy endpoint). Specifically, this study was claimed to have achieved the efficacy objective when the primary endpoint showed a significant treatment effect at two-sided alpha=0.05. Conditional on significance of the primary endpoint being established, the treatment effect on the key secondary endpoint (that is, 35% spleen volume reduction at the 24-week time point) would be tested at a two-sided alpha=0.05. No alpha adjustment was carried out for the multiple analyses of the remaining secondary endpoints.

6.2.2.7. Interim analysis

No interim analyses with stopping boundary were planned for early stop due to efficacy or sample size adjustment. An independent DSMB assessed risk and study conduct at pre-defined time points.

6.2.2.8. Participant flow

Subject disposition of the 219 patients in the FAS population is summarised below in Table 36.

Table 36: Study 352 – Subject disposition; FAS.

	Ruxolitinib N = 146 n (%)	BAT N = 73 n (%)	Total N = 219 n (%)
Subjects			
Ongoing in Randomized Treatment or entered into Extension Phase	120 (82.2)	49 (67.1)	169 (77.1)
Ongoing in Randomized Treatment Phase	91 (62.3)	31 (42.5)	122 (55.7)
Discontinued Randomized Treatment Phase	55 (37.7)	42 (57.5)	97 (44.3)
Reasons for discontinuation from Randomized Treatment Phase			
Entered extension phase ruxolitinib [1]	29 (19.9)	18 (24.7)	47 (21.5)
Adverse event(s)	12 (8.2)	4 (5.5)	16 (7.3)
Consent withdrawn	2 (1.4)	9 (12.3)	11 (5.0)
Disease Progression	1 (0.7)	3 (4.1)	4 (1.8)
Protocol deviation	2 (1.4)	0	2 (0.9)
Non-compliance with study medication	2 (1.4)	0	2 (0.9)
Non-compliance with study procedures	0	1 (1.4)	1 (0.5)
Other	7 (4.8)[2]	7 (9.6)[3]	14 (6.4)

[1] Treatment with ruxolitinib after disease progression event qualifying for entering extension phase. [2] Other reasons for discontinuation from the ruxolitinib group included allogeneic transplant (3 patients), period of not taking study drug longer than 8 weeks (1 subject), investigator decision (1 subject), inefficient response at 10 mg bd (1 subject), lack of efficacy (1 subject). [3] Other reasons for discontinuation from the BAT group included investigator decision, splenectomy, treatment failure, poor subject condition, refusal of follow-up, bone marrow transplant, and thrombocytopenic event confirming disease progression (1 subject each).

Comment: The proportion of patients ongoing in the randomised treatment phase, as of 4 January 2011, was greater in the ruxolitinib group than in the BAT group (62.3% versus 42.5%, respectively). The major reason for discontinuation from the randomised treatment phase in both groups was treatment with ruxolitinib in the extension phase after disease progression qualifying event (19.9% of patients randomised to ruxolitinib versus 24.7% of patients randomised to BAT and crossed-over to ruxolitinib). In the BAT group, withdrawal of consent was the second most frequently reported reason for discontinuation from the randomised treatment phase (12.3%) but was infrequently observed in the ruxolitinib group (1.4%). Treatment discontinuation from the randomised treatment phase due to AEs was observed more frequently in the ruxolitinib group than in the BAT group (8.2% and 5.5%, respectively), while the reverse was observed discontinuations due to disease progression (0.7%, ruxolitinib versus 4.1%, BAT).

6.2.2.9. Major protocol deviations

Major protocol deviations in the study were reported in a total of 17 (7.8%) patients in the FAS population; 9 (6.2%) in the ruxolitinib group and 8 (11.0%) in the BAT group. The most common major protocol deviations in the ruxolitinib group were use of prohibited concomitant medications in 6 patients (hydroxyurea, interferon, thalidomide, busulfan, lenalidomide, or anagrelide) and unconfirmed diagnosis of PMF, PPV-MF, PET-MF in 5 patients. The most common major protocol deviations in the BAT group were cross-over into the ruxolitinib group without meeting the protocol definition of disease progression in 6 patients, change in therapy after baseline MRI and before start of study drug in 1 patient, and no palpable spleen volume ≥ 5 cm in 1 patient.

Comment: It is considered unlikely that the major protocol deviations observed in this study have significantly biased the efficacy results in the FAS analysed by the ITT principle. Patients with major protocol deviations were excluded from the PP population.

6.2.2.10. Baseline data

Demographics: The mean age of the total population was 65.2 years (range: 35, 85), and 52.0% were aged > 65 years. There were 57.1% males and 42.9% females and 84.5% were White. The baseline demographic characteristics were well balanced between the two treatment groups.

Baseline disease characteristics: In the total population, PMF, PPV-MF and PET-MF occurred in 53.0%, 31.1%, and 16.0% of patients, respectively. The frequency of PMF was similar in ruxolitinib and BAT groups (52.7% and 53.4%, respectively), the frequency of PPV-MF was marginally higher in the ruxolitinib group compared with the BAT group (32.9% versus 27.4%), and the frequency of PET-MF was marginally lower in the ruxolitinib group compared with the BAT group (14.4% versus 19.2%, respectively).

Baseline IWG prognostic risk categories: In both treatment groups, 51% of patients were in the intermediate-2 risk stratum at randomisation (ruxolitinib: 74 patients; BAT: 37 patients) and 49% were in the high-risk stratum (ruxolitinib: 72 patients; BAT: 36 patients) as per investigator assessment. However, after clinical confirmation of risk categories, intermediate-2 risk stratum was reported for 39.7% of patients in both treatment groups and high-risk stratum was reported for 60.3% of patients in the ruxolitinib group and 58.9% of patients in the BAT group.

Prior medications: Prior medications for MF had been taken by 83.6% (n=122/146) of patients (FAS) in the ruxolitinib group and 78.1% (n=57/73) of patients in the BAT group. Prior medications taken by at least 10% of patients in either treatment group (ruxolitinib versus BAT) were: hydroxyurea (75.3% versus 68.5%); thalidomide (11.6% versus 16.4%); anagrelide/anagrelide HCl (11.0% versus 20.5%); and prednisone (7.5% versus 12.3%). Prior treatment with anti-anemic medications was observed in 13.0% of patients in the ruxolitinib group and 8.2% of patients in the BAT group.

Concomitant medication or therapy after start of treatment: Platelet aggregation inhibitors represented the most commonly reported medications taken concomitantly after the start of study drug, with similar frequencies in both groups (ruxolitinib: 45.2%; BAT: 39.7%). The most frequently reported concomitant medication by preferred term was acetylsalicylic acid (ruxolitinib: 39.0%; BAT: 35.6%). Anti-anemic medications such as darbepoetin alfa and epoetin alfa (which was discouraged in the ruxolitinib group) were infrequently reported in both the ruxolitinib group (1.4% and 4.8%, respectively) and the BAT group (0% and 2.7%, respectively).

6.2.2.11. Results for primary efficacy outcome

The results for the primary efficacy endpoint in the FAS are summarised below in Table 37.

Table 37: Study #352 - Patients with ≥ 35% reduction in spleen volume from baseline at Week 48; FAS.

	Ruxolitinib N=144	BAT N=72
Number of subjects with ≥35% spleen volume reduction	41 (28.5%)	0
95% CI	(21.3, 36.6)	(0.0, 5.0)
p-value [1]	<0.0001	

[1] P-value (CMH; exact test).

In the PP set, the results for patients with a ≥ 35% reduction in spleen volume from baseline at Week 48 were 29.6% (95% CI: 22.1, 38.1) in the ruxolitinib group versus 0% (95% CI: 0.0, 5.6) in the BAT group; n=40/135 for ruxolitinib and n=0/64 for BAT.

Comment: The study met its primary endpoint in the FAS. The result in the PP set (sensitivity analysis) was consistent with the result in the FAS. The analysis showed that 97.1% (n=132/136) 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% (n=35/63) of patients in the BAT group (median increase approximately 8.5%).

6.2.2.12. Results for secondary efficacy outcomes

The key secondary efficacy endpoint of proportion of patients with ≥ 35% reduction in spleen volume from baseline at Week 24 showed a statistically significant result in favour of ruxolitinib compared with BAT (see Table 38, below).

Table 38: Study #352 - Patients with at ≥ 35% reduction in spleen volume from baseline at Week 24; FAS.

	Ruxolitinib N=144	BAT N=72
Number of subjects with ≥35% spleen volume reduction	46 (31.9%)	0
(95% CI)	(24.4, 40.2)	(0.0 , 5.0)
p-value [1]	<0.0001	

[1] P-value (CMH; exact test).

