CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	202192
Submission Date	June 03, 2011
Applicant Name	Incyte Corporation
Generic Name	Ruxolitinib
Proposed Indication	Myelofibrosis
Primary Reviewer	Christian Grimstein, Ph.D.
Secondary Reviewer	Issam Zineh, Pharm.D., M.P.H.

1 Background

Ruxolitinib is an inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2. The proposed indication is for the treatment of patients with myelofibrosis, including primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF), and post-essential thrombocythemia-myelofibrosis (PET-MF). As part of the development plan, the sponsor performed an exploratory analysis in Phase 3 clinical studies to assess whether JAK2-V617F mutation status affects response (i.e. ≥ 35% reduction from baseline in spleen volume) to ruxolitinib treatment. Somatic JAK2-V617F mutation is a gain of function mutation rendering JAK2 kinase constitutively active (Frequency: PMF: 35-50%, ET: 32-57%, PV: 95%). According to the literature, JAK2-inhibitors are active in patients, irrespective of JAK2 mutation status (PMID: 19573914). JAK2-V617F mutation status information was available for review.

2 Submission Contents Related to Genomics

The sponsor conducted two Phase 3 studies in patients with PMF, PPV-MF or PET-MF and determined the effect of JAK-V617F mutation on response. INCB 18424-351 is a Phase 3, double-blind, randomized, placebo-controlled study conducted in 309 patients. CINC424A2-352 is a Phase 3, open-label, randomized, best available therapy-controlled study, conducted in 219 patients in Europe.

3 Key Issues and Summary of Findings

3.1 Effect of JAK mutation status on response

JAK2-V617F allele burden [%JAK(mut)/JAK(wt+mut) haematopoetic cells in whole blood] was determined in all patients in the Phase 3 trials. According to the sponsor, mutation status was determined on site using an analytically validated (but not further specified) assay. No information was given whether patients were homo- or heterozygous with respect to JAK2-V617F mutation. JAK2-V617F allele burden was reduced by 11% and 21.5% on week 24 and 48 (Study 351), respectively. According to the sponsor's exploratory analysis, JAK2-V617F mutation positive patients tend to have a higher response rate (proportion of subjects achieving ≥ 35% reduction from baseline in spleen volume) compared to JAK2-V617F negative subjects (approximately 47% vs. 27% at week 24 in study 351; approximately 34% vs. 14% at week 48 in study 352). FDA analysis confirmed the sponsors assessment (see Clinical Pharmacology

review, DARRTS date 10/27/11). Of note, according to the sponsor's analysis, patients receiving ruxolitinib showed significant improvement over best available therapy, irrespective of mutation status.

3.2 Safety

The safety profile of ruxolitinib does not appear to be affected by JAK2-V617F mutation status. Thrombocytopenia and anemia were the most common AEs and were dose related. SAE with higher incidence in treatment group compared to control included anemia, diarrhea and hip fracture but occurred at low frequency.

4 Summary and Conclusions

Determination of JAK2-V617F mutation status prior to treatment initiation is not warranted because: 1) the sponsor's exploratory assessment was performed in a small number of patients 2) a response to ruxolitinib over best available therapy was observed irrespective of JAK2-V617F mutation 3) the mutation status did not appear to affect the safety profile. The sponsor's analysis suggests a non-significant higher response rate in patients with JAK2 mutation. However, no meaningful alternative treatment option for the indicated patient population is currently available.

5 Recommendations

The data support approval of ruxolitinib for myelofibrosis in patients irrespective of JAK2-V617F mutation status. See Clinical Pharmacology review for more details.

5.1 Post-marketing studies

No recommendations from the Genomics Group for PMR/PMC.

5.2 Label Recommendations

None.

Christian Grimstein, Ph.D. Reviewer, Genomics Group, OCP	Issam Zineh, PharmD., M.P.H. Associate Director, Genomics Group, OCP

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 202192	Submission Date(s): 6/3/11 (SD 1), 7/12/11 (SD 4), 8/1/11 (SD 5), 9/27/11 (SD 15), 9/28/11 (SD 16)
Brand Name	JAKAFI
Generic Name	Ruxolitinib Phosphate
CP Reviewer	Joseph A. Grillo, Pharm.D.
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PM Team Leader	Christine Garnett, Pharm.D.
OCP Division	5
OND division	OHOP/DHP
Sponsor	Incyte Corporation
Relevant IND(s)	77456
Submission Type; Code	Original NDA (NME), Expedited review (6 months)
Formulation; Strength(s)	5 mg, 10 mg, 15 mg, 20 mg, and 25 mg tablets
Indication	Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

Table of Contents

1 EXECUTIVE SUMMARY

JAKAFI (Ruxolitinib Phosphate) is an orally administered inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs) that is proposed for the treatment of patients with myelofibrosis (MF) including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPVMF) and post-essential thrombocythemia myelofibrosis (PETMF). The proposed starting dose of JAKAFI is [redacted] (b) (4) 15 mg given orally twice daily for patients with a platelet count between 100 X 10^9/L and 200 X 10^9/L, and 20 mg twice daily for patients with a platelet count of > 200 X 10^9/L.

Two prospectively randomized trials in the treatment of patients with MF (including PMF, PPVMF, and PETMF) with anemia, splenomegaly and with symptoms that justified therapy showed a statistically significant increase in the percentage of patients who (by 24 weeks on INCB-351 and by 48 weeks on INCB-352) achieved a ≥35% SVR as measured by MRI in favor of JAKAFI compared to placebo (INCB-351) or best supportive care (INCB-352). The major side effect of thrombocytopenia appeared to be limited by the proposed dose titration and monitoring scheme.

Based on a population pharmacokinetic/pharmacodynamic model, exposure-response relationships were simulated for efficacy and safety endpoints. The simulations support the proposed initial dosing based on baseline platelet count and the titration to a maximum of 25 mg BID. These doses will likely achieve effective reductions in mean spleen volume and symptom scores with a low probability causing severe thrombocytopenia (i.e., platelet count < 50 X 109/L). However, patients on average daily doses ≤10 mg (5 mg BID) did not yield a 35% reduction in spleen volume or symptom score (based on limited data).

Ruxolitinib exhibits near-complete oral absorption achieving maximal plasma concentration (Cmax) at approximately 1-2 hours post-dose with linear pharmacokinetics over a dose range of 5 to 200 mg. Administration with food did not affect ruxolitinib overall exposure. Ruxolitinib is eliminated almost completely by oxidative metabolism with a terminal elimination half-life of approximately 3 h (approximately 5.8 hours for ruxolitinib + metabolites). The metabolism of ruxolitinib is predominantly by CYP3A4. Ex vivo PK/PD analysis (based on cytokine-induced pSTAT3 inhibition) suggests that the sum total of all active metabolites contributes to 18 % of the overall PD activity of ruxolitinib in healthy subjects.

The pharmacokinetics of ruxolitinib in patients with MF was similar to that in healthy adult subjects. In a population pharmacokinetic analysis, body weight and sex were found to be significant predictors of volume of distribution and oral clearance, respectively, but these differences are not expected to be clinically relevant.

Based on the clinical pharmacology studies and the exposure safety relationship, adjustment of the initial ruxolitinib dose should be considered for patients a platelet count between 100 $\times$ 10^9/L and 150 $\times$ 10^9/L, with hepatic impairment, moderate or severe renal impairment , or with ESRD on dialysis. Patients with platelet counts less than 100 $\times$ 10^9/L who are taking strong systemic CYP3A4 inhibitors should also have the initial dose of ruxolitinib adjusted.

In vitro, ruxolitinib and its M18 metabolite are unlikely inhibitors the major CYP and transporter pathways. Ruxolitinib is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 at clinically relevant concentrations. In addition ruxolitinib is an unlikely P-gp substrate.

1.1 Recommendation

From a clinical pharmacology perspective, this application is ACCEPTABLE provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Post Marketing Requirements

- None

1.3 Post Marketing Commitments

- None

1.4 Comments to the Applicant

- None

1.5 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

JAKAFI (Ruxolitinib Phosphate) is an orally administered inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs) that is proposed for the treatment of patients with myelofibrosis (MF) including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. The prop starting dos AKAFI is (b) (4) (b) (4) 15 mg given orally twice daily for patients with a platelet count between 100 X 10 /L and 200 X 10^9/L, and 20 mg twice daily for patients with a platelet count of > 200 X 10^9/L.

Two prospectively randomized trials were carried out in the treatment of patients with high risk or intermediate-2 risk MF (including PMF, PPVMF, and PETMF) who had anemia, splenomegaly and symptoms that justified therapy. The first trial (INCB-351, pivotal trial) randomized patients who were intolerant/refractory/ineligible for available therapy to receive continuous ruxolitinib therapy or to receive placebo. The second supporting trial (INCB-352) randomized patients who had received prior therapy or no prior therapy, but who were not candidates for allogeneic stem cell transplantation, to continuous ruxolitinib or best available therapy (BAT). The primary endpoint in both trials was a statistically significant difference between the two arms in the percentage of patients who (by 24 weeks on INCB-351 and by 48 weeks on INCB-352) achieved a ≥35% SVR as measured by MRI. In INCB-351, 41.9% of patients receiving ruxolitinib compared to 0.7% ($p< 0.0001$) of patients receiving placebo achieved the primary endpoint. Similarly INCB-352 reported 29% of patients receiving ruxolitinib compared to 0% of patients receiving best available therapy ($p< 0.0001$) achieved the primary endpoint. The major side effect (thrombocytopenia) appeared to be limited by the proposed dose titration and monitoring scheme which did not appear to prevent the benefit otherwise generated by ruxolitinib.

Based on a population pharmacokinetic/pharmacodynamic model, exposure-response relationships were simulated for efficacy and safety endpoints. The simulations support the proposed initial dosing based on baseline platelet count and the titration to a maximum of 25 mg BID. These doses will likely achieve effective reductions in mean spleen volume and symptom scores with a low probability causing severe thrombocytopenia (i.e., platelet count < 50 X 10^9/L). However, patients on average daily doses ≤10 mg (5 mg BID) did not yield a clinically meaningful benefit of 35% reduction in spleen volume or symptom score (based on limited data). (b) (4) Importantly, if a patient were to be maintained at a dose of 5mg BID, a high risk of thrombocytopenia (platelet < 50 g/L) would be present with minimal, if any, benefit in spleen volume reduction and total symptom score.

Pharmacokinetics of ruxolitinib following oral dosing was evaluated in six healthy volunteer trials, including single-dose, multiple-dose, a ^{14}C-labeled mass balance trial, interaction trials with CYP inhibitors and inducer, hepatic dysfunction, renal dysfunction and a thorough QTc trial. Additionally, the pharmacokinetics of ruxolitinib were characterized in myelofibrosis patients in a phase 2 and two phase 3 trials using primarily a population based approach which also characterized the relationship between exposure and efficacy or safety parameters. Ruxolitinib capsule and tablet formulations for oral dosing were developed in two strengths, 5 mg and 25 mg, to support clinical development.

Based on a mass balance study in humans, oral absorption of ruxolitinib was estimated to be at least 95%. Following a single oral dose, maximal plasma concentrations (Cmax) are achieved approximately 1-2 hours post-dose. Linearity in pharmacokinetics was apparent over a dose range of 5 to 200 mg administered as single doses. The effect of food on the ruxolitinib exposure (4% increase in AUC, 90% CI 96.8 – 113%) is not considered substantial. The apparent volume

of distribution of ruxolitinib at steady-state is 53-65 L in myelofibrosis patients. Binding to plasma proteins in vitro is approximately 97%, mostly to albumin. Ruxolitinib is an unlikely substrate for the P-gp transporter based on an in vitro study. Ruxolitinib is eliminated almost completely by oxidative metabolism with a terminal elimination half-life of approximately 3 h. The mean half-life of ruxolitinib + metabolites is approximately 5.8 hours. Excretion is in urine and feces with less than 1% of ruxolitinib-related material excreted as unchanged parent drug.

The pharmacodynamics (PD) of ruxolitinib were primarily characterized in clinical pharmacology studies by an ex vivo whole blood assay that involves quantitation of pSTAT3 following IL-6 stimulation. Following single or multiple oral dose administration in healthy subjects, ruxolitinib an approximate dose-dependent inhibition of cytokine-induced pSTAT3 was observed. Maximal inhibition occurred 1-2 h after administration and returned to near baseline by 8-10 hours in both healthy subjects and myelofibrosis patients.

The oxidative metabolites of ruxolitinib retain pharmacological activity with 1/2 to 1/5th of the activity of the parent compound. Ex vivo PK/PD analysis (based on cytokine-induced pSTAT3 inhibition) suggests that the sum total of all active metabolites contributes to 18% of the overall PD activity of ruxolitinib in healthy subjects.

The PK of ruxolitinib in patients with MF was similar to that in healthy adult subjects. In a population PK analysis in MF patients, ruxolitinib plasma concentrations were adequately described by a two compartment model with first order absorption. Body weight and gender were found to be significant predictors of volume of distribution of the central compartment and oral clearance, respectively, with male subjects having a slightly higher apparent clearance compared with female subjects, although this was within the variability of CL/F for the population.

Population models were built to understand the exposure-response relationship for key efficacy and safety parameters and to identify the influence of covariates towards interindividual variability in response. Two of the covariates evaluated were found to be associated with spleen volume reduction, female gender and positivity for JAK2V617F mutation. The exposure-response modeling for symptoms based on the modified MFSAF v2.0 total symptom score did not identify any covariates for response to ruxolitinib. The exposure-response analysis involving safety parameters (platelet counts, hemoglobin and ANC) also did not identify covariates for variability in response. As the proposed dosing for ruxolitinib is to titrate to a positive benefit/risk ratio, dose adjustment based on significant covariates, such as gender and JAK2V617F mutation, is not necessary.

In vitro metabolism studies suggest that CYP3A4 is the predominant human CYP isozyme responsible for the metabolism of ruxolitinib. Systemic co-administration of oral ketoconazole, a potent CYP3A4 inhibitor, resulted in a 91% increase of plasma AUC, whereas erythromycin, a moderate CYP3A4 inhibitor, caused a 27% increase in exposure. The PD data (inhibition of pSTAT3) in the presence of CYP3A4 inhibitors was generally consistent with the corresponding PK data. Based on these results, the recommended starting dose should be reduced to 10 mg twice daily for patients with a platelet count $\geq$ 100 X 10^9/L when a strong CYP3A4 inhibitor is used as concomitant medication

In the presence of rifampin, a potent inducer of CYP3A4, a 71% decrease in plasma AUC of ruxolitinib was observed. In contrast, the PD data (inhibition of cytokine-induced pSTAT3) showed only a 10% decrease with co-administration of rifampin. The approximate 100% increased in the combined relative abundance of all ruxolitinib active metabolites as a percent of parent drug plasma AUC following induction by rifampin may explain this discrepancy. Therefore concurrent use of a CYP3A4 inducer should not require a dose adjustment.