The duration of response for reduction in spleen volume ≥ 35% was assessed for 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 (Method 1). A total of 69 patients in the ruxolitinib arm were reported with at least one spleen volume reduction ≥ 35%, and 43 were still responding at the time of the cut-off and were censored, while 26 had lost their response by the cut-off. In the placebo group, 1 subject was reported with a ≥ 35% response and was still responding at the cut-off and was censored. The median duration of maintenance of response could only be assessed in the ruxolitinib group, and in patients in this group was 48 weeks (95% CI: 35.9, N/A). The Kaplan-Meier estimates of probabilities of response in the ruxolitinib group of at least 12, 24, 36 and 48 weeks were 0.78 (95% CI: 0.78), 0.67 (95% CI: 0.54, 0.77), 0.58 (95% CI: 0.44, 0.70), and 0.39 (95% CI: 0.10, 0.67), respectively. The median duration of response calculated by Methods 2 and 3 were consistent with that for Method 1.

The median time to first occurrence of ≥ 35% reduction in spleen volume was 12.3 weeks in the ruxolitinib group. Only 1 subject in the BAT group achieved a ≥ 35% reduction and the time to reduction was 15.4 weeks. Spleen volume measurements were recorded on the exact day on which they were obtained, rather than at a scheduled study visit. In patients in the ruxolitinib group with a ≥ 35% spleen volume reduction, the probability estimates that time to first 35% reduction would occur by Weeks 12, 24, 36, and 48 weeks were 0.23, 0.67, 0.87, and 0.97, respectively.

PFS, LFS, and OS were estimated by the Kaplan-Meier method. The stratified analyses showed no statistically significant differences between the two treatment groups for PFS, LFS, and OS (see Table 39, below). The median duration of PFS was 60.4 weeks (95%CI: 60.1, N/A) in the ruxolitinib group and 60.1 weeks (95% CI: 49.4, N/A) in the BAT group, while the median time of LFS and OS was not reached in either treatment group. Kaplan-Meier probability estimate of PFS at 48 weeks was 0.75 (95% CI: 0.67, 0.82) for the ruxolitinib group and 0.73 (95% CI: 0.59, 0.83) for the BAT group. The most common disease progression event was increase in spleen volume of at least 25% from nadir, seen in 40 patients (27.4%) in the ruxolitinib group and 13 patients (17.8%) in the BAT group. The 10 reported events of leukemic transformation were all deaths. The unstratified analyses of PFS, LFS, and OS were not markedly different from the stratified analyses.

Table 39: Study #352 - Progression-free survival, leukemia-free survival, overall survival by treatment; FAS.

Endpoint	Outcome	Ruxolitinib (N=146)	BAT* (N=73)	Log-rank p-value	HR** (95% CI)
Progression free survival [1]	No. of events	44 (30.1%)	19 (26.0%)	0.46	0.81 (0.47,1.39)
	No. censored	102 (69.9%)	54 (74.0%)		
Leukemia free survival [1]	No. of events	6 (4.1%)	4 (5.5%)	0.51	0.65 (0.18,2.31)
	No. censored	140 (95.9%)	69 (94.5%)		
Overall survival [2]	No. of events	11 (7.5%)	4 (5.5%)	0.95	1.01 (0.32,3.24)
	No. censored	135 (92.5%)	69 (94.5%)		

[1] = cut-off date 4 January (original CSR); [2] = cutoff date 1 March 2011 (CSR addendum). *Five patients in the BAT treatment arm crossed over to receive ruxolitinib treatment and did not meet the criteria for disease progression, which was classified as a major protocol deviation. **HR of ruxolitinib over BAT; HR < 1 denotes benefit to ruxolitinib arm, while HR > 1 denotes benefit to BAT arm.

It is not possible to make any meaningful conclusions regarding the bone marrow histomorphology analysis at Week 48 due to the large number of patients for whom bone marrow fibrosis data are missing (that is, 57% of the ruxolitinib group, 75% of the BAT group).

6.2.2.13. Results for exploratory efficacy analyses

(a) Subgroup analyses

The study included a number of pre-specified subgroup analyses of the primary efficacy endpoints.

Comment: The subgroup analyses are considered to be exploratory as the study was not designed to confirm therapeutic differences between the two treatment groups. In patients in the ruxolitinib arm, the primary efficacy response was greater in female versus males patients (33.3% versus 24.7%, respectively), and similar in patients aged ≤ 65 years and > 65 years (29.4% versus 27.6%, respectively). The response in the three types of MF were notably different with highest response in PPV-MF (41.7%) followed by PET-MF (35.0%) and PMF (18.4%). The response in patients with baseline prognostic category intermediate risk-2 was higher than patients with high risk disease (32.4% versus 24.3%, respectively). The response in patients starting treatment with the higher dose of 20 mg bd with baseline platelet count > 200 x 10^9/L was greater than in patients starting treatment with the lower dose of 15 mg bd with platelet count 100-200 x 10^9/L (35.2% versus 17.9%, respectively). The response was higher in patients without than with previous hydroxyurea use (36.1% versus 25.9%). In the post-hoc subgroup analysis based on JAK2V617F mutation status, in the ruxolitinib group

the response in mutation-positive patients was 33.3% (n=36) compared with 14.3% (n=5) in mutation-negative patients.

(b) Quality of life and symptoms

Exploratory analyses of Quality of life and change in symptoms were assessed using the EORTC QLC-C30. In general, the results showed that patients in the ruxolitinib group had greater improvement in overall QoL, functioning and symptoms compared with patients in the BAT group. For global health status/QoL, role functioning, fatigue, pain, dyspnoea, insomnia, appetite loss, and diarrhoea subscales, the difference in mean change from baseline score between the ruxolitinib and BAT groups was clinically significant (more than 10% of the scale range) in favour of ruxolitinib for at least one time point between Weeks 8 and 48.

The EORTC QLQ-C30 is not disease-specific and does not fully capture symptoms specific to patients with MF. Therefore, in the supportive Phase III study the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) questionnaire was used to supplement the collection of QoL data, and to specifically capture symptoms associated with MF. The FACT-Lym consists of a generic core questionnaire (FACT-General [FACT-G], 27 items) and a disease-specific questionnaire (Lymphoma subscale [LymS], 15 items). This instrument asks the subject to answer questions considering the "past 7 days". The FACT-G is a compilation of general questions divided into 4 primary QoL domains: physical well-being (WB), social/family WB, emotional WB, and functional WB. A number of derived scores can be calculated, including the FACT-G total (score range = 0 - 108) = Physical WB + Social/family WB + Emotional WB + Functional WB; the FACT-Lym total (score range = 0 - 168) = FACT-G total + LymS; and the FACT-Lym TOI (score range = 0 - 116) = Physical WB + Functional WB + LymS. Higher scores indicate better QoL.

Greater improvements were observed in the LymS score, FACT-Lym Trial Outcome Index (TOI) score, FACT-G total score and FACT-Lym total score in patients in the ruxolitinib group compared with patients in the BAT group. The difference between treatments ranged from 4.7 (7.8% of the scale range) for the LymS score to 13.8 (8.2% of the scale range) for FACT-Lym total score. The FACT-Lym total score, and FACT-TOI score consistently worsened in the BAT group through Week 48 while both scores improved and then stabilized in the ruxolitinib group over the same time period. In addition, for FACT-Lym total and lymphoma subscales, time to definitive deterioration was used to further assess the treatment effect, and results were statistically significant and in favour of ruxolitinib in both scores (FACT-Lym total score HR = 0.40 (95% CI: 0.21, 0.76); LymS score HR =0.40 (95% CI: 0.19, 0.85).

6.2.3. Analyses performed across trials (pooled analyses and meta-analyses)

There were no analyses based on pooled data.

6.3. 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).

7. Clinical safety

7.1. 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 40, 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 40: 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.

7.2. 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 41.

Table 41: 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.

7.3. Disposition in the phase III MF population, safety set

The disposition of patients in the randomised treatment phase of the Phase III MF studies is summarised below in Table 42. Disposition in the randomised treatment phase allows comparisons between the ruxolitinib and control treatment arms, not confounded by cross-over of patients from the control arms to ruxolitinib.

Table 42: Phase III MF studies – Disposition in the randomised treatment phase; safety set.

	Study INCB 18424-351		Study CINC424A2352		Total
	ruxolitinib	Placebo	ruxolitinib	BAT	ruxolitinib
Patient disposition	**N=155**	**N=151**	**N=146**	**N=73**	**N=301**
Reason	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Ongoing in randomized treatment phase [1]	135 (87.1)	78 (51.7)	91 (62.3)	31 (42.5)	226 (75.1)
Discontinued randomized treatment phase	20 (12.9)	73 (48.3)	55 (37.7)	42 (57.5)	75 (24.9)
Crossed over to ruxolitinib [2]		36 (23.8)		18 (24.7)	
Continued in Extension [3]	0		29 (19.9)		29 (9.6)
Death [4]	0	0	0	0	0
Adverse event(s)	16 (10.3)	14 (9.3)	12 (8.2)	4 (5.5)	28 (9.3)
Consent withdrawn	1 (0.6)	7 (4.6)	2 (1.4)	9 (12.3)	3 (1.0)
Protocol deviation	0	0	2 (1.4)	0	2 (0.7)
Disease progression	3 (1.9)	13 (8.6)	1 (0.7)	3 (4.1)	4 (1.3)
Non-compliance with study medication	0	0	2 (1.4)	0	2 (0.7)
Non-compliance with study procedures	0	0	0	1 (1.4)	0
Other	0	3 (2.0)	7 (4.8)	7 (9.6)	7 (2.3)

[1] Receiving randomized treatment
[2] Crossed over to ruxolitinib after protocol-defined disease progression on Placebo/BAT to qualify for cross-over
[3] Treatment with ruxolitinib after disease progression event qualifying for entering extension phase
[4] Includes only those patients for whom death was reported as the primary reason for discontinuation of therapy
Source: [SCS Appendix 1–Table 1.3-6.1]

Comment: In both Phase III MF studies, the proportion of patients in the ongoing randomised treatment phase was greater in the ruxolitinib group than in the control group. In both Phase III MF studies, the major reason for discontinuation in the randomised treatment phase in the ruxolitinib groups was adverse events and these occurred more commonly in the ruxolitinib groups than the control groups. Discontinuations due to disease progression were notably more common in the ruxolitinib groups than in the control groups as were discontinuations due to withdrawn consent. In both Phase III MF studies, about 25% of patients in both control groups discontinued the randomised treatment phase and crossed-over to ruxolitinib in the extension phase due to protocol defined disease progression. In the all cancer safety set (n=617), 70.3% of patients were receiving ongoing ruxolitinib treatment and 29.7% had discontinued treatment. The main reasons for discontinuation of ruxolitinib treatment in the all cancer safety set were adverse events (6.3%) and disease progression (6.3%).

7.4. Adverse events in the phase III MF population

7.4.1. Overview

In the SCS, AEs were presented using MedDRA coding and included all treatment emergent AEs occurring after the first dose of study drug and starting no later than 28 days after study drug discontinuation. A patient with multiple occurrences of an AE was counted only once in the MedDRA preferred term. AEs were reported separately for those occurring regardless of relationship to study treatment and those suspected to be related to study treatment. AEs resulting in permanent treatment discontinuation and in dose interruptions or reductions were also reported. Similar reporting of SAEs to reporting of AEs was also provided. Deaths occurring on study or within 28 days after discontinuation of study drug were summarised (including data from the extension phases).

The SCS included grouping of selected AEs with clinically related preferred terms to identify clinically notable AEs (CNAEs). AEs grouped using specific Standard MedDRA Query (SMQ) definitions were thrombocytopenia, erythropenia, leucopenia, haemorrhagic events and malignancies. AEs grouped by selected preferred terms were urinary tract infections, herpes zoster infections, dizziness and bruising events.

7.4.2. Common adverse events

(a) AEs regardless of drug relationship by SOC.

The most common AEs by MedDRA "system, organ, class (SOC)" regardless of relationship to study drug reported in ≥ 50% of patients in the pooled ruxolitinib population 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 occurring ≥ 2% more commonly in the ruxolitinib group than in the control group in both Phase III studies are summarised below in Table 43. SOC disorders occurring ≥ 2% more commonly in the control group than the ruxolitinib group in both Phase III studies are summarised below in Table 44.

Table 43: Phase III MF studies – Adverse events by SOC occurring in ≥ 2% more patients in the ruxolitinib group than in the control group in both studies; n (%), safety set.

	Pivotal Study #351		Supportive Study #351		Total ruxolitinib
Primary SOC	Rux (n=166)	Placebo (n=161)	Rux (n=148)	BAT (n=73)	(n=301)
Blood and lymphatic system disorders	85 (54.8%)	56 (37.1%)	103 (70.5%)	18 (24.7%)	188 (62.5%)
Investigations	69 (44.5%)	62 (41.1%)	49 (33.6%)	20 (27.4%)	118 (39.2%)
Nervous system disorders	57 (36.8%)	35 (23.2%))	42 (28.8%	15 (20.5%)	99 (32.9%)
Injury, poisoning & procedural complications	47 (30.3%)	22 (14.6%)	23 (15.8%)	6 (8.2%)	70 (23.3%)
Cardiac disorders	28 (18.1%)	21 (13.9%)	29 (19.9%)	8 (11.0%)	57 (18.9%)

	Pivotal Study #351		Supportive Study #351		Total ruxolitinib
Primary SOC	Rux (n=166)	Placebo (n=161)	Rux (n=148)	BAT (n=73)	(n=301)
Psychiatric disorders	31 (20.0%)	27 (17.9%)	20 (13.7%)	8 (11.0%)	51 (16.9%)
Ear and labyrinth disorders	9 (5.8%)	4 (2.6%)	10 (6.8%)	3 (4.1%)	19 (6.3%)

Table 44: Phase III MF studies – Adverse events SOC occurring in ≥ 2% more patients in the control group than in the ruxolitinib group in both studies; n (%), safety set

	Pivotal Study #351		Supportive Study #351		Total ruxolitinib
Primary SOC	Rux (n=166)	Placebo (n=161)	Rux (n=148)	BAT (n=73)	(n=301)
Skin and subcutaneous tissue disorders	43 (27.7%)	73 (48.3%)	48 (32.9%)	28 (38.4%)	91 (30.2%)
Renal and urinary disorders	17 (11.0%)	25 (16.6%)	19 (13.0%)	12 (16.4%)	36 (12.0%)
Hepatobiliary disorders	8 (5.2%)	21 (13.9%)	8 (5.5%)	7 (9.6%)	16 (5.3%)

(b) AEs regardless of drug relationship by preferred term and maximum CTC grade.

In the Phase III MF population, adverse events (all grades) regardless of the relationship to the study drug occurred in 98.3% (n=296/301) of patients in the combined ruxolitinib group and the corresponding figures for Grade 3 and Grade 4 events were 35.9% (n=108/301) and 9.3% (n=28/301), respectively. The majority of AEs in the combined ruxolitinib group were Grade 1 or 2 in severity. AEs (all grades) reported in ≥ 20% of patients in the combined ruxolitinib group were thrombocytopenia (39.2%), anaemia (35.9%), diarrhoea (23.3%) and peripheral oedema (20.3%).

In the pivotal Phase III study, AEs (any) were reported in 97.4% of patients in the ruxolitinib groups and 98.0% of patients in the placebo group and the corresponding figures in the supportive Phase III study were 99.3% in the ruxolitinib group and 90.4% in the BAT group. In both studies, Grade 3 events (any) occurred more frequently in patients in the ruxolitinib group than in the control group (ruxolitinib, 35.5% versus 35.1%, placebo, [#351]; ruxolitinib, 36.3% versus 12.3%, BAT, [#351]). Grade 4 events (any) occurred more frequently in the ruxolitinib group than in the placebo group in the pivotal Phase III study (11.6% versus 9.3%, respectively), while in the supportive Phase III study Grade 4 events (any) occurred more frequently in the BAT group than in the ruxolitinib group (12.3% versus 6.8%, respectively).

AEs (any) occurring notably more commonly in patients in the ruxolitinib group than in the control group in both the pivotal Phase III and supportive Phase III studies were (ruxolitinib versus placebo; ruxolitinib versus BAT): thrombocytopenia (34.2% versus 9.3%; 44.5% versus

9.6%); anaemia (31.0% versus 13.9%; 41.4% versus 12.3%); diarrhoea (23.2% versus 21.2%; 23.3% versus 12.3%); headache (14.8% versus 5.3%; 10.3% versus 4.1%); pyrexia (11.0% versus 7.3%; 13.7% versus 9.6%); pain in extremity (12.3% versus 9.9%; 11.6% versus 4.1%); arthralgia (11.0% versus 8.6%; 12.3% versus 6.8%); dizziness (14.8% versus 8.6%; 7.5% versus 5.5%); vomiting (12.3% versus 9.9%; 8.9% versus 1.4%); constipation (12.9% versus 11.9%; 7.5% versus 5.5%); and contusion (14.2% versus 5.3%; 2.1% versus 1.4%). Other less frequently reported AEs occurring in ≥ 5% of patients in any treatment group in the pivotal Phase III and supportive Phase III studies and more commonly in the ruxolitinib group than in the control group in both studies were weight increased, urinary tract infection, haematoma, bronchitis, cardiac murmur, exertional dyspnoea, chills, cystitis and flatulence.