In vitro, ruxolitinib and its M18 metabolite are unlikely inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Ruxolitinib is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 at clinically relevant concentrations. In addition ruxolitinib is an unlikely P-gp substrate. In vitro, Ruxolitinib and its M18 metabolite are also unlikely inhibitors of the P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1 or OAT3 transport systems at clinically relevant concentrations.

In patients with various degrees of renal impairment including ESRD requiring dialysis receiving a single ruxolitinib dose of 25 mg, the pharmacokinetics of ruxolitinib was similar to that in matching healthy subjects. However, the AUC and half-life of ruxolitinib metabolites increased with increasing severity of renal impairment. The increase in the AUC of ruxolitinib + metabolites was highest in ESRD patients receiving ruxolitinib after hemodialysis (approximately 70%). Based on these results and the exposure safety relationship, patients with moderate (Clcr 30-59 mL/min) or severe renal impairment (Clcr 15-29 mL/min) and a platelet count between 100×10^9/L and 150×10^9/L should have the starting dose of JAKAFI reduced to 10 mg twice daily. Patients with ESRD on dialysis should initiate dosing with a single dose of 15 mg or 20 mg, based on platelet counts, with subsequent doses only following each dialysis session.

In a hepatic impairment study, the pharmacokinetics of ruxolitinib were assessed following a single ruxolitinib dose of 25 mg. The mean AUC for ruxolitinib was increased by 87%, 28% and 65%, respectively, in patients with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment compared to patients with normal hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). Based on these results and the exposure safety relationship, patients with any degree of hepatic impairment for patients and a platelet count between 100×10^9/L and 150×10^9/L should have the starting dose of JAKAFI reduced to 10 mg twice daily.

The effect of single dose ruxolitinib 25 mg and 200 mg on QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 47 healthy subjects. The upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 200 mg is adequate to represent the high exposure clinical scenario.

Ruxolitinib phosphate has been designated a Class 1 compound in the Biopharmaceutical Classification System based on the aqueous solubility (over a pH range of 1-8), stability in gastrointestinal fluids, in vitro permeability and extent of in vivo oral absorption in healthy subjects, and in vitro dissolution profiles of product. Biowaivers are requested for 1) bioequivalence studies for tablets of the 10 mg, 15 mg, 20 mg and 25 mg strengths; and 2) vivo bioequivalence data comparing a disperse solution/suspension and the intact tablets. These are deemed acceptable in the 10/20/11 ONDQA review of this NDA. A waiver for pediatric studies is also requested based on the Orphan status of JAKAFI.

Signatures

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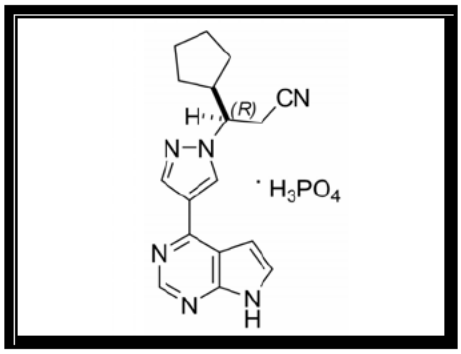
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?



Established name:	ruxolitinib phosphate
Molecular Weight:	404.36 g/mole, (306.37 g/mole for free base)
Molecular Formula:	$C_{17}H_{21}N_6O_4P$; ($C_{17}H_{18}N_6$ for free base)
Chemical Name:	(*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate
Description:	Ruxolitinib phosphate is a non-hygroscopic, white to off-white to light pink powder.
Polymorphism:	(b) (4)
Solubility:	The drug substance in aqueous medium is pH dependent. It is most soluble in pH 1.0 buffer (0.54 mg/mL), and least soluble in pH 7.4 medium (0.15 mg/mL). It is also very soluble in MeOH, EtOH, 2-propanol and DMSO (at 25°C and 50°C) and freely soluble in acetonitrile (at 25°C and 50°C) and dichloromethane (at 25°C).
pKa-Values:	4.3 and11.8.
Partition Coefficient:	Octanol/pH 1.0 Buffer - 0.057 ± 0.004; Octanol/pH 4.3 Buffer - 2.562 ± 0.065; and Octanol/pH 7.4 Buffer - 2.814 ± 0.028

JAKAFI is supplied as tablets for oral administration containing 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib together with microcrystalline cellulose, lactose, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxyl propyl cellulose.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Ruxolitinib is an inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2. These kinases play a role in the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) known to be associated with dysregulated JAK1 and JAK2 signaling. Ruxolitinib is not considered a curative agent for MF but may affect disease related symptoms including splenomegaly. Since JAK1 and JAK2 also mediate signaling of multiple cytokines and growth factors including IL-2, IL-3, IL-5, IL-6, EPO, TPO, and GM-CSF, ruxolitinib related hematologic

abnormalities (i.e., thrombocytopenia, anemia, and neutropenia) are likely the result of inhibition of these JAK dependent hematopoietic pathways.

The proposed indication for JAKAFI is for treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The applicant proposes the following starting doses (Table 1):

Table 1: Proposed starting doses

Platelet Count	Starting dose
> 200 × 10^9/L	20 mg orally twice daily
100 × 10^9/L to 200 × 10^9/L	15 mg orally twice daily
[redacted] (b) (4)	

Source: Applicant's proposed labeling

The applicant proposes that complete blood counts be monitored every 2-4 weeks until doses are stabilized, and then as clinically indicated. Treatment should be interrupted for platelet counts less than 50 X 10^9/L or absolute neutrophil counts less than 0.5 X 10^9/L. After recovery of platelet and neutrophil counts above these levels, dosing may be restarted at 5 mg twice daily and gradually increased based on careful monitoring of counts. Dose reductions should be considered if the platelet counts decrease below 100 X 10^9/L with the goal of avoiding dose interruptions for thrombocytopenia.

If efficacy is considered insufficient and platelet and neutrophil counts are adequate, doses may be increased by a maximum of 5 mg twice daily. Starting doses should not be increased within the first four weeks of therapy and no more frequently than at 2 week intervals. The maximum dose is 25 mg twice daily.

The applicant is also proposing a [redacted] (b) (4) dose reduction for any hepatic impairment, severe renal impairment and with concurrent administration with a strong CYP3A4 inhibitor.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Ruxolitinib was administered to 198 healthy subjects as single, repeat single, or multiple doses of up to 10 days duration; 32 subjects with various degrees of renal impairment; 24 subjects with various degrees of hepatic impairment; 59 subjects with rheumatoid arthritis; over 500 patients with MF; and over 100 subjects with prostate cancer, multiple myeloma, polycythemia vera or essential thrombocythemia (Table 2).

Table 2: Clinical Studies with Ruxolitinib

Phase 1	Single, multiple dose and food effect: 18424-131, -132, -139 (SR formulation) Mass balance: -134 Drug interactions: -133 (ketoconazole, erythromycin); -135 (rifampin); -136 (methotrexate) Hepatic impairment: -137; Renal impairment: -142 Thorough QT: -138
Phase 2	Rheumatoid arthritis - 231 Myelofibrosis: -251 Prostate: -254 Multiple myeloma: -255 Polycythemia vera or essential thrombocythemia: -256
Phase 3	Myelofibrosis: 18424-351 (COMFORT-I), CINC424A2352 (COMFORT-II)

Source: Applicant's proposed labeling

Study INCB 18424-351 was a randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ruxolitinib to placebo in subjects with PMF, PPV-MF, or PET-MF. Subjects were randomized to receive ruxolitinib or matching placebo tablets. The concentrations up to Week 24 from this study were pooled for population pharmacokinetic analysis. Pharmacodynamic endpoints included pSTAT3 and plasma pharmacodynamic biomarkers such as TNFα, IL-6, and CRP. Study INCB 18424-352 was an open label, randomized study comparing the efficacy and safety of ruxolitinib tablets versus best-available therapy, as selected by the investigator. The predictive performance of final population PK model was evaluated by the plasma concentrations from this study used as external validation dataset. Pharmacodynamic endpoints examined plasma biomarkers, including 20 cytokines and other plasma protein markers.

The primary endpoint in both Phase 3 studies was reduction in spleen volume by ≥ 35% from Baseline as measured by MRI or CT. In Study INCB 18424-351, the endpoint was assessed after 24 weeks of treatment and in Study INCB 18424-352, it was assessed after 48 weeks of treatment. Study INCB 18424- 351 also included type I error controlled secondary endpoints that assessed changes in symptoms as measured using the modified Myelofibrosis Symptom Assessment Form version 2.0 diary.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary endpoint in both Phase 3 studies was reduction in spleen volume by ≥ 35% from Baseline as measured by MRI or CT. In Study INCB 18424-351, the endpoint was assessed after 24 weeks of treatment and in Study INCB 18424-352, it was assessed after 48 weeks of treatment. Study INCB 18424- 351 also included type I error controlled secondary endpoints that assessed changes in symptoms as measured using the modified Myelofibrosis Symptom Assessment Form version 2.0 diary. These endpoints were considered clinically meaningful and were part of a SPA agreement in July 2009 for study INCB 18424-351.

The STAT3 transcription factor is directly phosphorylated by JAKs in response to cytokine stimulation and was used as a pharmacodynamic (PD) marker for JAK inhibition in the clinical and clinical pharmacology related studies. An ELISA assay was established that measures cytokine-induced STAT3 phosphorylation (pSTAT3) in human whole blood with acceptable sensitivity, intra-assay, and inter-assay reproducibility and variability (see Section 2.6.10).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes (see Section 2.6).

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

There is evidence of exposure-response for both spleen volume reduction and total symptom score for ruxolitinib in the pivotal trials. Evaluation of % spleen size reduction as a function of average daily total dose (Figure 1) yields a clear relationship with the maximal effect on the primary endpoint being at daily doses >40 mg (>20 mg BID). Patients with average daily doses of >20 mg (>10 mg BID) yielded a clinically relevant benefit of spleen volume reduction. Of note, patients administered average daily doses ≤10 mg (≤5 mg BID) did not yield a clinically meaningful benefit of 35% reduction in spleen volume.

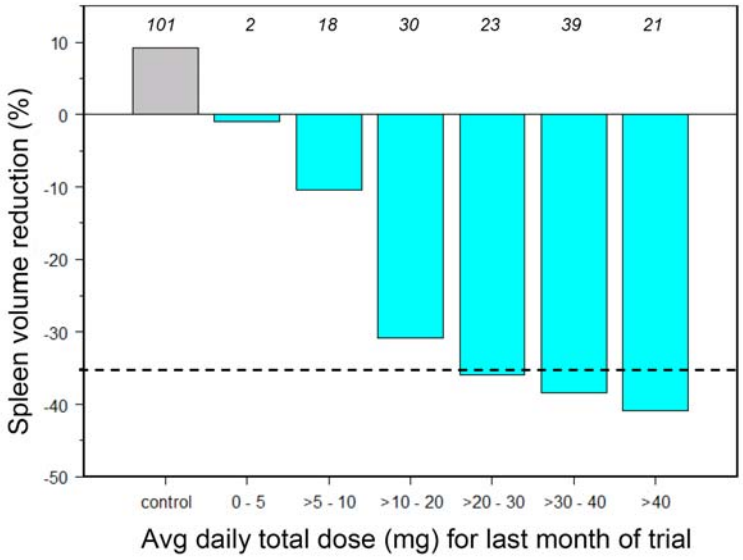


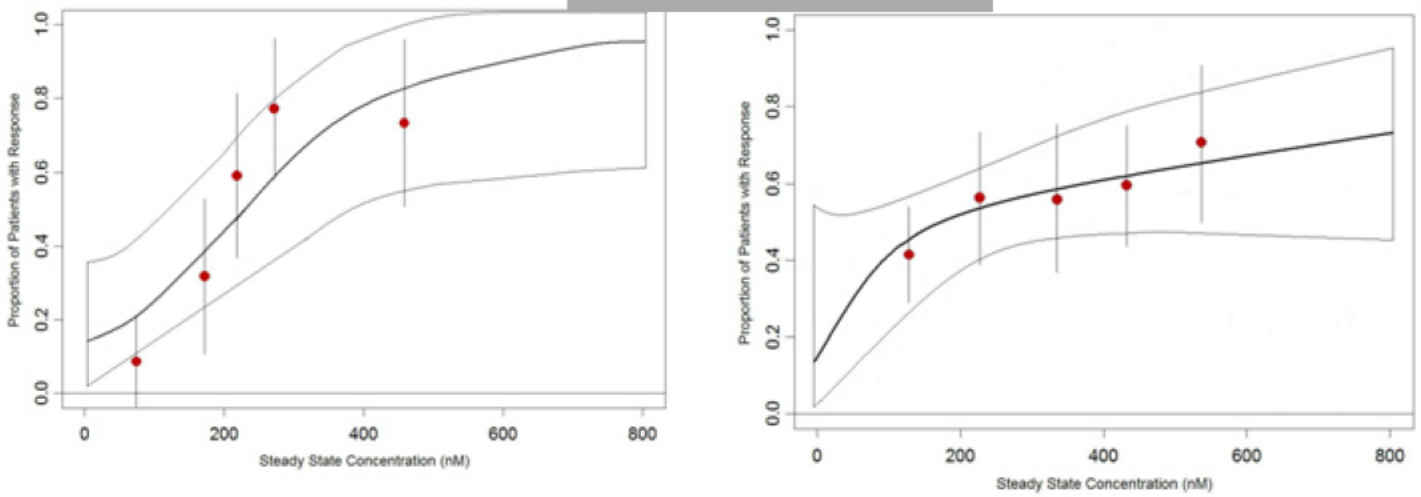
Figure 1: FDA analysis of spleen volume reduction as a function of average daily total dose for trial 351. Grey bar represents the placebo arm and the lighter grey bars represent the ruxolitinib average daily doses ranging from 0-5 mg to >40 mg. The dashed line represents the clinically relevant effect of 35% reduction. The number above the bars represents the number of subjects in each dosing category.

With regard to exposure-response for spleen volume reduction and total symptom score, patients with pharmacokinetic samples from trial 351 (N=309) were divided into quantiles based on their model predicted steady state concentrations and the % of patients achieving a ≥35% spleen volume reduction and ≥50% total symptom score reduction were determined for each quantile (Figure 2).