Grade 3 AEs occurring more commonly in patients in the ruxolitinib group than in the control group in both the pivotal Phase III and supportive Phase III studies, in each study were (ruxolitinib versus placebo; ruxolitinib versus BAT): 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%). The only Grade 4 AE occurring more commonly in patients in the ruxolitinib group than in the control group in both the pivotal Phase III and supportive Phase III studies was thrombocytopenia (1.3% versus 0.7% [#351]; 0.7% versus 0% [#352]).

AEs occurring notably more commonly in patients in the control group than in the ruxolitinib group in both the pivotal Phase III and supportive Phase III studies (ruxolitinib versus placebo; ruxolitinib versus BAT) were: abdominal pain (41.1% versus 10.3%; 13.7% versus 11.0%); peripheral oedema (22.5% versus 18.7%; 26.0% versus 21.9%); back pain (7.9% versus 7.1%; 11.0% versus 9.6%); and pruritis (15.2% versus 4.5%; 12.3% versus 4.8%). Other AEs (any) occurring in ≥ 5% of patients in any treatment group in the pivotal Phase III and supportive Phase III studies and more commonly in the control group than in the ruxolitinib group in both studies were 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 in the ruxolitinib group in both the pivotal study (3.3% versus 3.2%, respectively) and the supportive study (2.7% versus 1.4%, respectively).

Comment: The most marked differences in the AE profiles of the treatment groups related to the higher incidence of thrombocytopenia, anaemia, diarrhoea, headache, pyrexia, pain in extremity, arthralgia, dizziness, vomiting, constipation and contusion in the ruxolitinib groups compared with the control groups. The increased incidence of thrombocytopenia and anaemia in the ruxolitinib group compared with the control group in both the pivotal and supportive studies was particularly notable.

(c) AEs with respected relationship to study drug

In the Phase III MF population, AEs (any) suspected of being related to study drug were reported in 77.4% of patients in the combined ruxolitinib group, compared with 55.6% in the placebo group and 19.2% in the BAT group. The most commonly occurring AEs suspected to be related to study drug reported in ≥ 5% of patients in the combined ruxolitinib group and ≥ 2% more frequently in this group than in both control groups were (ruxolitinib versus placebo versus BAT): thrombocytopenia (36.2% versus 5.3% versus 1.4%); anaemia (27.6% versus 6.0% versus 4.1%); diarrhoea (9.6% versus 5.0% versus 1.4%); platelet count decreased (8.0% versus 1.3% versus 1.4%); and haemoglobin decreased (5.6% versus 1.3% versus 1.4%). Grade 3 or 4 AEs suspected to be related to the study drug and reported more commonly in the combined ruxolitinib group than in both the control groups were thrombocytopenia Grade 3 and 4, anaemia Grade 3, diarrhoea Grade 3, fatigue Grade 3, platelet count decreased Grade 3, haemoglobin Grade 3 and 4, weight increased Grade 3, and headache Grade 3.

Comment: The general pattern of AEs suspected to be related to treatment in the ruxolitinib groups was similar to that of AEs reported regardless of relationship to treatment.

7.4.3. SAEs in the phase III MF population

In the Phase III MF population, SAEs (any) occurred in 28.9% of patients in the ruxolitinib combined group compared with 35.1% of patients in the control group and 28.8% of patients in the BAT group. SAEs reported in ≥ 1% of patients in the ruxolitinib combined group are summarised below in Table 45.

Table 45: Phase III MF population - Frequent serious adverse events regardless of study drug relationship by preferred term (at least 1% in any group); safety set.

	Study INCB 18424-351		Study CINC424A2352		Total
	ruxolitinib	Placebo	ruxolitinib	BAT	ruxolitinib
	N=155	N=151	N=146	N=73	N=301
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Any preferred term	43 (27.7)	53 (35.1)	44 (30.1)	21 (28.8)	87 (28.9)
Anaemia	5 (3.2)	3 (2.0)	7 (4.8)	3 (4.1)	12 (4.0)
Pneumonia	10 (6.5)	5 (3.3)	1 (0.7)	4 (5.5)	11 (3.7)
Fatigue	4 (2.6)	0	0	0	4 (1.3)
Gastrointestinal haemorrhage	2 (1.3)	2 (1.3)	2 (1.4)	0	4 (1.3)
Pyrexia	1 (0.6)	1 (0.7)	3 (2.1)	1 (1.4)	4 (1.3)
Abdominal pain	0	6 (4.0)	3 (2.1)	1 (1.4)	3 (1.0)
Diarrhoea	1 (0.6)	0	2 (1.4)	0	3 (1.0)
Dyspnoea	1 (0.6)	1 (0.7)	2 (1.4)	3 (4.1)	3 (1.0)
Haemoglobin decreased	3 (1.9)	0	0	0	3 (1.0)
Thrombocytopenia	3 (1.9)	1 (0.7)	0	1 (1.4)	3 (1.0)
Varices oesophageal	0	1 (0.7)	3 (2.1)	0	3 (1.0)
Cardiac failure	0	1 (0.7)	3 (2.1)	0	3 (1.0)

Comment: Overall, there were no notable consistent differences in the frequency of SAEs between ruxolitinib and the control groups in the pivotal and supportive studies.

7.4.4. Death

Across the 6 clinical studies with ruxolitinib data, 53 deaths were reported in 790 patients. In the Phase III MF population there were a total of 34 deaths in the 2 relevant studies.

In the pivotal Phase III study, death during treatment or within 28 days after discontinuation of treatment in the safety set 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, death during treatment or within 28 days after discontinuation of treatment in the safety set 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 after treatment discontinuation.

Comment: Overall, there were no obvious significant differences in the causes of death in the treatment groups in the pivotal and supportive Phase III studies. In the ruxolitinib group infections accounted for 4 (1.3%) deaths (pneumonia in 2 patients, sepsis and septic shock in 1 patient each) and 3 (2.0%) deaths in the placebo group (pneumonia, sepsis and staphylococcal infection); these events were considered by the investigator to be unrelated or unlikely to be related to the study drug. Intestinal perforation accounted for 1 (0.3%) death in the ruxolitinib group and 1 (0.7%) death in the placebo group and both events were considered by the investigator to be unrelated or unlikely to be related to the

study drug. Disease progression and events probably due to disease progression contributed to 1 (0.3%) death in the ruxolitinib group (acute myeloid leukemia) and 4 (2.6%) deaths in the placebo group (disease progression in 3 patients, MF in 1 patient). Bleeding events accounted for 3 (1.9%) deaths in the ruxolitinib group (subdural haematoma, retroperitoneal haemorrhage, cerebral haemorrhage) and 1 (0.7%) death in the placebo group (gastrointestinal haemorrhage). In the Phase I/II study (#251) in patients with MF, 12 deaths occurred during treatment or within 28 days after treatment, and most AEs leading to death were similar to those observed in the Phase III studies, including infections (2 deaths), neoplasms, GI bleeds and disease progression (1 death each). Other causes of death included myocardial infarction (2 deaths), cerebral hemorrhage and cardiac arrest (1 deaths each).

7.4.5. Discontinuations due to AEs in the phase III MF population

In the Phase III MF population, discontinuations due to AEs were reported in 11.0% of patients in the ruxolitinib group and 10.6% of patients in the placebo group in the pivotal study and 8.2% of patients in both the ruxolitinib and BAT groups in the supportive study. None of the discontinuations were reported in more than 2 patients in any group. In the pivotal study, the only AEs resulting in discontinuation of 2 patients in either of the treatment groups were: pneumonia (n=2 [1.3%], ruxolitinib versus n=1 [0.7%], placebo); acute myeloid leukemia (n=2 [1.3%], ruxolitinib versus n=0, placebo); disease progression (n=2 [1.3%], placebo versus n=0, ruxolitinib); and abdominal pain (n=2 [1.3%], placebo versus n=1 [0.6%], ruxolitinib). In the supportive study, the only AEs resulting in discontinuation of 2 patients in either of the treatment groups was respiratory failure (n=2 [2.7%], BAT versus n=0, ruxolitinib).

In the total Phase I/II/III MF safety set (n=509), discontinuation due to AEs regardless of the relationship to the study drug was reported in 10% (n=51) of patients. In this safety set, the only AEs reported as leading to discontinuation in ≥ 0.5% (n ≥ 3) of patients were thrombocytopenia (1.4%, n=7), anaemia (1.2%, n=6), acute myeloid leukemia (0.8%, n=4), and pneumonia (0.6%, n=3).

Comment: In the Phase III PMF population, discontinuations due to AEs were similar in the ruxolitinib and control groups.

7.4.6. Dose interruption or reduction due to AEs in the phase III MF population

Adverse events in the Phase III MF population requiring dose interruption or reduction (≥ 1% in total ruxolitinib group) are summarised below in Table 46.

Table 46: Phase III MF population - Adverse events requiring dose interruption or reduction regardless of study drug relationship by preferred term (≥ 1% in total ruxolitinib group); safety set.

	Study INCB 18424-351		Study CINC424A2352		Total
	ruxolitinib N=155	Placebo N=151	ruxolitinib N=146	BAT N=73	ruxolitinib N=301
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Any preferred term	79 (51.0)	39 (25.8)	92 (63.0)	11 (15.1)	171 (56.8)
Thrombocytopenia	45 (29.0)	9 (6.0)	60 (41.1)	1 (1.4)	105 (34.9)
Platelet count decreased	13 (8.4)	3 (2.0)	10 (6.8)	2 (2.7)	23 (7.6)
Anemia	9 (5.8)	2 (1.3)	7 (4.8)	1 (1.4)	16 (5.3)
Dyspnoea	2 (1.3)	1 (0.7)	1 (0.7)	0	3 (1.0)
Gastrointestinal haemorrhage	2 (1.3)	1 (0.7)	1 (0.7)	0	3 (1.0)
Neutropenia	2 (1.3)	0	1 (0.7)	0	3 (1.0)
Fatigue	3 (1.9)	2 (1.3)	0	1 (1.4)	3 (1.0)
Haematocrit decreased	3 (1.9)	0	0	1 (1.4)	3 (1.0)
Haemoglobin decreased	3 (1.9)	0	0	2 (2.7)	3 (1.0)
Pneumonia	3 (1.9)	1 (0.7)	0	0	3 (1.0)

In the pivotal study, 51.0% (n=79) of patients in the ruxolitinib group had an AE resulting in dose interruption or reduction compared with 25.8% (n=39) of patients in the placebo group. The most frequent AE leading to dose interruption or reduction in the ruxolitinib group was thrombocytopenia/platelet count decreased (37.4%, ruxolitinib versus 8.0, placebo). In the pivotal study, 40% (n=62) of patients in the ruxolitinib group had an AE resulting in dose reduction (rather than interruption) compared with 9.3% (n=14) of patients in the placebo group. The most frequent AE leading to dosage reduction was thrombocytopenia/platelet count decreased (32.9%, ruxolitinib versus 6.6%, placebo). The data show that in the pivotal Phase III study AEs in the ruxolitinib group were managed more frequently by dose reductions rather than dose interruptions. In the supportive study, no data for dose reductions or dose interruption alone due to AEs could be identified.

Comment: In the Phase III MF population, AEs requiring dose interruption or reduction occurred notably more frequently in the ruxolitinib group than in the control group in both the pivotal and supportive studies. The difference between the treatment groups was primarily accounted for by the markedly more frequent dose interruptions or reductions due of thrombocytopenia in the ruxolitinib groups compared with the control groups. The high frequency of dose interruptions or reductions in the ruxolitinib groups due to thrombocytopenia resulted from protocol mandated dosage changes for patients with this event. The only other AEs of note resulting in more frequent dose interruptions or reductions 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.

7.4.7. Analysis of clinically notable AEs in the phase III MF population

7.4.7.1. Thrombocytopenia defined using a specific SMQ

Thrombocytopenia SMQ in the Phase III MF population is summarised below in Table 47. The SMQ was primarily accounted for by the preferred term of thrombocytopenia with a minor contribution from platelet count decreased.

Table 47: Phase III MF population – Thrombocytopenia SMQ; safety set.

	Phase III Study # 351 (pivotal)		Phase III Study #352 (supportive)		Total ruxolitinib
Patient groups	**RUX n=155**	**Placebo n=146**	**RUX n=146**	**BAT n=73**	**n=301**
Any AE	65 (41.9%)	16 (10.6%)	73 (50.0%)	9 (12.3%)	138 (45.8%)
AE related to study drug	58 (37.4%)	10 (6.6%)	70 (47.9%)	2 (2.7%)	128 (42.5%)
Grade 3 or 4 AE	15 (9.7%)	3 (2.0%)	12 (8.2%)	3 (4.1%)	27 (9.0%)
AE leading to study drug discontinuation	1 (0.6%)	1 (0.7%)	1 (0.7%)	1 (1.4%)	2 (0.7%)
AE leading to dose reduction	52 (33.5%)	11 (7.3%)	66 (45.2)	0	118 (39.2%)

7.4.7.2. Leucopenia defined using a specific SMQ

Leukopenia SMQ in the Phase III MF population is summarised below in Table 48. The SMQ was primarily accounted for by the preferred term of neutropenia with minor contributions from various other AEs. Febrile neutropenia was reported in only 2 (0.7%) patients in the total ruxolitinib group compared with 1 (0.7%) patient in the placebo group and 1 (1.4%) patient in the BAT group.

Table 48: Phase III MF population – Leukopenia SMQ; safety set.

	Phase III Study # 351 (pivotal)		Phase III Study #352 (supportive)		Total ruxolitinib
Patient groups	**RUX n=155**	**Placebo n=146**	**RUX n=146**	**BAT n=73**	**n=301**
Any AE	8 (5.2%)	4 (2.6%)	6 (4.1%)	1 (1.4%)	14 (4.7%)
AE related to study drug	6 (3.9%)	1 (0.7%)	3 (2.1%)	0	9 (3.0%)
Grade 3 or 4 AE	2 (1.3%)	1 (0.7%)	4 (2.7%)	1 (1.4%)	6 (2.0%)
AE leading to study drug discontinuation	1 (0.6%)	0	0	0	1 (0.3%)
AE leading to dose reduction	2 (1.3%)	0	0	0	2 (0.7%)

7.4.7.3. Erythropenia defined using specific SMQ

Erythropenia SMQ in the Phase III MF population is summarised below in Table 49. The SMQ was primarily accounted for by the preferred term of anaemia with minor contributions from various other AEs.

Table 49: Phase III MF population – Erythropenia SMQ; safety set.

	Phase III Study # 351 (pivotal)		Phase III Study #352 (supportive)		Total ruxolitinib
Patient groups	**RUX n=155**	**Placebo n=146**	**RUX n=146**	**BAT n=73**	**n=301**
Any AE	55 (35.5%)	23 (15.2%))	62 (42.5%	9 (12.3%)	117 (38.9%)
AE related to study drug	42 (27.1%)	9 (6.0%)	46 (31.5%)	3 (4.1%)	88 (29.2%)
Grade 3 or 4 AE	27 (17.4%)	7 (4.6%)	18 (12.3%)	3 (4.1%)	45 (15.0%)
AE leading to study drug discontinuation	1 (0.6%)	1 (0.7%)	0	0	1 (0.3%)

	Phase III Study # 351 (pivotal)		Phase III Study #352 (supportive)		Total ruxolitinib
Patient groups	**RUX n=155**	**Placebo n=146**	**RUX n=146**	**BAT n=73**	**n=301**
AE leading to dose reduction	8 (5.2%)	0	8 (5.5%)	2 (2.7%)	16 (5.3%)

7.4.7.4. Haemorrhagic events defined using specific SMQ

Haemorrhagic SMQ in the Phase III MF population is summarised below in Table 50. The SMQ was primarily accounted for by the preferred AE term "bruising". Bruising events were identified as the main cause for the observed higher frequency of haemorrhagic events in the ruxolitinib patients than in the control groups (19.3% total ruxolitinib, 14.6% placebo, 5.5% BAT). All but one bruising AE were Grade 1 or 2 events (one Grade 3 hematoma was reported), while no bruising events were reported as SAEs or resulted in dose reductions or discontinuations. The most frequent bruising AE in the total ruxolitinib group was contusion (8.3%), followed by haematoma (6.0%), ecchymosis (3.0%) and petechiae (1.3%). All other bruising AEs were reported in less than 1% of patients in the total ruxolitinib groups. Other types of haemorrhages included intracranial (0.6%, ruxolitinib versus 0.7%, placebo; 1.4%, ruxolitinib versus 0%, BAT); gastrointestinal (3.9%, ruxolitinib versus 4.0%, placebo; 5.5%, ruxolitinib versus 0%, BAT), and other (11.0%, ruxolitinib versus 8.6%, placebo; 13.0%, ruxolitinib versus 13.7%, BAT).

Table 50: Phase III MF population – Haemorrhagic SMQ; safety set.