Spleen volume reductions of ≥35% are observed in the patients with higher drug exposure in the upper quantiles (74%) compared to in the lower quantiles (9%). However, the difference in spleen volume reduction may not only be due to ruxolitinib concentrations but is also likely due to other factors that are not balanced between the quantiles. For example, it was shown from the PK/PD model for spleen volume reduction that female, JAK 2V617F positive patients have more response compared to male JAK 2V617F negative patients (see Section 4.3.2 Figure 7).

To account for these confounding factors, the proportion of patients who achieved a ≥35% reduction in spleen volume from baseline to last observation was analyzed using a multivariate logistic regression model, including baseline factors (see Section 4.3.2 Table 9). The step-wise logistic regression analysis identified average ruxolitinib steady state concentration, sex and mutation status as significant predictors of ≥35% SVR in trial 351. As the titration of ruxolitinib is primarily based on SVR and safety (i.e., platelet count), dose adjustment is not proposed. For total symptom score, greater proportion of relevant reduction in symptom scores were observed in the upper quantiles (64%) compared to the lower quantiles (40%). No covariates were observed in the response rates of total symptom score.

As early as 4 weeks subjects in the ruxolitinib group achieved a >50% reduction in palpable spleen length compared with 3 (2.0%) subjects in the placebo group. The majority of subjects who were responders at the end of the trial (week 24) achieved spleen volume reduction at approximately 12 weeks. For duration of response, the data is limited as the assessment only was conducted until 24 weeks.

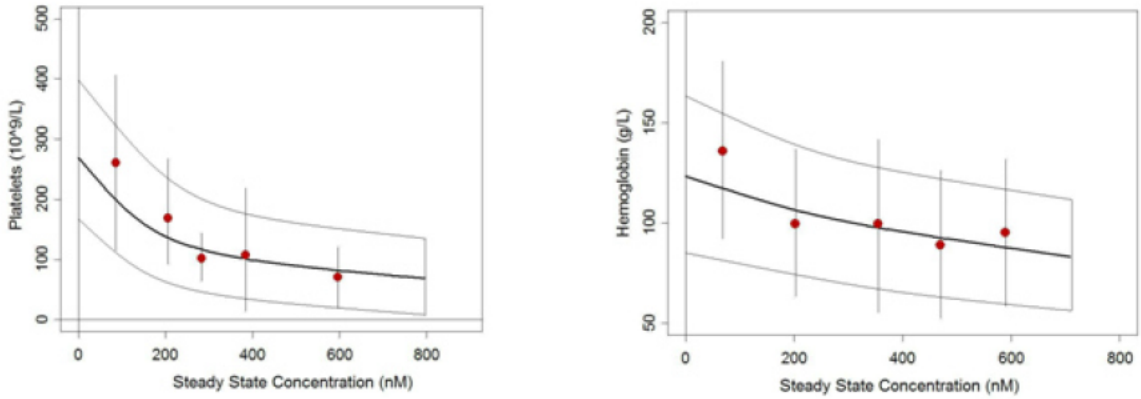


A B

Figure 2: Proportion of patients achieving ≥35% spleen volume reduction (A) and ≥50% reduction in total symptom score (B) versus average steady state concentrations of ruxolitinib in trial 351. Solid round symbols represent the observed efficacy measure in each $C_{ss\ average}$ quantile. The vertical black bars represent the 95% confidence interval (CI_{95}). The logistic regression is denoted by the solid black line along with the CI_{95} for the regression.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

There is evidence of exposure-response for safety measures including platelet count and hemoglobin (hgb). As the case for efficacy, the evaluation of exposure-response for platelet count and hemoglobin incorporated patients with pharmacokinetic samples from trial 351 (N=309) observations were divided into quantiles based on their model predicted steady state concentrations and the platelet count and hemoglobin were determined for each quantile (Figure 3).



A B

Figure 3: FDA Analysis of platelet count (A) and hemoglobin (B) versus average steady state concentrations of ruxolitinib in trial 351. Solid round symbols represent the observed efficacy measure in each $C_{ss\ average}$ quantile. The vertical black bars represent the CI_{95}. The model predicted relationship is denoted by the solid black line (with CI_{95}).

The exposure-response relationship depicts a decrease in platelet count with increasing ruxolitinib exposure. Approximately a 2.7 fold-difference in platelet count is observed between the lowest quantile ($C_{ss\ average}$ ~78 nM) and the highest quantile ($C_{ss\ average}$ ~588 nM). The exposure-response relationship for changes in platelet counts was also evaluated and no covariates, including baseline platelet count could predict response. This indicates that subjects with lower platelet counts are not likely to be inherently more sensitive to ruxolitinib, but rather, that they may be more prone to thrombocytopenia as their platelet counts are decreasing from a lower baseline value.

For hemoglobin measures, the exposure-response relationship depicts a gradual decrease in hemoglobin with increasing ruxolitinib exposure. Approximately a 20 g/L difference in hemoglobin is observed between the lowest quantile ($C_{ss\ average}$ ~51 nM) and all other quantiles. Further assessment of the exposure-response relationship for hemoglobin yielded no other covariates for predicting response.

2.2.4.3 Does this drug prolong the QT or QTc interval? (You must answer this question, unless this is addressed in the question above.)

The applicant submitted a randomized, partially blinded, four-period crossover study thorough QT (TQT) study where 50 healthy subjects received INCB018424 25-mg single dose, INCB018424 200-mg single dose, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 3. The FDA Interdisciplinary Review Team (IRT) for QT Studies reviewed the results of the TQT study and concludes that no significant QTc prolongation effect of INCB018424 (25-mg single dose and 200-mg single dose) was detected (See the 09/06/2011 IRT consult). The reviewer agrees with the IRT analysis and its proposed labeling (see Section 3).

Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for INCB018424 (25 mg and 200 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
INCB018424 25 mg	24	2.2	(-0.5, 4.9)
INCB018424 200 mg	12	2.2	(0.0, 4.4)
Moxifloxacin 400 mg*	1.5	10.4	(7.4, 13.5)

Source: 09/06/2011 IRT consult

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues? (In some cases, it may be possible to combine this with 2.2.4.2 and 2.2.4.3.)

The exposure-response relationship for efficacy and safety does support the recommended initial dose based on platelet count, as proposed in the label. The PK/PD model for platelet count over time was utilized to perform simulations for the continual dosing of 15 mg BID for those patients with an initial platelet count at 100 $x10^9$/L and 20 mg BID with an initial platelet count of 200$x10^9$/L. On average, platelet counts were above the threshold of 50$x10^9$/L for both dosing groups, further supporting the applicant's dosing justification for initial platelet count.

The exposure-response relationship for efficacy and safety does support the titration of ruxolitinib to 25 mg BID, as proposed in the label. Based on the dose-response analysis for the reduction in spleen volume (Figure 1) the maximal effect was observed at daily doses >40 mg (>20 mg BID). Moreover, 81% of the patients who were titrated to an average daily dose of >40 mg had reached a clinically relevant beneficial effect of >35% reduction in spleen volume and >50% reduction in total symptom score (Table 4).

Table 4: Percent of Responders Who Reached Both Efficacy Endpoints in Each Average Daily Dose Group

Average daily dose (mg)	>40	>30-40	>20-30	>10-20	>5-10	0-5
% reaching both TSS and SPV	81%	39%	8%	0%	0%	0%

On the other hand, patients on average daily doses ≤10 mg (≤5 mg BID) did not yield a clinically meaningful benefit of 35% reduction in spleen volume. (b) (4) Importantly, if a patient were to be maintained at a dose of 5mg BID, a high risk of thrombocytopenia (platelet < 50 g/L) would be present with minimal, if any, benefit in spleen volume reduction and total symptom score. Using the exposure-response relationship for platelet count, simulations for a typical patient with a baseline platelet count of 50 g/L, maintained at a 5 mg BID dose, was performed (Figure 4). Results show that an individual, with low platelet count, maintained on a dose of 5 mg BID would be at risk of thrombocytopenia.

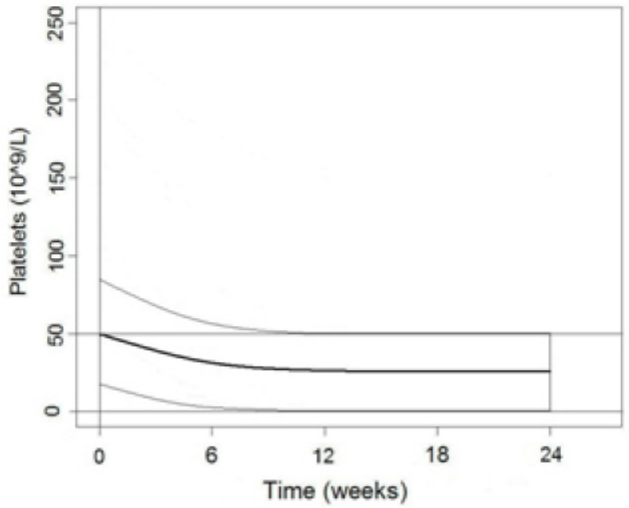


Figure 4: Simulated average platelet count over time for maintaining a starting dose of 5 mg BID for a baseline platelet count of 50 x 109/L. Dark line represents model prediction along with 95% prediction interval. The minimum threshold for platelet count is denoted by the solid black line at 50 g/L.

2.2.5 What are the PK characteristics of the drug and its major metabolites?

2.2.5.1 What are the single dose and multiple dose PK parameters?

Ruxolitinib safety, pharmacokinetics and pharmacodynamics following single dose administration was evaluated the applicants trial INCB 18424-131. A capsule formulation of ruxolitinib was administered orally in the fasted state to healthy adult subjects at single doses of 5 mg to 200 mg. The pharmacokinetic parameters are summarized in Table 5 and are deemed acceptable by the reviewer.

Table 5: Summary of Ruxolitinib Pharmacokinetic Parameters Following Single Doses Using the Capsule Formulation

Dose	n	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (nM*h)	CL/F (L/h)	Vz/F (L)
5 mg	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 ± 40.1 74.9
10 mg	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 ± 34.5 90.7
25 mg	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
50 mg	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
100 mg	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
200 mg	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

Values are mean ± SD and geometric mean
Source: Study report for trial INCB 18424-131

Ruxolitinib and metabolite safety, pharmacokinetics and pharmacodynamics following single dose administration was evaluated the applicant's TQT trial INCB 18424-138. This was a randomized, 4-way cross over study with the primary objective of evaluating the effects of placebo, 25 mg INCB018424 tablet, 200 mg INCB018424 (as 8 25 mg tablets), and 400 mg moxifloxacin tablet on the heart-rate corrected QT interval in healthy subjects (see Section 2.2.4.3). There was a 7 day washout between trial periods. The study was double-blind with regard to INCB018424 and placebo and open-label for moxifloxacin. Pharmacokinetic parameters following 25 or 200 mg of ruxolitinib are summarized in Table 5 and are deemed acceptable by the reviewer. Pharmacokinetic parameters following comparable doses were similar to that reported in trial INCB 18424-131.

Table 6: Summary of Ruxolitinib Pharmacokinetic Parameters Following Single Doses Using the Tablet Formulation

Dose (mg)	n	Cmax (nM)	Tmax (h)	t1/2 (h)	AUC0-t (nM·h)	$AUC_{0-\infty}$ (nM·h)	CL/F (L/h)	Vz/F (L)
25	47	1510 ± 400 1460	0.96 ± 0.5 0.86	2.6 ± 0.9 2.5	5290 ± 1640 5060	5320 ± 1680 5080	16.8 ± 5.01 16.1	59.1 ± 11.4 58.0
200	48	11500 ± 3120 11100	1.1 ± 0.4 1.1	2.7 ± 0.55 2.6	42800 ± 14300 40600	43000 ± 14500 40700	16.9 ± 5.45 16.0	62.6 ± 15.0 60.9

Values are mean ± SD and geometric mean
Source: Study report for trial INCB 18424-138

In addition, the pharmacokinetic parameters of eight mono-oxygenated metabolites of ruxolitinib deemed active (see Section 2.2.6) following a single 25 mg dose was determined in a separate analysis (report INCYTE-DMB-10.55.1) using plasma concentration data from trial INCB 18424-138 described above (see Section 2.2.4.3). Pharmacokinetic parameters for these eight ruxolitinib metabolites are summarized in Table 7 and are deemed acceptable by the reviewer.

Table 7: PK parameters of ruxolitinib metabolites in subjects with high, medium, and low AUC values for INCB018424 following administration of 25 mg ruxolitinib in Study INCB 18424-138

Analyte	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (nM*h)	$AUC_{0-\infty}$ (nM*h)	%parent $AUC_{0-\infty}$
INCB025255 (M9)	22.1 (42.5%)	0.50 (0.50-1.5)	3.1 (35%)	80.4 (28.2%)	87.9 (26.1%)	1.60%
INCB025256 (M11)	84.1 (38.1%)	1.0 (0.50-1.5)	3.6 (31%)	448 (26.8%)	461 (26.1%)	8.60%
INCB025257 (M7)	49.1 (31.6%)	1.8 (1.0-4.0)	3.5 (29%)	286 (26.4%)	298 (25.4%)	5.60%
INCB025258 (M8)	66.0 (35.0%)	1.8 (0.50-3.0)	4.0 (23%)	404 (28.1%)	417 (27.5%)	7.80%
INCB025262 (M27)	81.5 (37.5%)	2.8 (1.0-4.0)	4.5 (20%)	585 (30.6%)	606 (30.3%)	11%
INCB025264 (M16)	26.7 (34.8%)	0.50 (0.50-1.5)	3.0 (22%)	116 (24.7%)	124 (23.0%)	2.30%
INCB027598 (M18)	143 (31.8%)	1.8 (0.50-4.0)	5.8 (33%)	1260 (40.1%)	1364 (44.7%)	25%
INCB041092 (M14)	10.2 (33.4%)	3.0 (0.50-6.0)	7.5 (44%)	106 (40.1%)	129 (46.9%)	2.40%
Total						**65%**

Pharmacokinetic parameter values are geometric mean (CV%) except that median (range) is reported for Tmax.
Source: Report INCYTE-DMB-10.55.1

When metabolite data were available for a particular study the exposure of all drug related substances (i.e., ruxolitinib + observed metabolites), accounting for the relative activity (see Section 2.2.6) of each metabolite, was calculated by the reviewer using the following formula:

$$AUC_{Combined} = AUC_{Parent} + \sum\left(AUC_{metabolite} \times \frac{IC_{50}[parent]}{IC_{50}[metabolite]} \right)$$

Ruxolitinib safety, pharmacokinetics and pharmacodynamics following multiple dose administration was evaluated the applicant's trial INCB 18424-132. Ruxolitinib was administered as once-daily or twice-daily dosing regimens, using the capsule formulation that was used in Part 1 of study INCB 18424-131, for 10 days in healthy subjects. The multiple dose PK parameters from the 15 mg q12h, 25 mg q12h, 50 mg q24h, 50 mg q12h and 100 mg q24h dose levels following the last dose of ruxolitinib on Day 10 are summarized in Table 8 and are deemed acceptable by the reviewer. Pharmacokinetic parameters following comparable first doses were similar to that reported in the single dose trials INCB 18424-131 and -138.