	Phase III Study # 351 (pivotal)		Phase III Study #352 (supportive)		Total ruxolitinib
Patient groups	**RUX n=155**	**Placebo n=146**	**RUX n=146**	**BAT n=73**	**n=301**
Any AE	51 (32.9)	38 (25.2)	38 (26.0)	12 (16.4)	89 (29.6)
AE related to study drug	12 (7.7)	2 (1.3)	11 (7.5)	0	23 (7.6)
Grade 3, 4 or 5 AE	6 (3.9)	4 (2.6)	6 (4.1)	2 (2.7)	12 (4.0)
AE leading to study drug discontinuation	2 (1.3)	1 (0.7)	1 (0.7)	0	3 (1.0)
AE leading to dose reduction	0	0	1 (0.7)	0	1 (0.3)

7.4.8. Other clinically notable adverse events

- The SOC of "Infections and infestations" was reported in 50.5% of patients in the total ruxolitinib group compared with 41.7% of patients in the placebo group and 43.8% of patients in the BAT group. The increased incidence of these disorders in the total ruxolitinib group compared with the placebo and BAT groups was due to urinary tract infections (UTIs) (7.0% versus 4.6% versus 2.7%, respectively) and herpes zoster infections (3.3% versus 0.7% versus 0%, respectively). The analysis of UTI by grouped terms showed that the

frequency of these events in the total ruxolitinib group was 11.6% (n=35) compared with 5.3% (n=8) in the placebo group and 6.8% (n=5) in the BAT group. The major preferred term AE contributing to the difference in UTI by grouped terms was UTI (7.0%, total ruxolitinib group), followed by cystitis (3.3%, total ruxolitinib group) and urosepsis (1.0%, total ruxolitinib group). The analysis of herpes zoster by grouped terms showed that the frequency of these events in the total ruxolitinib group was 3.7% (n=11) compared with 0.7% (n=1) in the placebo group and 0% in the BAT group. The herpes zoster grouped term events were accounted for almost exclusively by the preferred term herpes zoster.

- Malignancies SMQ (narrow) were reported in 4.0% (n=12) of patients in the total ruxolitinib group compared with 7.9% (n=12) of patients in the placebo group and 5.5% (n=4) of patients in the BAT group. 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).
- The grouped term of dizziness was reported more commonly in patients in the total ruxolitinib group (14.3%, n=43) than in the placebo group (7.3%, n=11) and the BAT group (8.3%, n=6). The AE preferred term of dizziness accounted for the majority of events contributing to the grouped term (11.3% [n=34], total ruxolitinib group versus 6.6% [n=10], placebo group versus 5.5% [n=4], BAT group). Other preferred terms contributing to the grouped term and occurring in ≥ 1% of patients in the total ruxolitinib group were vertigo (2.0%) and balance disorder (1.3%). Only 1 patient with the grouped term of dizziness had a dose reduction due to the event (ruxolitinib group in Study #352), and no patients discontinued the study drug due to this grouped event.
- The grouped term of weight gain was reported notably more commonly in the total ruxolitinib group (8.3%, n=25) than in the placebo group (1.3%, n=2) and the BAT group (0%). The AE preferred term of weight increased accounts for 24 of the 25 grouped term events in the total ruxolitinib group with the remaining event being abnormal weight gain. Only 2 patients with weight gain grouped term had a dose reduction due to the event (both in the ruxolitinib group in Study #352) and no patients discontinued the study drug due to this grouped event.

7.5. Transfusions – PRBC

The SCS included an assessment in the Phase III MF population comparing the frequency of packed red blood cell (PRBC) transfusions between the ruxolitinib and control groups while on treatment. While on treatment, transfusion frequency was calculated as transfusions per exposure duration including the 28 day period after discontinuation of study drug or the time period between discontinuation and start of a new treatment.

In the pivotal study (#351), 12.9% (n=20) of patients randomised to ruxolitinib received one or more PRBC transfusions per month in the 12 weeks prior to screening compared with 11.9% (n=18) of patients randomised to placebo. While on treatment, 59.4% (n=92) of patients in the ruxolitinib group received at least one PRBC transfusion compared with 37.1% (n=56) of patients in the placebo group. The mean number of transfusions per month was 0.92 in the ruxolitinib group and 0.75 in the placebo group.

In the supportive study (#352), 11.6% (n=17) of patients randomised to ruxolitinib received one of more PRBC transfusions per month in the 12 weeks prior to screening compared with 16.4% (n=12) of patients randomised to BAT. While on treatment, 51.4% (n=75) in the ruxolitinib group received at least one PRBC transfusion compared with 38.4% (n=28) of patients in the BAT group. The mean number of transfusions per month was 0.86 for the ruxolitinib group and 0.91 for the BAT group.

When analysed by baseline platelet count, the overall percentage of patients in the total ruxolitinib group requiring transfusions was slightly higher for patients with baseline platelet counts > 200 x 10^9/L corresponding to a starting dose of 20 mg bd, compared with patients with baseline platelet counts 100 to 200 x 10^9/L, corresponding to a starting dose of 15 mg bd (that is, 57.4% [n=109/190] versus 52.3% [n=58/111], respectively). However, the pivotal and supportive studies showed inconsistent results for the number of transfusions received by patients who started ruxolitinib at the different dose levels. In the pivotal study, a smaller percentage of patients starting on 20 mg bd received one of more PRBC transfusions on treatment compared with patients starting on 15 mg bd (57%, mean 7.4 units, mean exposure 8.5 months versus 63.6%, 7.6 mean units, mean exposure 7.8 months). In the supportive study, a higher percentage of patients starting on 20 mg bd received one or more PRBC transfusion on treatment compared with patients starting on 15 mg bd (57.8%, mean 10.5 units, mean exposure 8.5 months versus 41.3%, mean 6.1 units, mean exposure 10.4 months).

Comment: Overall, the data showed that a greater percentage of patients in the ruxolitinib groups received at least one PRBC transfusion while on treatment compared with the 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 and the mean number of transfusions per month was 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 and the mean number of transfusions per month was 0.86 and 0.91 respectively. The combined data 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.

7.6. Clinical laboratory tests

7.6.1. Haematology

Laboratory data in the SCS were classified into CTC Grades according to NCI CTCAE v3.0 criteria. A severity grade of 0 was assigned when the value was within normal limits. The SCS provided haematology laboratory data for the pivotal (#351) and supportive (#352) studies summarised according to: (1) newly occurring or worsening haematologic abnormalities; (2) haematology shift tables; and (3) Kaplan-Meier estimates of time to onset of first new or worsening grade 3 or 4 thrombocytopenia, grade 3 or 4 neutropenia and grade 2 or higher anaemia. The summaries included all laboratory assessments collected up to 28 days after study treatment discontinuation.

In the Phase III MF population, the most frequent newly occurring or worsening haematology abnormality of any grade in the total ruxolitinib group was decreased haemoglobin concentration (81.7%, total ruxolitinib versus 41.7%, placebo versus 49.3%, BAT), and decreased platelet count (67.4%, total ruxolitinib versus 19.2%, placebo versus 36.0%, BAT). In the total ruxolitinib group, most of the decreased platelet counts (84.2%) were Grade 1 or 2 events and 50.4% of the newly occurring or worsening decreased haemoglobin concentrations were Grade 1 or 2 events.

The shift tables showed that the majority of patients entered the pivotal and supportive studies with baseline Grade 1 and 2 abnormal haemoglobin levels. In patients in the ruxolitinib groups, haemoglobin grades mostly worsened to the grade immediately above their baseline level, while 11.0% (versus 3.3% placebo) of patients in the pivotal study and 8.2% (versus 10.0% BAT) of patients in the supportive study worsened to Grade 4 at any time during the study.

The shift tables showed that the majority of patients entered the pivotal and supportive studies with baseline Grade 0 (normal) platelet counts. In patients in the ruxolitinib groups who were Grade 0 at baseline, the majority of patients remained at Grade 0 or worsened to Grade 1 during the study with Grade 3 or 4 levels occurring in 9.0% and 3.9%, respectively, in the pivotal study and 6.2% and 2.1%, respectively, in the supportive study. In the placebo and BAT groups, the majority of patients with Grade 0 platelets at baseline remained at this grade throughout the study with worsening to Grade 3 and 4 being reported in 1.3% and 0%, respectively, of patients in the placebo group and 4.3% and 2.9%, respectively, in the BAT group.

The majority of Grade 3 or 4 thrombocytopaenia reported in the total ruxolitinib group from the pivotal and supportive studies occurred within the first three 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 total ruxolitinib group was 2 weeks (95% CI: 1.29, 2.14). 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 1.45 months (95% CI; 1.41, 1.87).

7.6.2. Clinical chemistry

7.6.2.1. Liver and renal function

In the total ruxolitinib group, the most frequent newly occurring or worsening biochemistry abnormality was Grade 1 alanine aminotransferase (ALT) increased (total ruxolitinib, 23.9% versus 7.3%, placebo versus 6.8, BAT) and Grade 1 Gammaglutamyltransferase (GGT) increased (total ruxolitinib, 20.6% versus 17.2%, placebo versus 11.0%, BAT). ALT Grades 3 or 4 were reported in 1.3% and 0% of patients in the total ruxolitinib group, respectively, compared with 0.7% and 0%, respectively, in the placebo group and 0% for both grades in the BAT group. Grade 1 aspartate aminotransferase (AST) newly occurring or worsening abnormalities on treatment were observed in 17.9% of patients in the total ruxolitinib group compared with 6.0% in the placebo group and 2.7% in the BAT group, while no more than 1 patient in all groups in the individual studies had AST Grade 2 events and no patients had AST Grade 3 or 4 events. There were no marked differences between the ruxolitinib and control groups in newly occurring or worsening abnormalities while on treatment for bilirubin, ALP, or creatinine. Liver function abnormalities in the Phase III MF population are summarised below in Table 51.

Table 51: Phase III MF population – Liver function test abnormalities.

	Study INCB 18424-351				Study CINC424A2352				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	5 (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	5 (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: LFT abnormalities reported in the Phase III MF population showed that 1 patient treated with ruxolitinib in the supportive study had an ALT or AST > 3.0 x upper limit of normal (ULN) and bilirubin ≥ 2 x ULN and ALP < 2 x ULN. This patient was a 66 year old male who died due to hepatic failure, portal vein thrombosis and cerebral haemorrhage. The patient had a history of squamous cell carcinoma of the skin affecting the forehead and was diagnosed on Day 253 with metastatic disease to the face, temple area and neck and underwent wide local excision, parotidectomy and radical neck dissection. On Day 302, the patient was noted to have increased ALT, GGT and ALP levels as well as thrombocytopenia. Both liver

enzymes and platelet count deteriorated over time. On Day 323, the patient experienced decompensated liver disease with disseminated intravascular coagulation, an abdominal ultrasound ruled out metastatic disease to the liver. On Day 324, the patient experienced massive portal vein thrombosis and further decompensation of liver function. On Day 326, the patient experienced cerebral haemorrhage and on the same day the patient died due to hepatic failure, portal vein thrombosis and cerebral hemorrhage. The investigator suspected a possible relationship between hepatic failure and portal vein thrombosis and an unlikely relationship between metastatic squamous cell carcinoma of skin and the study medication. Based on the submitted narrative it is considered that ruxolitinib induced hepatotoxicity cannot be excluded as the abnormal liver function data appear to fit the criteria for Hy's law.

ALT or AST increases > 3 x ULN were reported in 5 (0.7%) patients in the total ruxolitinib group. Newly occurring or worsening ALT or AST abnormalities occurring in the total ruxolitinib group were predominantly Grade 1 in severity and occurred notably more commonly than in the control groups. Overall, the provided data suggest that significant liver toxicity is unlikely with ruxolitinib. However, there appears to be one case of fatal hepatic failure possibly related to ruxolitinib treatment (0.3% of patients in the total ruxolitinib MF group).

7.6.2.2. Other clinical laboratory abnormalities of note

1. The only other clinical laboratory abnormality of note related to changes in cholesterol levels. In the pivotal study, patients in the ruxolitinib group had a median increase from baseline in total cholesterol of 20.7% at Week 24 (2.8 to 3.6 mmol/L) compared with a median decrease in patients in the placebo group of 4% (2.9 to 2.6 mmol/L); $p < 0.0001$. Low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) concentrations also increased in the ruxolitinib group (32% and 39%, respectively), but the ratio between total cholesterol and High-Density Lipoprotein Cholesterol (HDL-C) improved relative to baseline (4.21 ⟶ 3.64; -10%).

7.6.2.3. Urinalysis

Examination of the urinalysis shift tables for patients in the ruxolitinib and placebo groups showed that results for nearly all standard parameters remained within the normal range in both the pivotal and supportive Phase III studies.

7.6.3. Vital signs

In the Phase III MF population, vital signs were generally comparable among the treatment groups (that is, heart rate; blood pressure; respiratory rate). However, the frequency of increased sitting systolic blood pressure ≥ 25% from baseline was notably higher in the total ruxolitinib group compared with the placebo and BAT groups (16.4% versus 7.3% versus 10.1%, respectively). There were no notable differences in the ECG relating to significant changes in the QTcF interval among the treatment groups.

7.6.4. Safety in special groups in the phase III MF population

7.6.4.1. Age

In the Phase III MF population, nearly all patients aged ≤65 years (45.6%, n=135) and > 65 years (54.4%, n=161) in the combined ruxolitinib group experienced an AE (97.1% versus 99.4%, respectively). However, there were specific SOCs and preferred term AEs that occurred more commonly in patients aged > 65 years compared with patients aged ≤ 65 years. The following frequencies for SOCs and AE preferred terms relate to the combined ruxolitinib group and all bracketed comparisons relate to the group aged > 65 years versus the group aged ≤ 65 years, respectively. The SOC of "Blood and lymphatic system disorders" was reported at a higher frequency in older patients (69.1% versus 54.7%). This imbalance was largely due to higher

frequencies in the older group of anaemia (38.9% versus 32.4%) and thrombocytopenia (42.6% versus 35.3%). The SOC of "Cardiac disorders" also had a higher frequency in older patients (23.5% versus 13.7%), without any one preferred term predominating. "Infections and infestations" occurred more frequently in older patients (56.2% versus 43.9%), with the largest differences by preferred terms being cystitis (4.9% versus 1.4%) and pneumonia (8% versus 2.2%). The SOC of "Injury, poisoning and procedural complications" had a higher frequency in older patients (31.5% versus 13.7%), largely due to differences in contusions (11.7% versus 4.3%) and falls (4.9% versus 0.7%). There were minimal differences in the SOC of "Respiratory, thoracic and mediastinal disorders" between the age groups (40.7% versus 44.4%), except for dyspnoea which was more common in older patients (21.0% versus 11.5%). The SOC of "Vascular disorders" was seen at a higher frequency in older patients (24.1% versus 11.5%), with the largest difference by preferred terms being hematoma (8.6% versus 1.4%). The frequency of SAEs (any) in the total ruxolitinib group was also notably higher in older patients (39.5% versus 16.5%).

7.6.4.2. Gender

In the Phase III MF population, nearly all patients in the male (55.2%, n=290) and female (46.2%, n=139) subgroups in the combined ruxolitinib treatment group experienced at least one AE (98.1% versus 98.6%, respectively). However, there were specific SOCs and preferred term AEs that occurred more commonly in female than in male patients and vice versa. The following frequencies for SOCs and AE preferred terms relate to the combined ruxolitinib group, unless otherwise stated. The SOC of "Blood and lymphatic system disorders" was reported more frequently in females than in males (69.1% versus 56.8%), mainly due to increased frequency in the preferred terms of anemia (43.2% versus 29.6%) and haemoglobin decreased (11.5% versus 6.2%). However, anaemia was nearly twice as common in females (18.5%) compared with males in the placebo group (10.5%) of Study #351, suggesting a greater baseline frequency of anemia in females with MF. In the combined ruxolitinib group, other AEs reported at a higher frequency in females than in males included UTI (11.5% versus 3.1%), cystitis (7.2% versus 0%), haematoma (8.6% versus 3.7%), fall (5% versus 1.2%), night sweats (10.1% versus 4.3%) and weight increased (13.7% versus 3.1%).

The SOC of "Hepatobiliary disorders" was reported more frequently in males than in females (7.4% versus 2.9%) but without any single preferred term accounting for the imbalance. There was also a substantial imbalance of preferred terms in the SOC "Hepatobiliary disorders" among men compared with women in the placebo group of Study #351 (17.4% versus 9.2%). AEs reported at a higher frequency in males than in females included anorexia (6.2% versus 1.4%), without a substantial difference in the placebo groups between males and females but with a higher frequency in the BAT groups in males compared with females. Herpes zoster was reported more frequently in males than in females (4.9% versus 1.4%).

SAEs (any) were reported more frequently in males than in females (32.7% versus 24.5%), with the higher frequency in males being mainly due to higher number of preferred terms being reported.

7.6.4.3. Race

In the Phase III MF population, since most of the patients were "White" (87.6%) it is not considered clinically meaningful to compare the safety profile of ruxolitinib among the racial groups.