Table 8: Summary of Ruxolitinib Steady-State Pharmacokinetic Parameters from Study INCB 18424-132

Regimen	n	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)	C_{min} (nM)	$AUC_{0-\tau}$ (nM*h)	Cl/F (L/h)	Vz/F (L)
15 mg q12h	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 q12h	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 q12h	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 q24h	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 q24h	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

Values are mean ± SD and geometric mean; Source: Study report for trial INCB 18424-132

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

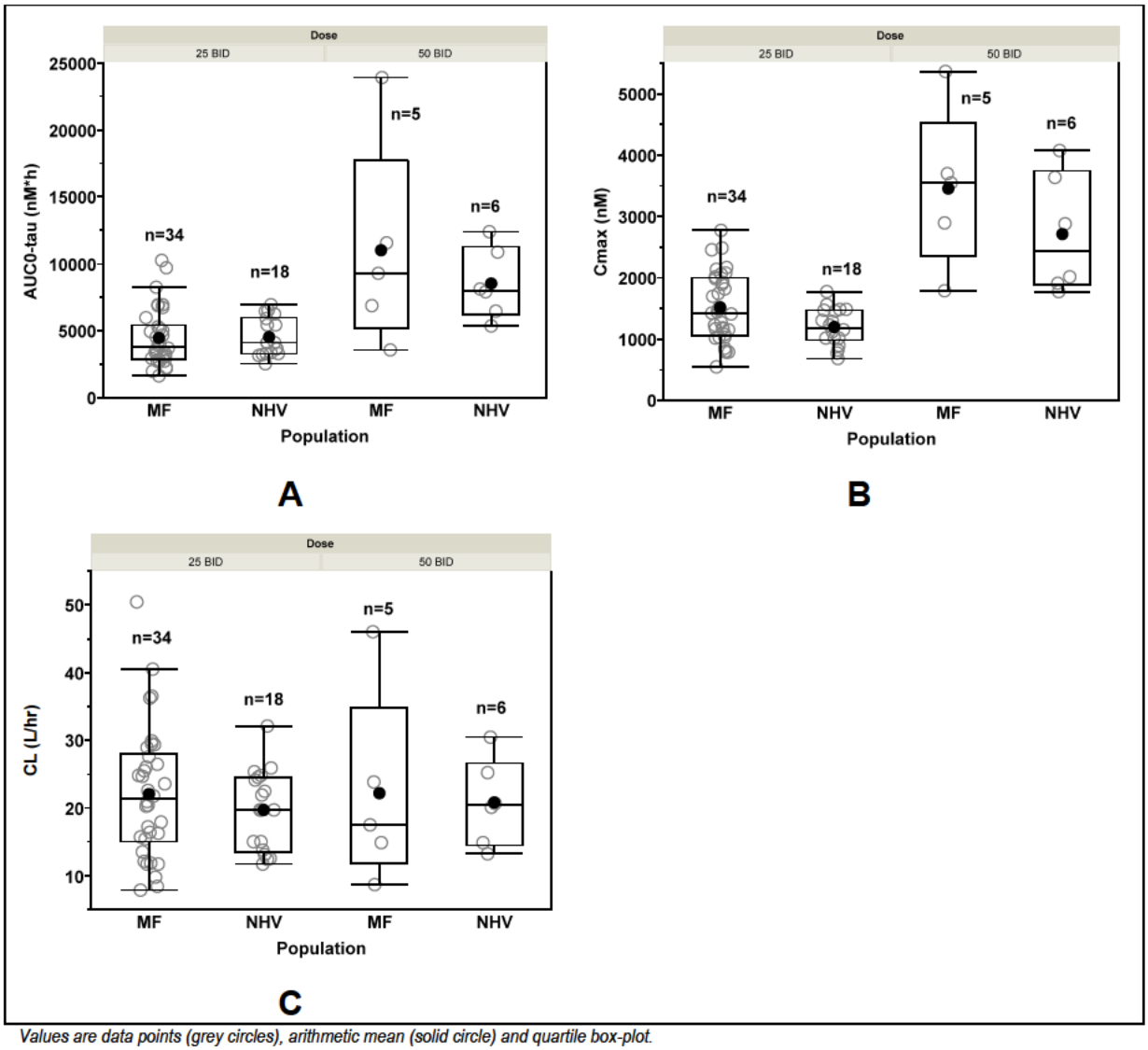
The safety, efficacy, pharmacokinetics and pharmacodynamics of ruxolitinib was evaluated a multicenter, open-label, non-randomized, dose escalation study to subjects with Primary Myelofibrosis (PMF), Post Polycythemia Vera Myelofibrosis (PPV-MF), or Essential Thrombocythemia Myelofibrosis (PET-MF). Part 1 evaluated two dose levels of 25 mg bid and 50 mg bid, Part 2 studied five dose regimens of 10 mg bid, 25 mg bid, 25 mg qd, 50 mg qd and 100 mg qd and Part 3 assessed six dose regimens of 10 mg bid, 15 mg bid, 25 mg bid, 50 mg qd, 100 mg qd and 200 mg qd. 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 pharmacokinetic parameters at steady state are summarized in Table 9, respectively and are deemed acceptable by the reviewer.

Table 9: Summary of ruxolitinib Steady-State Pharmacokinetic Parameters in Myelofibrosis Patients

Regimen	n	C_{max} (nM)	t_{max} (h)	C_{min} (nM)	$t_{1/2}$ (h)	$AUC_{0-\tau}$ (nM*h)	Cl/F (L/h)	Vz/F (L)
Part 1								
25 mg bid	27	1481 ± 575 1374	0.83 ± 0.45 0.74	47± 54 --	1.94 ± 0.50 1.88	4363 ± 2066 3949	22.7 ± 10.1 20.7	60 ± 23 56
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	22.2 ± 14.3 19.1	56 ± 30 51
Part 2								
25 mg qd	6	1417 ± 150 1410	0.84 ± 0.38 0.78	0 ± 0 --	1.60 ± 0.36 1.57	3567 ± 777 3494	23.9 ± 5.5 23.4	53 ± 6.7 53
50 mg qd	1	3380	1.00	16	3.14	15211	10.7	49
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	19.7 ± 3.65 19.4	53 ± 7.4 53
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	25.6 ± 10.1 23.7	65 ± 27 60
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	19.9 ± 8.1 18.3	53 ± 16 50

Values are mean ± SD and geometric mean.
Source: Study report for trial INCB 18424-251

A reviewer generated analysis of the distribution of steady-state $AUC_{0-\tau}$ (A), C_{max} (B), and oral clearance (C) of ruxolitinib in myelofibrosis patients and in healthy subjects receiving either 25 mg bid or 50 mg bid is shown in Figure 5 and does not show a clear trend towards any difference between the two populations. It should be noted that there are some differences in the demographics between the two trials. The mean±SD age for healthy subjects and myelofibrosis patient groups in is 29±11.2 and 63.9±8.9 and the latter trial is ~95% Caucasian compared to ~50% in the healthy volunteer trial. The distribution of gender was similar in the two trials.



Values are data points (grey circles), arithmetic mean (solid circle) and quartile box-plot.
Source: Raw data sets for trials INCB 18424-132 and 18424-251

Figure 5: Comparison of Steady-state Ruxolitinib AUC0-τ (A), Cmax (B), and Oral Clearance (C) in Healthy Subjects (Study INCB 18424-132) and Patients with MF (Study INCB 18424-251) receiving either 25 mg bid or 50 mg bid and Provided Rich Sampling for Pharmacokinetics

The population pharmacokinetics of ruxolitinib (see Section 4.3.2) were also assessed in patients with myelofibrosis. Data from trials INCB 18424-251, INCB 18424-351 and INCB 18424-352 were used in this analysis and report an estimated oral clearance of 22.1 L/hr and 17.7 L/hr for male and female subjects, respectively. These estimates are consistent with those reported from the noncompartmental analysis in trial INCB 18424-251.

2.2.5.3 What are the characteristics of drug absorption?

Although a formal bioavailability study was not conducted, the mass balance trial (INCB 18424-134) suggests almost compete absorption (95.5 ± 4.9 % recovered) following a single dose of 25 mg of ruxolitinib solution containing approximately 100 µCi ^{14}C-ruxolitinib. This is expected from this BCS Class 1 drug (see Section 2.5.1). The maximal plasma concentration (C_{max}) is generally achieved at approximately 1-2 hours post-dose (see Section 2.2.5.1). Based on the pop-PK analysis, the estimated mean population absorption half-life is approximately 0.168 hours (~10

minutes) following an estimated typical absorption lag time of less than 5 minutes (0.0545 hours). The mean absorption first order rate constant (k_a) for ruxolitinib is 4.12 hr^{-1}.

In Caco-2 cell monolayers, ruxolitinib exhibited a high apparent permeability. Transport experiments from study INCYTE-DMB-08.147.1 using 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/sec, respectively) and suggest that concentration-independent permeability is likely and saturable transport is unlikely in the absorption process. Further, in the presence of P-glycoprotein (P-gp) inhibitors (i.e., cyclosporine A and quinidine), the bi-directional transport ratio was not significantly altered (Table 10), indicating that it is unlikely that ruxolitinib is a substrate of P-gp.

Table 10: Permeability of INCB018424 in Caco-2 Monolayers

Concentration (µM)	Inhibitor		Permeability * (x 10^{-6} cm/sec)		Ratio *
	Compound	Concentration (µM)	(A-B)	(B-A)	(B-A/A-B)
1	NA	NA	28.6	22.4	0.79
	CSA	5	32.3	21.7	0.67
	Quinindine	100	30.6	20.5	0.67
10	NA	NA	20.0	17.5	0.88
	CSA	5	23.1	17.0	0.74
	Quinindine	100	21.8	13.9	0.64
100	NA	NA	17.9	12.9	0.72
	CSA	5	18.8	13.4	0.71
	Quinindine	100	17.4	12.3	0.71
50 **	NA	NA	21.5	NA	NA

** N=3 - 6*
*** In the presence of 4% bovine serum albumin (BSA)*
NA = not applicable
Source: Study report for study INCYTE-DMB-08.147.1

These findings are deemed acceptable by the reviewer.

2.2.5.4 What are the characteristics of drug distribution?

The apparent volume of distribution at steady-state is 53-65 L in myelofibrosis patients (Table 9) and 82-90 L in healthy volunteers (Table 8) receiving twice daily dosing which the reviewer considers moderate. Body weight was found to be a significant covariate (see Sections 2.2.5.10 and 2.3.1) for central volume of distribution (Vc/F). The Vc/F appears to increase with increasing body weight, with Vc/F ranging from 36.2 L for a 45-kg person to 120.6 L for a 150-kg person. The typical population Vc/F for a subject with a median weight of 72.9 kg was estimated to be 58.6 L which is consistent with noncompartmental estimates.

In human plasma, ruxolitinib mainly binds to serum albumin. The mean fraction unbound *in vitro* in human plasma and serum as determined by equilibrium dialysis is 3.3% and 3.2%, respectively, and similar at 3 and 10 µM of ruxolitinib concentrations (study INCYTE-DMB-07.11.1). In a separate study (study INCYTE-DMB-10.05.1), the mean fraction unbound of ruxolitinib increased with decreasing concentrations of human serum albumin (2.9%, 3.8%, 5.3%, 7.9% and 14.8% at human serum albumin concentrations of 50, 40, 30, 20 and 10 mg/mL, respectively.

The mass balance trial (INCB 18424-134; INCYTE-DMB-08.150.1) reports the mean ruxolitinib C_{max} and $AUC_{0-\infty}$ values for blood cells, following a single dose of 25 mg of ruxolitinib solution containing approximately 100 µCi 14C-ruxolitinib, were 3034 nM and 18258 nM·h, respectively, with a range for the 6 subjects of 2091 to 3836 nM and 13904 to 21545 nM·h, respectively. The mean C_{max} and $AUC_{0-\infty}$ values for plasma were 1355 nM and 6631 nM·h, respectively, with a range for the 6 subjects of 910 to 2874 nM and 5598 to 10576 nM·h, respectively. The mean ratio of C_{max} and $AUC_{0-\infty}$ for blood cells compared to plasma was 2.6 (range: 1.3 to 3.5) and 2.9 (range: 2.0 to 3.3), respectively. This suggests preferential partitioning of into blood cells, but it should not be considered substantial. These findings are deemed acceptable by the reviewer.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination? (This may include table with results of mass balance study).

Renal. The mass balance trial INCB 18424-134 reports that following a single dose of 25 mg of ruxolitinib solution containing approximately 100 µCi ^{14}C-ruxolitinib the total recovery of administered radioactivity was 95.53 ± 4.93%, with 73.61 ± 10.18% and 21.92 ± 5.95% in urine and feces, respectively (Table 11). Less than 1% of the dosed ruxolitinib-derived radioactivity recovered in urine and feces was parent drug. Table 12 quantifies observed metabolites, as percent of dose, in human urine and feces. These findings are deemed acceptable by the reviewer.