7.6.4.4. Baseline platelet count

In the Pivotal Phase III PMF population, when analysed by baseline platelet count category (< 200 x 10^9/L versus ≥ 200 x 10^9/L), which was the criterion for starting doses of 15 mg bd or 20 mg bd respectively, nearly all patients in the combined ruxolitinib treatment group experienced at least one AE (99.1% [n=108/109] versus 97.9% [188/192], respectively). However, in the combined ruxolitinib treatment group the frequencies of some AEs were higher in the lower

baseline platelet count group compared with the higher baseline platelet group, including thrombocytopenia (55.0% versus 30.2%), neutropenia (5.5% versus 1.6%), atrial fibrillation (4.6% versus 0.5%), abdominal pain (14.7% versus 7.8%), melaena (3.7% versus 1.6%), fatigue (24.8% versus 15.1%), anorexia (6.4% versus 2.6%), pruritus (9.2% versus 2.1%), and night sweats (10.1% versus 5.2%). Conversely, in the combined ruxolitinib treatment group AEs that were more frequently reported in the higher baseline platelet count group than the lower baseline platelet count group included anaemia (38.0% versus 32.1%), palpitations (5.2% versus 0.9%), chills (4.7% versus 1.8%), cystitis (4.2% versus 1.8%), dyspnoea (21.1% versus 14.1%), weight increased (9.4% versus 5.5%) and dizziness (13.5% versus 6.4%). SAEs were generally well balanced between the two platelet count groups.

7.7. 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 26.0% 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, and 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 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 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).

8. First round benefit-risk assessment

8.1. First round assessment of benefits

It is 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 it is recommended that the proposed indication be amended. It is 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 is 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 is 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.

8.2. 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 age ≤ 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 grade 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.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of ruxolitinib, given the amended proposed usage, is 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. It is 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 it is considered that treatment with ruxolitinib should not be initiated in these patients.

9. First round recommendation regarding authorisation

It is 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.

It is 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. It is recommended that ruxolitinib should not be started in patients with baseline platelet counts < 100 x 10^9/L.

10. Clinical questions

10.1. 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.

10.2. Pharmacodynamics

Nil.

10.3. 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.

10.4. Safety

1. 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 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.

11. Second round evaluation of clinical data submitted in response to questions

11.1. Pharmacokinetics

11.1.1. 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.

11.1.1.1. 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*" 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)- ruxolitinb 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, 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[h]] 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.

11.1.2. 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

[h]<http://www.tga.gov.au/pdf/euguide/ewp140198rev1.pdf>

please justify the recommendation that no adjustment of ruxolitinib is required when the drug is co-administered with moderate CYP3A4 inhibitors.

11.1.2.1. 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[i]].

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 2-5 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.

11.1.3. Question c

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

11.1.3.1. 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 is satisfactory.

11.2. 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

[i]<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf>

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.*

11.2.1.1. Sponsor's response:

Table 52 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 52: 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 is satisfactory.

11.3. Safety

11.3.1. 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?

11.3.1.1. 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 53. 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	5 (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	5 (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[j]]. 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]."

11.3.2. Question b

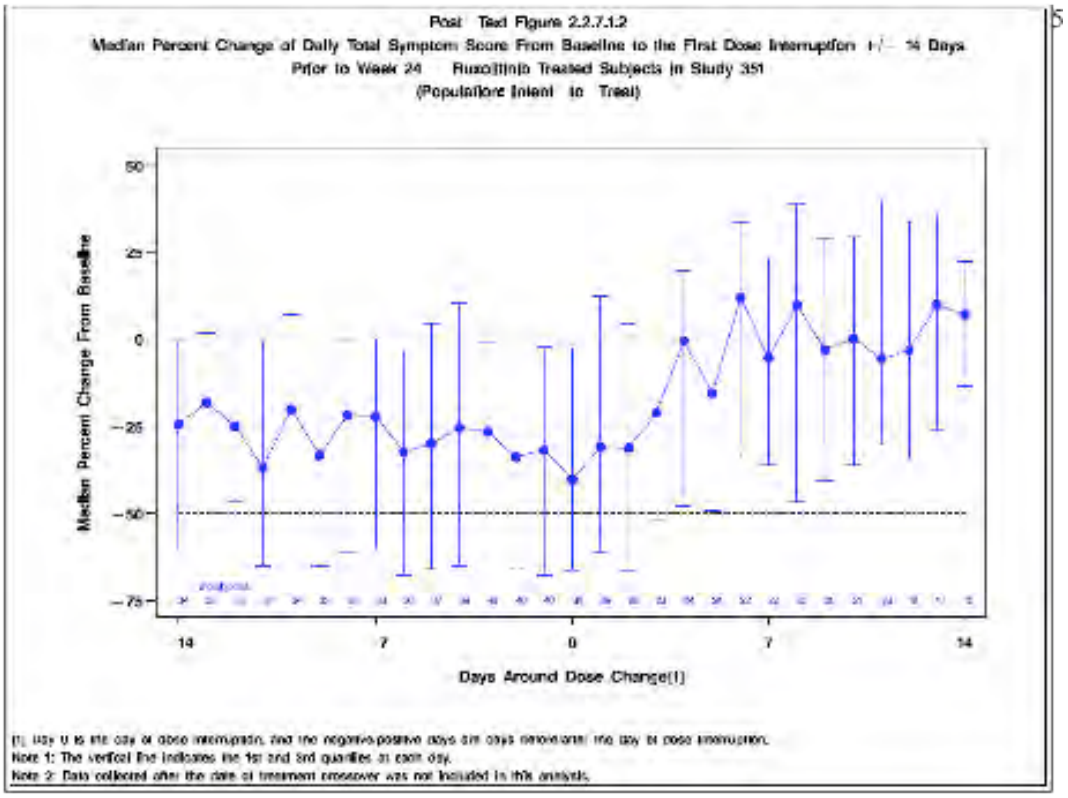
Does the sponsor have any specific data on withdrawal/rebound effects on patients discontinuing ruxolitinib? If so, please provide the data. It is noted that the Precautions and Adverse effects section of the PI includes information on withdrawal effects.

11.3.2.1. Sponsor's response:

When ruxolitinib therapy is discontinued, patients typically sustain a recurrence in clinical manifestations of their disease (Figure 2), including regrowth of an enlarged spleen and return of disease related symptoms such as fevers, night sweats, anorexia, abdominal discomfort and others.

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

Figure 2: Median percent change in daily total symptom score from baseline to first dose interruption.



11.3.2.1.1. 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 01 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 CTCAE grade 1 or 2; 32.0% (41/128) were grade 3 or higher. The mean last dose for 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.

11.3.2.1.2. 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 MFSAF 2.0 (Mesa 2009) 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.

11.3.2.1.3. 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:

11.3.2.1.4. 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).

11.3.2.1.5. 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).

11.3.2.1.6. 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).

11.3.2.1.7. 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).

11.3.2.1.8. Other AEs

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

11.3.2.1.9. 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 [information redacted] 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 (Verstovsek *et al,* 2012).

11.3.2.1.10. 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.

11.3.2.1.11. 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.

11.3.2.1.12. 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.

11.3.3. Question 7 (Indication)

It is 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, it is 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, it is considered that the indication should specifically refer to patients with high-risk or intermediate- risk level-2 MF.

11.3.3.1. 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 54, unpublished data available from the IPSS analysis (Cervantes 2011, 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 54: 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)

Since the first publication of prognostic criteria for MF, known as the Lille criteria (Dupriez *et al*, 1996), several additional prognostic classifications have been published including the International Working Group Classification which is known as IPSS 2009, DIPSS 2010 (Cervantes *et al,* 2009; Passamonti *et al*, 2010), and DIPSS-Plus 2011 (Gangat *et al*, 2011) 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 (Barosi *et al*, 2012). 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 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."*

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 55, below). Furthermore, there are no data on the risk-benefit balance for ruxolitinib treatment of intermediate-1 risk patients.

Table 55: 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 (Cervantes *et al,.*, 2009). The risk factors contributing to the IPSS are summarised below in Table 56.

Table 56: 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

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 (Barosi *et al,* 2012) 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 57. 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 57: Barosi *et al,*., 2012 - Response in spleen size and constitutional symptoms based on MF risk score (IPSS).

Response	High	Intermediate-2	Intermediate-1	Low
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 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, 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 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 s31 response is 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*".

12. Second round benefit-risk assessment

12.1. 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"* are unchanged from those identified in the first round evaluation report.

12.2. 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"* are unchanged from those identified in the first round evaluation report.

12.3. Second round assessment of benefit-risk balance

The benefit-risk balance of ruxolitinib is 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".

13. Second round recommendation regarding authorisation

It is 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 are provided in this second round clinical evaluation report.

14. References

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