Table 11: Excretion of Radioactivity in Urine and Feces in Healthy Human male Subjects After an Oral Dose of ^{14}C-ruxolitinib

Time (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 – 96a	73.5	18.8	92.3
0 – 192a	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.
Source: Study report for study INCB 18424-134

Table 12: Metabolite Quantitation as % of Dose in Urine and Fecal Samples Collected from Male Human Subjects

	Percent Total Dose					
Metabolite	**Urine**			**Feces**		
Interval	**0-8 hr**	**8-24 hr**	**24-48 hr**	**24-48 hr**	**48-72 hr**	**72-96 hr**
M43				0.60%	0.52%	0.59%
M44	1.38%	1.54%	0%			
M45				0.23%	0.25%	0%
INCB025257 (M7)	6.44%	3.11%	0%	0.97%	0.95%	0.66%
INCB025258 (M8)	8.02%	3.03%	0%	2.15%	2.11%	1.75%
INCB025256 (M11)	10.65%	4.87%	0%	0%	0.00%	0.09%
INCB025264 (M16)	2.35%	0.00%	0%	0.44%	0.00%	0%
INCB025262 (M27)	8.51%	6.13%	0.74%	1.41%	0.69%	0.24%
INCB027597 (M31)				0.44%	0.47%	0.57%
INCB027598 (M18)				0.61%	0.24%	0%
M28	0.59%	0.00%	0%			
M51	0.84%	0.64%	0%			
M37	0.64%	0.71%	0%			
Ruxolitinib	0.24%	0.14%	0.02%	0.12%	0.16%	0.08%
M49	4.96%	2.89%	0.45%	1.52%	2.01%	1.03%
Sum	**44.62%**	**23.08%**	**1.21%**	**7.88%**	**6.86%**	**4.43%**

Source: Study report for study INCB 18424-134

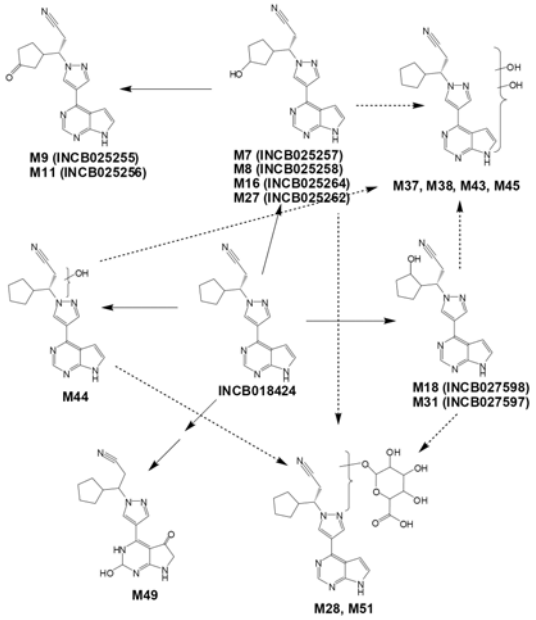
2.2.5.6 What are the characteristics of drug metabolism? (This may include data on extraction ratio; metabolic scheme; enzymes responsible for metabolism; fractional clearance of drug.)

The in vitro metabolism of ruxolitinib was investigated by the applicant using human recombinant CYP enzymes and human liver microsomes. Recombinant enzyme preparations of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 metabolized ruxolitinib with 86%, 60%, 53%, 82% and 2% of the initial concentration of ruxolitinib remaining after 30 minutes of incubation (60 minutes for CYP2C9), respectively. To determine the relative contribution of these CYP isozymes

to metabolism in humans, the applicant incubated ruxolitinib (1 μM) with human liver microsomes in the presence and absence of selective chemical inhibitors of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. In the absence of any CYP inhibitor, approximately 35% of parent compound remained after 30 min incubation. When ketoconazole (selective inhibitor for CYP3A4) was co-incubated with ruxolitinib, 74% of the parent compound remained, whereas co-incubations with selective inhibitors of CYP1A2, CYP2C9, CYP2C19 and CYP2D6 resulted in 38%, 40%, 35% and 42% of the initial concentration of ruxolitinib remaining, respectively. From these finding the reviewer agrees with the applicant that CYP3A4 is likely the predominant CYP isozyme responsible for the metabolism of ruxolitinib.

The metabolite profile of ruxolitinib was examined both in vitro (incubation with human liver microsomes and hepatocytes) and in vivo as part of the mass balance study INCB 18424-134. The prominent in vitro metabolic pathway in human liver microsomes was oxidation while oxidation and conjugation were observed in hepatocytes. Neither ruxolitinib nor any of its in vitro human metabolites appeared to form reactive glutathione adducts.

The mass balance trial INCB 18424-134 reports that following a single dose of 25 mg of ruxolitinib solution (100 μCi ^{14}C-ruxolitinib) parent drug was the predominant entity in circulation, representing 58% to 74% of the total radioactivity between 1 and 6 h post-dose. Metabolite M18 was observed at 17% of the total, circulating, drug-related material based on AUC and the other observed ruxolitinib mono- and di-hydroxylated and ketone metabolites represented less than 10% (Figure 6). Eight of these metabolites (M7, M8, M9, M11, M14, M16, M18 and M27) when added to parent drug, accounted for greater than 90% of the drug-related material in circulation (based on AUC). No metabolites were observed in human plasma after 12 h post-dose.



Source: Study report for study INCB 18424-134

Figure 6: Proposed Metabolic Pathways for Ruxolitinib in Human Plasma

Based on these in vitro findings and metabolic profiling from the mass balance study the reviewer agrees with the applicant's position that oxidation, is likely the major Phase I metabolic pathway for ruxolitinib and the hydroxylated metabolites may also undergo glucuronide conjugation. Potential conjugation pathways (e.g., UGT's) were not explored by the applicant. This is acceptable since these conjugates do not represent a substantial amount of circulating, drug-related material.

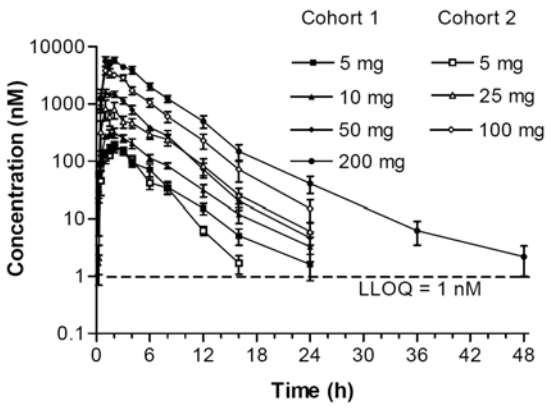
2.2.5.7 What are the characteristics of drug excretion?

The apparent oral clearance of ruxolitinib in healthy, adult subjects across all Phase 1 Clinical Trials ranged from 14.1 L/hr to 28.2 L/hr with a grand mean from all studies of 19.2 L/hr. The applicant speculates the 2 fold range of oral clearance may be related to intrinsic variability in CYP3A4 expression and activity; however, this could not be conclusively confirmed by the reviewer. Pop-PK modeling from the MF population (INCB 18424-251, INCB 18424-351 and INCB 18424-352) suggests gender may be a significant predictor of CL/F (see Sections 2.2.5.10 and 2.3.1), with male subjects having a slightly higher apparent clearance compared with female subjects (22.1 L/h versus 17.7 L/h, respectively).

In similar cross-study comparison, terminal phase elimination half-life values for ruxolitinib ranged from 2.3 to 4.0 hours with grand mean from all studies of 3.1 hours. Following a single oral dose of ^{14}C-INCB018424 solution in healthy male volunteers, the terminal t½ of total drug-related material (ruxolitinib + metabolites) in plasma was estimated to be 5.8 h (CV = 13%). The typical apparent terminal elimination (β) half-life for ruxolitinib in MF patients (INCB 18424-251, INCB 18424-351 and INCB 18424-352) estimated from the final population PK model was approximately 3.76 hours for males and 4.07 hours for females.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

A visual inspection of the exposure following single dose administration of ruxolitinib in healthy volunteers over the dose range of 5 mg to 200 mg in trial INCB 18424-131 (Table 5 and) suggests an approximately linear relationship. This is consistent with the applicant's analysis of the dose proportionality exponent (β) in INCB 18424-131 which was estimated from power-function regression analysis and was not statistically significantly different from 1 for C_{max} and $AUC_{0-\infty}$. A similar approximate linear relationship, defined as β not being statistically significantly different from 1 for Cmax and $AUC_{0-\tau}$ or $AUC_{0-\infty}$, is also suggests that following multiple dosing of ruxolitinib in both healthy volunteers over the dose range of 15-50 mg bid and 50-100 mg qd (INCB 18424-132) and MF patients (INCB 18424-251) over the range of 10-50 mg bid and 25-100 mg qd. Therefore, the reviewer finds the applicant's analysis acceptable and agrees with the applicant's position that ruxolitinib exhibits linearity in pharmacokinetics.



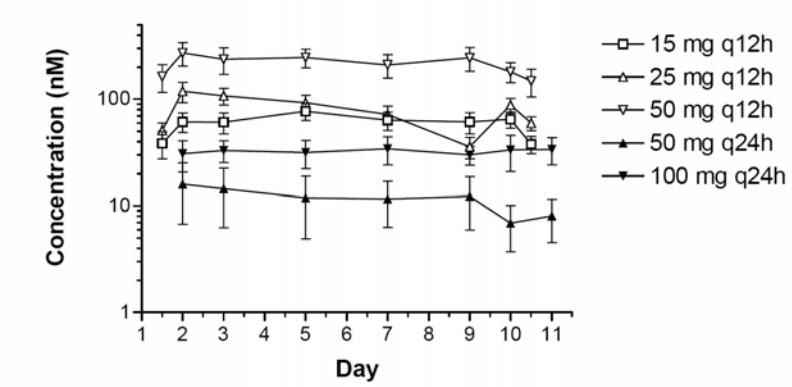
Source: Study report for trial INCB 18424-131

Figure 7: Ruxolitinib Plasma Concentrations (Mean ± SE) in Healthy Subjects Receiving Fasted, Oral, Single-Dose of Ruxolitinib

2.2.5.9 How do the PK parameters change with time following chronic dosing? (This may include time to steady-state; single dose prediction of multiple dose PK; accumulation ratio.)

The serial trough plasma concentrations from the ruxolitinib multiple dose trial INCB 18424-132 indicate that the healthy subjects were essentially at steady state by Day 2 for all regimens (Figure 8), which is consistent with the observed plasma terminal half-life of ruxolitinib of about 3 hours. This was not confirmed statistically by the applicant. The AUC accumulation index for ruxolitinib following bid dosing in this study ranged from 1 to 1.14, and Cmax accumulation index ranged from 0.99 to 1.22.

The AUC and Cmax accumulation indexes for ruxolitinib following 25 mg bid dosing in MF patients (n=27) in trial INCB 18424-132 was 1.19 and 1.06, respectively. This increased to 1.58 and 1.29 for the 50 mg bid population which was substantially smaller (n=5). Based on this information, the reviewer finds 10-20 reasonable estimate of accumulation following administration within the proposed dosing range (5 mg - 25 mg bid) in the MF population. This degree of accumulation is not considered substantial by the reviewer.



Source: Study report for trial INCB 18424-132

Figure 8: Ruxolitinib Trough Plasma Concentrations (Mean ± Standard Error) in Healthy Subjects Receiving Twice-daily or Once-daily Regimens

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

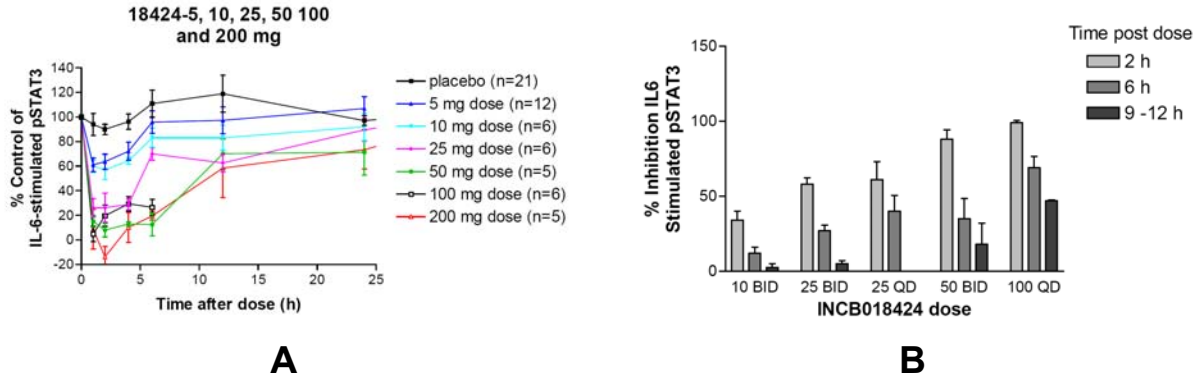
The ruxolitinib pharmacokinetic parameters reported in the single dose trial INCB 18424-131 in healthy volunteers exhibited intersubject variability (CV%), ranging from 19.0% (200 mg) to 55.9% (25 mg) for Cmax and from 8.59% (200 mg) to 34.0% (25 mg) for $AUC_{0-\infty}$. In multiple dose trial INCB 18424-132 in healthy volunteers the steady-state ruxolitinib pharmacokinetic parameters exhibited intersubject variability, ranging from 21.7 to 35.8% for Cmax and from 27.0 to 31.3% for $AUC_{0-\tau}$. This variability was somewhat higher in MF patients from trial INCB 18424-251 with the steady-state ruxolitinib pharmacokinetic parameters ranging from 2.2-44.1% for ruxolitinib Cmax and from 20-57% for AUC0-τ.

Using population based analysis, the inter-subject variability for apparent oral clearance is 39.1 %. Gender and body weight explains ~8% and ~3% of inter-subject variability on ruxolitinib clearance, respectively. The other causes are unexplained

2.2.6 What are the PD characteristics of the drug and its major metabolites?

The STAT3 transcription factor was used as a pharmacodynamic (PD) marker for JAK inhibition in the clinical and clinical pharmacology related studies (see Section 2.2.2). Following oral, single or multiple dose administration in healthy subjects, ruxolitinib demonstrated somewhat dose-dependent inhibition of cytokine-induced pSTAT3. Maximal inhibition occurred at 1-2 h after

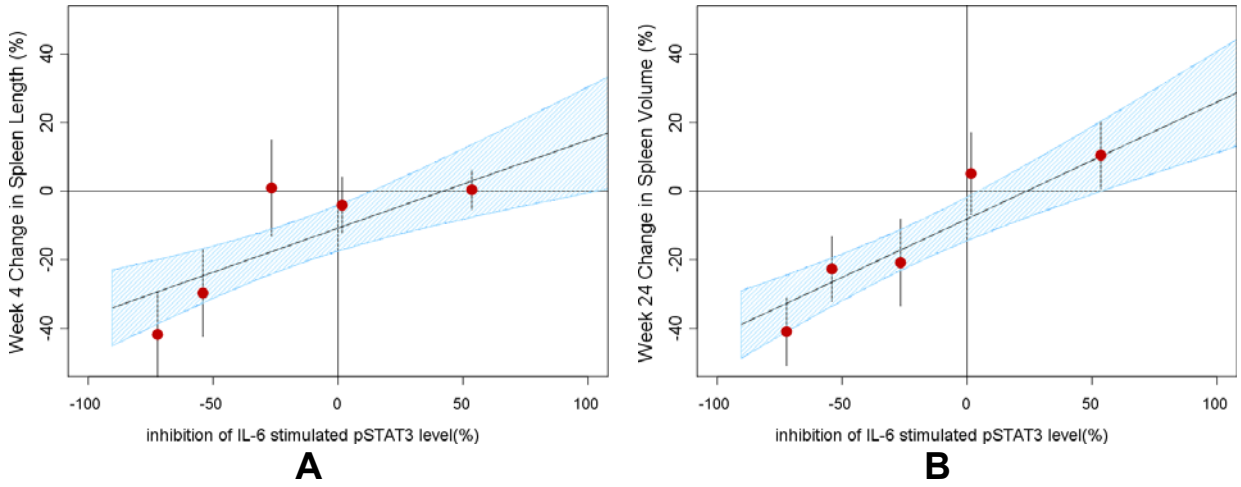
administration for all doses, coincident with maximal ruxolitinib plasma concentrations and returned to near baseline by 8-10 hours in both healthy subjects and myelofibrosis patients (Figure 9). Across multiple studies in healthy subjects, the calculated IC_{50} value for IL-6 induced pSTAT3 inhibition was reasonably consistent (0.23 - 0.35 μM) but the IC_{50} value may be lower in patients with myelofibrosis (0.14 μM). It is possible that elevated cytokines levels or the presence of the activating V617F mutation in patients with myelofibrosis may play a role in this difference; however, no definitive conclusions can be drawn from the data submitted.



Source: Applicants reports for study INCB 18424-131 and INCB 18424-251

Figure 9: Change in IL-6 Induced STAT3 Phosphorylation in Individuals in healthy subjects following single dose administration (A) and Myelofibrosis patients following multiple dose administration (B)

An FDA analysis of data from the INCB 18424-351 trial showed a relationship between IL-6 induced STAT3 Phosphorylation (collected at 4 weeks) and the change in both spleen length at 4 weeks (Figure 10a) as well as the 24 week change in spleen volume (efficacy endpoint (Figure 10b)). Therefore IL-6 induced STAT3 Phosphorylation is deemed acceptable biomarker in the clinical pharmacology trials.



Source: FDA generated using datasets from trial INCB 18424-351

Figure 10: Relationship between IL-6 Induced STAT3 Phosphorylation and the change in spleen length at week 4 (A) and the change in spleen volume at week 24 (B) in patients from trial 18424-351

Preclinical toxicology studies suggested the presence of active metabolites in the animal models studies. This was confirmed in a follow up *in vitro* study using spiked human whole blood. Samples were spiked with 10 μM of ruxolitinib or one of its eight common metabolites and assayed for IL-6 stimulated pSTAT3 inhibition using an ELISA (see Section 2.6.10). All of the metabolites showed weaker activity (~ 2 - 5-fold) relative to the parent compound, inhibiting

STAT3 phosphorylation (Table 13). Based on these IC_{50} values, the contribution of these metabolites to pharmacodynamic activity relative to parent is estimated to be 15-18% in healthy subject studies. This contribution changes in when various intrinsic or extrinsic factors are present (see Sections 2.3 and 2.4).

Table 13: Activity of INCB018424 Metabolites *In Vitro*

Analyte	IL-6 Stimulated pSTAT3 IC_{50} (μM)[a]
INCB018424 (ruxolitinib)	0.28
INCB025255 (M9)	0.43
INCB025256 (M11)	0.97
INCB025257 (M7)	1.5
INCB025258 (M8)	0.78
INCB025262 (M27)	0.66
INCB025264 (M16)	1.25
INCB027598 (M18)	1.5
INCB041092 (M14)	1.5

a= Using whole blood from Healthy Volunteers (n unknown)
Source: Applicants report INCYTE-IN VITRO-09.11.1

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Ruxolitinib is not considered a narrow therapeutic index drug. The major safety concern with increased exposure is cytopenia's and loss of symptomatic relief is the major efficacy concern with reduced exposure.

Body Weight

Body weight was found to be a significant covariate for Vc/F as seen in Figure 11. No body weight related modifications in the proposed JAKAFI dose are required at this time based on the magnitude of change noted.

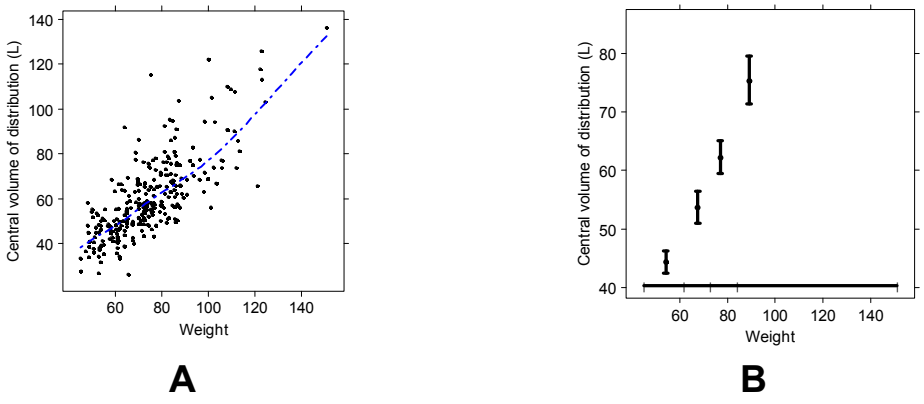


Figure 11: Inter-individual variability of CL vs weight by Scatter plot (A) and Quantile Plot (B)

Gender

The effects of sex and body weight on clearance were examined by the reviewer. Inclusion of sex or body weight as a covariate for clearance covariates resulted in the reduction in the objective function value (OFV) by 42 (Figure 12) and 36, respectively. Sex explains ~8% of inter-subject variability on ruxolitinib clearance.

The sex difference in pharmacokinetics can be primarily explained by the difference of body weight between males and females. Males have higher body weight and lower exposure at steady state compared to female patients (Figure 13). After replacing sex with body weight in the final model, no trend was observed regarding inter-patient variability of clearance vs. sex (Figure 14). After including sex or body weight as the covariate, the inter-patient variability for clearance are 40% and 42%, respectively.

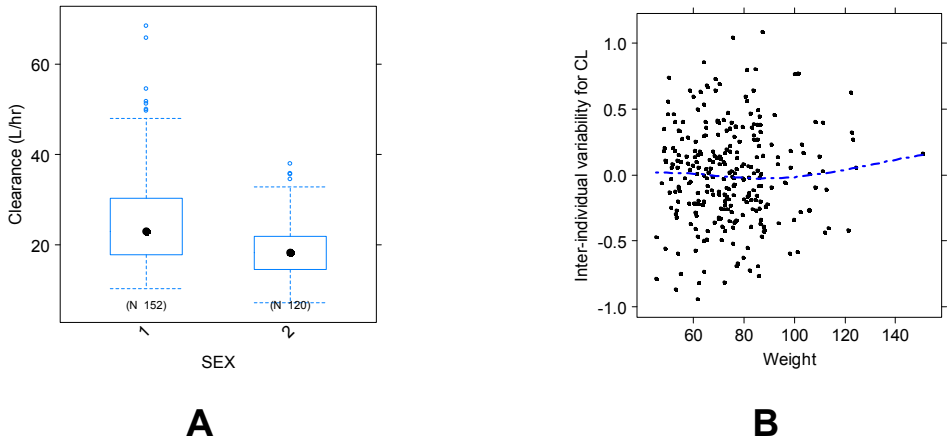


Figure 12: Plots of CL vs sex (A) and Inter-individual variability of CL vs. body weight (B) under the final model with sex as a covariate for clearance.

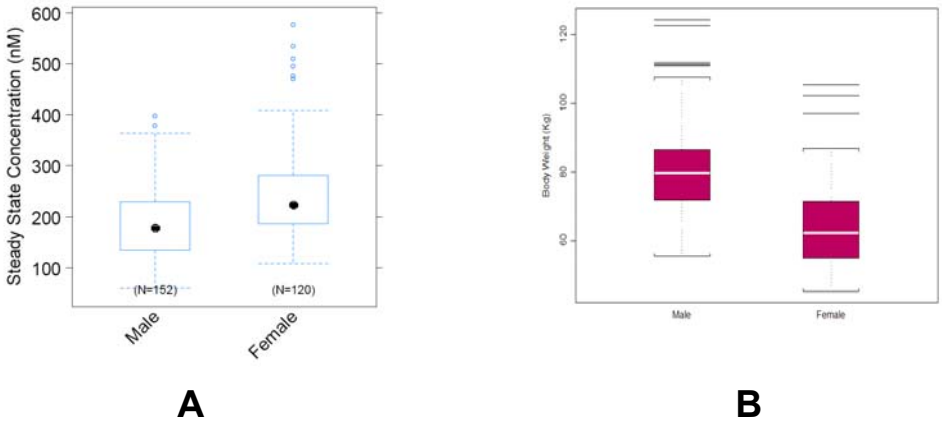
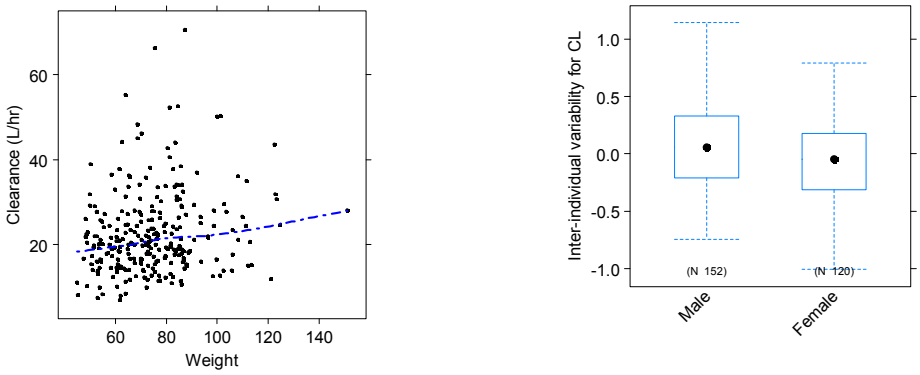


Figure 13: Comparisons of steady state concentration at 15 mg daily dose (A) and the body weight (B) between male and female patients.



A **B**

Figure 14: Plots of CL vs weight (A) and Inter-individual variability of CL vs sex (B) under the final model with body weight as a covariate for clearance.

Renal impairment

The applicant conducted an open-label trial (INCB 18424-142) of the effect of various degrees of renal impairment (normal (> 80 mL/min), mild (50-80 mL/min), moderate (30-50 mL/min) and severe (< 30 mL/min) and end stage renal disease (ESRD subjects on dialysis) on the pharmacokinetics and pharmacodynamics of a single 25 mg dose of ruxolitinib. The ESRD group was further split into those receiving ruxolitinib before or after dialysis. In addition, active metabolites of ruxolitinib were monitored in this study but were analyzed in a separate report (INCYTE DMB-10.55.1).

The applicant defined the treatment groups by creatinine clearance as noted above; however, it then states that the classification of subjects was based on the "MDRD Calculation for Creatinine Clearance (mL/min) [sic]." A reviewer analysis of the applicant's reported laboratory data, demographic data, MDRD data and the sample case report form show this "MDRD Calculation for Creatinine Clearance (mL/min)" is actually the modified MDRD [GFR (mL/min/1.73 m^2) = 186 x (Pcr) $^{-1.154}$ x (age) $^{-0.203}$ x (0.742 if female) x (1.210 if African American)]; however the units used by the applicant are incorrect.

The applicant reports that subjects enrolled and assigned to the various groups ultimately did not always meet the renal impairment criteria. The range of eGFR reported by the applicant are 79 – 122 mL/min/1.73 m^2, 44 – 74 mL/min/1.73 m^2, 35 – 47 mL/min/1.73 m^2, 7 – 28 mL/min/1.73 m^2 for normal, mild, moderate and severe renal impairment, respectively. The relative difference in the Cmax and $AUC_{0-\infty}$ of ruxolitinib in all degrees of renal impairment versus patients with normal renal function were < 25% and alone are not considered substantial. However, when the $AUC_{combined}$ (see Section 2.2.5.1) was considered, it is apparent that the there is an increase in overall exposure with renal impairment that is driven by the active metabolites of ruxolitinib. In this analysis the reviewer calculated the change in $AUC_{combined}$ using the applicant's group assignments and also reassignment based on calculated eGFR (MDRD) or CLcr (Cockcroft-Gault). These data also suggest that some of these active metabolites may be dialyzable; however, there was not sufficient information to draw a firm conclusion.

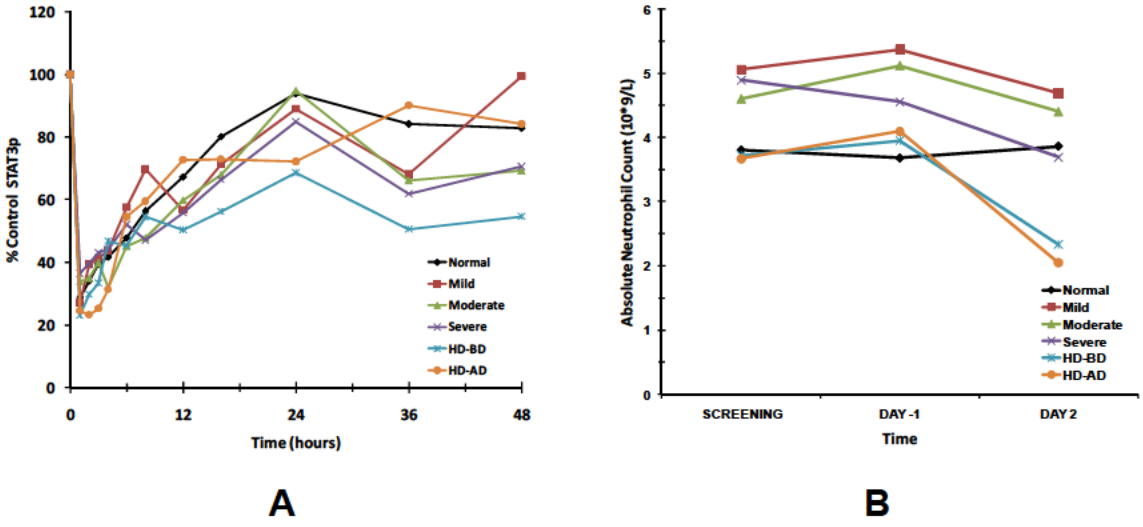
Table 14: Geometric Mean Relative Change in $AUC_{combined}$ compared to the Normal Renal Impairment Group

Group [Clcr (mL/min)]	Normal >80	Mild 50-80	Moderate 30-50	Severe <30	HD-BD	HD-AD
Actual assignment	1 (n=8)	1.16 (8)	1.4 (8)	1.3 (8)	1.7 (4)	1.36 (4)
MDRD based reassignment (mL/min/1.73)	1 (n=6)	1.19 (7)	1.34 (11)	1.37 (8)	ND	ND
Cockcroft-Gault based reassignment (mL/min)	1 (n=9)	1.06 (12)	1.38 (7)	1.46 (4)	ND	ND

BD=before dose; AD=after dose; ND not determined

Source: Applicants reports INCB 18424-142 and INCYTE DMB-10.55.1

The findings for $AUC_{combined}$ are consistent with the results (Figure 15) of the PD analysis using STAT3 phosphorylation levels and the safety analysis using absolute neutrophil count (ANC). Figure 15a the PD activity is prolonged in subjects with moderate to severe renal impairment and in ESRD when the ruxolitinib dose is administered after dialysis (HD-BD) this is consistent with the markedly elevated plasma levels of ruxolitinib active metabolites observed. In addition, decreases in mean ANC for all renally-impaired groups (Cohorts 2 through 6) were observed with the greatest decreases compared to normal subjects were noted in the moderate to severe and ESRD Cohorts.



BD=before dose; AD=after dose

Source: Applicants reports INCB 18424-142

Figure 15: Comparison of Interleukin-6-induced STAT3 Phosphorylation Levels (A) and Absolute Neutrophil Count (B) following a Single 25 mg Oral Dose of INCB018424 in Healthy Subjects versus Subjects with Mild, Moderate, Severe Renal Impairment and ESRD with Dialysis

The effect of renal impairment was also assessed using data from the integrated safety database. The estimated glomerular filtration rate (eGFR based on the modified diet in renal disease (MDRD) formula) was used to classify subjects as normal (eGFR ≥90 mL/min), mild renal impairment (eGFR ≥60 to <90 mL/min), moderate renal impairment (eGFR ≥30 to <60 mL/min) or severe renal impairment (eGFR <30 mL/min). Most subjects had mild (395 subjects; 288 dosed with ruxolitinib) or moderate (231 subjects; 156 administered ruxolitinib) renal impairment, while fewer (155 subjects; 114 administered ruxolitinib) had normal renal function. Only 5 subjects (4 administered ruxolitinib) had severely impaired renal function.

The distribution of average total daily doses was similar across the renal impairment groups. Mean and median changes in Hgb, ANC, and platelets appeared similar in subjects with normal, mild, or moderate renal impairment. Higher rates of treatment-emergent ≥Grade 3 anemia or

thrombocytopenia were seen with worsening renal impairment grade. There was a trend toward a higher rate of new onset transfusion dependence in subjects with moderate renal impairment.

Hepatic impairment

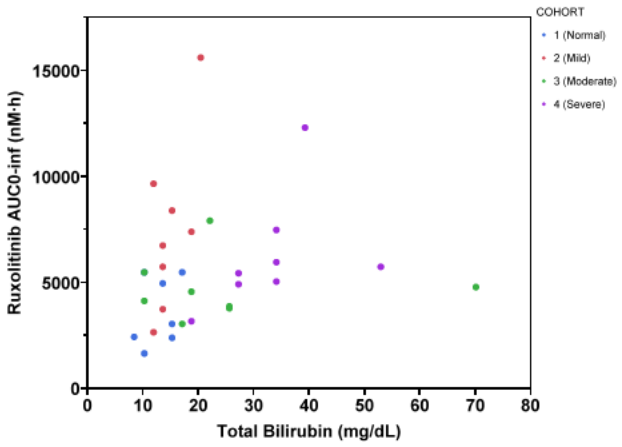
The applicant conducted an open-label trial (INCB 18424-137) of the effect of various degrees of hepatic impairment on the pharmacokinetics of a single 25 mg dose of ruxolitinib. The trial included healthy subjects and patients with varying degrees of hepatic impairment (mild, moderate and severe hepatic impairment based on the Child-Pugh classification). The mean total AUC of ruxolitinib was higher in subjects with hepatic impairment compared with healthy subjects (Table 12). The mean Cmax of ruxolitinib was not substantially different for subjects with various degrees of hepatic impairment compared with healthy controls. The relative $AUC_{combined}$ for subjects with hepatic impairment compared to healthy subjects was slightly lower than the AUC reported ruxolitinib alone perhaps owing to reduced metabolic turnover. Interestingly the change in metabolite abundance relative to parent was not markedly different between the hepatic impairment groups. The hepatic impairment groups did differ from the healthy group (~10% vs 16%, respectively).

Table 15: Geometric Mean Relative Change in Ruxolitinib and combined Ruxolitinib and metabolite Exposure in Patients with Hepatic Impairment Compared to the Healthy Subjects

	Ruxolitinib		Ruxolitinib + Metabolites
	Cmax	$AUC_{0-\infty}$	$AUC_{combined}$
Normal	1	1	1
Mild	0.92	1.87	1.77
Moderate	0.78	1.28	1.21
Severe	0.85	1.65	1.59

Source: Applicants reports INCB 18424-137 and INCYTE DMB-10.55.1

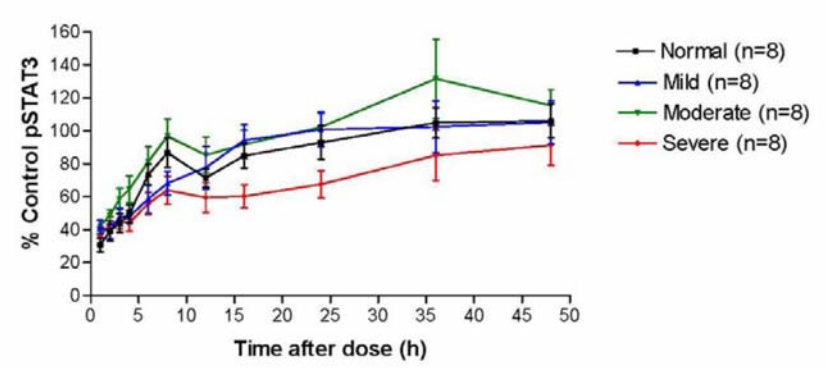
While the mean ruxolitinib AUC in each of the three hepatic impairment cohorts was higher than that of the healthy subjects, it did not necessarily coincide with the severity of hepatic impairment. It is not clear why this discrepancy exists; however, the higher AUC in the mild group can be assigned to 3 female subjects with a relatively high BMI. A relationship between total bilirubin and ruxolitinib $AUC_{0-\infty}$ is apparent if these three subjects are removed (Figure 16).



Source: Applicants raw dataset for report INCB 18424-137

Figure 16: Relationship between between total bilirubin and ruxolitinib $AUC_{0-\infty}$ in healthy and hepatically impaired subjects

The observed ruxolitinib PD activity (inhibition of IL-6 stimulated pSTAT3 in whole blood) was consistent with the corresponding plasma concentrations of ruxolitinib except in the severe hepatic impairment cohort where the PD activity was more prolonged in some subjects than what was expected based on plasma concentrations of ruxolitinib (Figure 17).



Source: Applicants raw dataset for report INCB 18424-137

Figure 17: Comparison of STAT3 Phosphorylation Levels following a Single 25 mg Oral Dose of INCB018424 in Healthy Subjects versus Subjects with Mild, Moderate, or Severe Hepatic Dysfunction

The effect of hepatic impairment was also assessed using safety data from the integrated safety database. Subjects were classified as normal (≤ 1.0 ULN (ULN, upper limit of normal), mild hepatic impairment (> 1.0 to ≤ 1.5 ULN), moderate hepatic impairment (> 1.5 to ≤ 3 ULN) and severe hepatic impairment (> 3 ULN) by the modified NCI Organ Dysfunction Working Group (ODWG) criteria using Baseline total bilirubin as the sole criterion. Most subjects had normal hepatic function (662 subjects; 466 dosed with ruxolitinib), 88 subjects (69 dosed with ruxolitinib) had mild impairment, and 33 subjects (25 dosed with ruxolitinib) had moderate hepatic impairment. Only 2 subjects had severe hepatic impairment (1 dosed with ruxolitinib). Compared with subjects with normal hepatic function, the mean and median total daily dose was lower for subjects with mild hepatic impairment in Study INCB 18424-351 which is consistent with the unexplained changes in ruxolitinib exposure in the mild impairment group of the dedicated hepatic impairment trial. The incidence of anemia and thrombocytopenia was somewhat higher in the moderate hepatic impairment group, but the analysis was hampered by the small number of subjects.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

Age was not a significant covariate in the in the final pop-PK evaluations. The overall AE incidence in the ruxolitinib groups during the Phase 3 randomized treatment period was similar in subjects in the 2 age categories (97.1% for subjects aged ≤ 65 years [younger subjects] and 99.4% for subjects aged > 65 years [older subjects]. In general, the incidence of most AE preferred terms was higher in older subjects. Therefore, no age related modifications in the proposed JAKAFI dose are required at this time.

2.3.2.2 Pediatric patients

No pediatric studies were conducted. Waiver requested In accordance with 21 CFR 314.55(d) Exemption for orphan drugs.

2.3.2.3 Gender

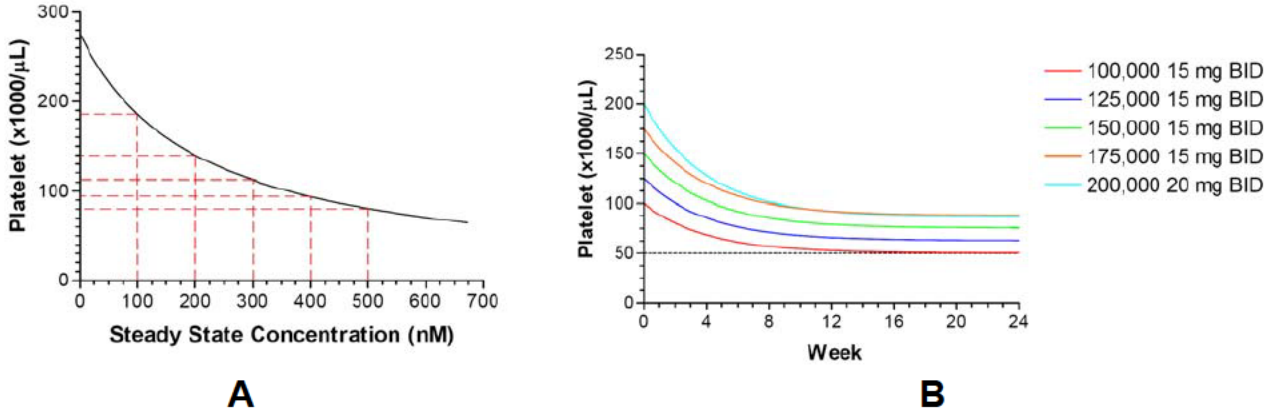
The exposure difference between males and females explains 26% of the difference of spleen volume reductions between male and female patients. Dose adjustment based on gender does not seem to benefit the clinical outcome. Furthermore, the small effect of body weight on exposure does not support body-size based dosing.

2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

Two-thirds of the pharmacokinetic profiles in healthy subjects came from Whites so evaluation of race related effects is limited. Comparing across different races, mean ruxolitinib oral clearance and terminal phase elimination half-life values were generally similar. Although mean ruxolitinib CL/F appeared lower in the American Indian (n=6) and Asian (n=9) trial subjects (~13 L/h) compared to other races (White (n=195), Black (n=75), Hispanic (n=4)) studied (17.4 – 20.2 L/h), the small sample size make these findings indeterminate. In addition, race was not a significant covariate in the pop-PK evaluations. Therefore, no race related modifications in the proposed JAKAFI dose are required at this time.

2.3.2.5 Renal impairment

Based on the reports from trial INCB 18424-142 and the metabolite analysis INCYTE DMB-10.55.1 the applicant proposes (b) (4) [redacted] As demonstrated in Figure 18a, as steady state concentrations of ruxolitinib increase above 300 nM the relative effect on platelet count at week 24 is much less pronounced. Further, Figure 18b suggests, from a safety perspective, it is of greater importance to exposure match patients with baseline platelet counts between 100-150 $\times$ 10^9/L to assure exposure does not go beyond that expected for 15 mg bid.



Source: Applicants report INCYTE-DMB-11.05.1

Figure 18: Simulations for Exposure-Response Relationship Between Platelet Counts at Week 24 and Average Steady-State Concentration of Ruxolitinib (A) and Simulated Time Course of Platelet Counts, Stratified by Baseline Platelet Count, for the 15 mg BID and 20 mg BID Ruxolitinib Dosing Regimens (B)

Therefore, the reviewer recommends that the applicant's proposal be modified such that only patients with a baseline platelet count between 100 $\times$ 10^9/L and 150 $\times$ 10^9/L and moderate (Clcr 30-50 mL/min) or severe renal impairment (Clcr less than 30 mL/min) should have the starting dose of JAKAFI reduced to 10 mg twice daily. JAKAFI should be avoided in patients with any

degree of renal impairment a baseline platelet count < 100 × 10^9/L. As indicated in Table 16 below, this proposed regimen allows for exposure matching of the patient population most at risk for thrombocytopenia while allowing maximum potential benefit (Figure 2) for other patients at lower risk for thrombocytopenia. Additional dose modifications should be made with careful monitoring of safety and efficacy. The reviewer finds the applicant's proposal for dosing in ESRD with dialysis acceptable.

Table 16: Estimated Steady State Concentration (Css (nM/L)) for FDA Proposed JAKAFI Dosing Regimen in Patients with Varying Degrees of Renal Impairment

Dose	Normal[a]	Observed[b]			Cockcroft-Gault[b]		
		Mild	Moderate	Severe	Mild	Moderate	Severe
25 bid	355.2	413.4	497.9	479.9	375.1	489.5	519.3
20 bid	295	343.3	413.5	398.6	311.5	406.5	431.3
15 bid	226.6	263.7	317.6	306.1	239.3	312.2	331.2
10 bid	139.6	162.4	195.6	188.6	147.4	192.3	204

Yellow = baseline platelet count > 200 × 10^9/L; Grey = baseline platelet count 100-200 × 10^9/L; Blue = baseline platelet count 151-200 × 10^9/L; Green = baseline platelet count 100-150 × 10^9/L
a = normal values for Css represent mean values from trials 251 and 351
b= based on relative change in $AUC_{combined}$ from Table 14
Source: Applicants reports INCB 18424-142 and INCYTE-DMB-11.05.1

2.3.2.6 Hepatic impairment

Based on the reports from trial INCB 18424-137 and the metabolite analysis INCYTE DMB-10.55.1 the applicant proposes (b) (4) [redacted] Therefore, the reviewer again attempted to further optimize the applicant's proposed JAKAFI dose modifications using the same approach and rationale discussed in section 2.3.2.5. Based on this approach the reviewer recommends that the applicant's proposal be modified such that only patients with a baseline platelet count between 100 × 10^9/L and 150 × 10^9/L and any degree of hepatic impairment should have the starting dose of JAKAFI reduced to 10 mg twice daily. JAKAFI should be avoided in patients with any degree of hepatic impairment and a baseline platelet count < 100 × 10^9/L. As indicated in Table 17 below, this proposed regimen allows for exposure matching of the patient population most at risk for thrombocytopenia while allowing maximum potential benefit for other patients at lower risk for thrombocytopenia. Additional dose modifications should be made with careful monitoring of safety and efficacy.

Table 17: Estimated Steady State Concentration (Css (nM/L)) for FDA Proposed JAKAFI Dosing Regimen in Patients with Varying Degrees of Hepatic Impairment

Dose	Normal[a]	Ruxolitinib[b]			Ruxolitinib + Metabolites[c]		
		Mild	Moderate	Severe	Mild	Moderate	Severe
25 bid	355.2	665	455.1	588.3	629.4	431.1	487.8
20 bid	295	552.3	378	488.6	522.7	358	405.1
15 bid	226.6	424.2	290.3	375.3	401.5	275	311.2
10 bid	139.6	261.3	178.8	231.1	247.3	169.4	191.7

Yellow = baseline platelet count > 200 × 10^9/L; Grey = baseline platelet count 100-200 × 10^9/L; Blue = baseline platelet count 151-200 × 10^9/L; Green = baseline platelet count 100-150 × 10^9/L
a = normal values for Css represent mean values from trials 251 and 351
b= based on relative change in $AUC_{0-\infty}$ from Table 15
c= based on relative change in $AUC_{combined}$ from Table 15
Source: Applicants reports INCB 18424-137 and INCYTE-DMB-11.05.1

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not

No pharmacogenetics information was provided in this submission. The genomics team was initially consulted but stated a genomics review of this submission was not warranted.

2.3.2.8 What pregnancy and lactation use information is there in the application?

There are no human data on the use of ruxolitinib in pregnancy and lactation. The lacteal excretion of ^{14}C-ruxolitinib-derived radioactivity was assessed following a single oral administration of 30 mg/50 µCi/kg 14C-ruxolitinib to lactating female Sprague Dawley rats at 10 days postpartum (Lactation Day 10; LD 10). Mean milk:plasma concentration ratios of radioactivity were greater than one at all measurable sampling times with a ratio of 13.4 based on $AUC_{0-\infty}$, suggesting that ruxolitinib-derived radioactivity preferentially partitions into milk. The reviewer finds the applicant's proposal that women taking JAKAFI should not breast-feed.

2.3.2.9 Other human factors that are important to understanding the drug's efficacy and safety

None

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Drugs that are strong inducers or inhibitors CYP 3A4 (see Section 2.4.3.2) may influence dose-exposure and/or -response of ruxolitinib and/or its active metabolites. See Section 2.3.1 regarding the impact of any differences in ruxolitinib exposure on response.

Drugs that are inhibitors of CYP3A4

The applicant conducted an open-label, one-way interaction trial (INCB 18424-133) to evaluate the effect of multiple-dose ketoconazole (strong inhibitor of CYP 3A4) or erythromycin (moderate inhibitor of CYP 3A4) administration on the pharmacokinetics and pharmacodynamics of a single 10 mg dose of ruxolitinib in healthy, primarily African American (~75%) subjects. Subjects received single, oral doses of 10 mg ruxolitinib (two 5-mg tablets) on 2 separate occasions: once as monotherapy on Day 1 and once as combination therapy with the CYP3A4 inhibitor on Day 5. From Day 2 through Day 5, subjects received twice-daily, oral doses of either 200 mg ketoconazole or 500 mg erythromycin based on the assigned Cohort.

When co-administered with ketoconazole, mean ruxolitinib Cmax and AUC increased by 33% and 91%, respectively, and the mean terminal elimination half-life of ruxolitinib increased from 3.7 h to 6.0 h. Consistent with the PK data, the $AUC_{0-\infty}$ for pSTAT3 inhibition was increased by 98%; however, Imax did not change substantially. Active metabolite concentrations and PK were not collected in this trial and is considered a limitation. However, given the concordance between the overall pSTAT3 inhibition and ruxolitinib exposure it is unlikely that the metabolite information would have substantially changed the conclusions of this part of the trial. Therefore, the reviewer agrees with the applicant's conclusions regarding the estimated exposure change and the need for dose modification of JAKAFI with co administration with strong CYP3A4 inhibitors (see Section 2.4.2.1).

Co-administration of erythromycin with ruxolitinib resulted in an 8% and 27% increases in mean ruxolitinib Cmax and $AUC_{0-\infty}$, respectively. Consistent with the PK findings, a substantial change in pSTAT3 inhibition was not seen. Active metabolite concentrations and PK were also not collected in this trial and is considered an acceptable limitation by the reviewer for the reasons stated above. In addition, dosing erythromycin twice daily rather than three times daily in this trial is not considered ideal, but is deemed acceptable by the reviewer. The reviewer also agrees with

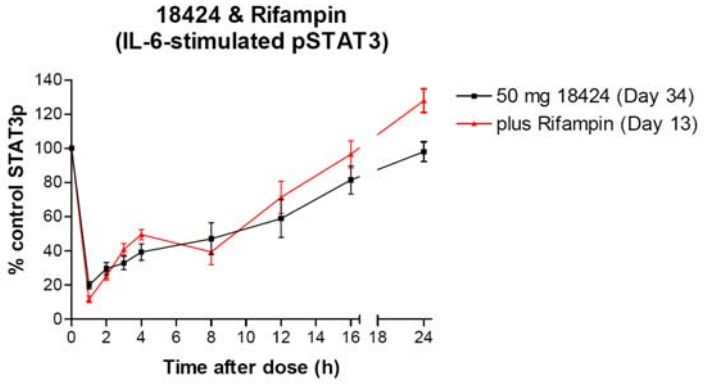
the applicant's position that dose modification is not required for co-administration with mild to moderate CYP3A4 inhibitors.

Drugs that are strong inducers of CYP3A4

The applicant conducted an open-label trial (INCB 18424-133) to assess the effect of the CYP3A4 inducer rifampin on ruxolitinib pharmacokinetics and pharmacodynamics in a primarily male African American healthy volunteer population. A 50 mg (two 25-mg tablets) single dose of ruxolitinib was used in the study. Ruxolitinib was dosed on Days 1 (control) and 13 (following multiple dosing of rifampin). From Day 3 through Day 13, subjects received once-daily, oral doses of 600 mg rifampin (two 300-mg tablets). The applicant states that an additional dosing session was performed on Day 34 following administration of 50 mg ruxolitinib alone because some of the blood samples collected on Day 1 for pSTAT3 evaluation were lost in transportation. Active metabolites of ruxolitinib were monitored in this study but were analyzed in a separate report (INCYTE DMB-10.55.1).

Comparison of the pharmacokinetics of ruxolitinib on Day 13 vs Day show a decreased the geometric mean ruxolitinib Cmax and AUC by 52% and 71%, respectively while the mean terminal elimination half-life decreased from 3.3 to 1.7 h. Similar results were obtained by comparing data from Day 13 vs Day 34, with decreases of 32% and 61%, respectively, in geometric mean ruxolitinib Cmax and AUC. In addition, the decrease in Day 13 vs Day 34 $AUC_{combined}$ (see Section 2.2.5.1) was estimated to be 47%.

However, with co-administration of rifampin, $AUC_{0-\infty}$ and Imax for pSTAT3 inhibition were reduced 10% and 3%, respectively, despite the reported 61-71% decrease in ruxolitinib plasma AUC above (Figure 19).



18424 = ruxolitinib
Source: Applicants report INCB 18424-135

Figure 19: Change in Interleukin-6 Induced STAT3 Phosphorylation in Individuals receiving ruxolitinib alone or following multiple dosing with rifampin

Two possible explanations were provided by the applicant regarding this discrepancy. First, at a dose of 50 mg of ruxolitinib, the average plasma concentration (calculated as average AUC_{0-t}/ 24h) over the 24 hour period post-dose (421 nM, on Day 34) was greater than the IC_{50} value (234 nM) for STAT3 phosphorylation. The pSTAT3 inhibition vs. 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 that sigmoidal curve such 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 and therefore plasma concentrations of the eight ruxolitinib metabolites were determined with and without rifampin treatment. 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. The

reviewer finds both of these possibilities plausible. In addition, the reviewer notes that although the AUC for individual metabolites did not change between dosing ruxolitinib alone or following multiple dose of rifampin, an approximately 2 fold change in metabolite Cmax was reported (Table 18). This may have also played a role in this discrepancy.

The reviewer agrees with the applicant's conclusions regarding the estimated exposure and PD changes following concurrent use of ruxolitinib with a strong inducer of CYP3A4.

Table 18: Cmax (nM/L) of 8 Active Metabolites of Ruxolitinib Following Administration of Ruxolitinib Alone or Following Multiple Administration of Rifampin

Metabolite	Ruxolitinib	+ Rifampin	Ratio
(M9)	31.2	54.4	1.74359
(M11)	147	213	1.44898
(M7)	83.1	157	1.88929
(M8)	89.4	232	2.595078
(M27)	124	265	2.137097
(M16)	35.2	90.1	2.559659
(M18)	226	474	2.097345
(M14)	15	40.2	2.68

Source: Applicants report INCYTE DMB-10.55.1

2.4.2 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

2.4.2.1 Drugs that are strong inhibitors of CYP3A4

Based on the reports from trial INCB 18424-133 the applicant propose (b) (4) [redacted] To address this, the reviewer again attempted to further optimize the applicant's proposed JAKAFI dose modifications using the same approach and rationale discussed in Section 2.3.2.5. Based on this approach (Table 19), the reviewer recommends that the applicant's proposal be modified such that the recommended starting dose be lowered to 10 mg twice daily for all patients with a platelet count $\geq 100 \times 10^9$/L and receiving a strong CYP3A4 inhibitor concurrently. Additional dose modifications should be made with careful monitoring of safety and efficacy. JAKAFI should be avoided in patients with a baseline platelet count < 100×10^9/L and receiving a strong CYP3A4 inhibitor concurrently.

Table 19: Estimated Steady State Concentration (Css (nM/L)) for FDA Proposed JAKAFI Dosing Regimen in Patients with concurrent strong CYP3A4 treatment

Dose	Normal[a]	Ruxolitinib + Strong CYP3A4 Inhibitor[b]
25 bid	355.2	678.5
20 bid	295	563.5
15 bid	226.6	432.7
10 bid	139.6	266.6

Pink = baseline platelet count ≥ 100×10^9/L
a = normal values for Css represent mean values from trials 251 and 351
b= based on relative change in AUC $_{0-\infty}$ from Section 2.4.1
Source: Applicants reports INCB 18424-133

2.4.2.2 Drugs that are strong inducers of CYP3A4

The reviewer agrees with the applicant's position that there is not sufficient evidence to warrant a dose modification at this time. The current close monitoring required during the titration phase of therapy should be sufficient to assure optimal benefit is achieved in this group.

2.4.3 Drug-drug interactions

2.4.3.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. Based on in vitro studies, CYP3A4 is likely the predominant CYP isozyme responsible for the metabolism of ruxolitinib. Further, incubation in presence and absence of selective CYP inhibitors suggested the potential for an interaction with the strong CYP3A4 inhibitor ketoconazole. See Section 2.2.5.6 for additional details regarding these in vitro studies.

2.4.3.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes. Based on in vitro studies, CYP3A4 is likely the predominant CYP isozyme responsible for the metabolism of ruxolitinib (Section 2.2.5.6). The influenced by genetics on the metabolism of ruxolitinib is unknown.

2.4.3.3 Is the drug and/or metabolites an inhibitor and/or an inducer of CYP enzymes?

No. The potential of ruxolitinib to inhibit human CYP enzyme activities was examined in vitro with human recombinant CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 using high-throughput fluorescent substrates and in human liver microsomes using standard probe substrates. The potential of the M18 metabolite of ruxolitinib to inhibit activity of these CYPs in human liver microsomes was also investigated in vitro. Substrates were incubated at Km concentrations with final concentrations of ruxolitinib typically ranging from 0 to 25 μM for ruxolitinib and 0 to 3.0 μM for M18.

Ruxolitinib did not appear to be 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 appear to show inhibition of human liver microsomal CYP3A4 using two preferred probe substrates, midazolam and testosterone, with some 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 an unlikely mechanism-based inhibitor of CYP3A4. The reviewer agrees with the applicant's position that, since the mean Cmax at the highest proposed therapeutic dose for ruxolitinib in humans (25 mg bid) is 1.2 μM (0.04 μM unbound), the ratio of Cmax/IC_{50} for the CYPs tested is <0.1, suggesting the potential for ruxolitinib to cause clinical drug interactions via inhibition of these CYPs is low.

The metabolite M18 also did not appear to inhibit human liver microsomal CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 IC_{50} > 3.0 μM). The reviewer agrees with the applicant's position that, since the mean plasma Cmax of M18 in humans, after an oral 25 mg dose of ruxolitinib, was 0.14 μM and the approximate steady-state Cmax ($Cmax_{ss}$) value estimated to be 0.20 μM, the potential for M18 to cause clinical drug interactions via inhibition of these CYPs is also low ($Cmax_{ss}$/ IC_{50}<0.1).

The potential for ruxolitinib to induce human CYP3A isozymes was studied in vitro using the human PXR assay. Gene induction was within 2-fold of the vehicle control at 3 μM ruxolitinib and 5.5- and 10.1-fold at concentrations of 10 and 30 μM, respectively. In comparison, the known CYP3A4 inducer, rifampin (30 μM), resulted in a 38-fold gene induction compared to the control. The potential for CYP1A2 and CYP2B6 induction was investigated using three preparations of human hepatocytes. Ruxolitinib at concentrations up to 10 μM did not induce CYP1A2 or CYP2B6 activity whereas the respective positive controls showed expected levels of induction. Therefore the reviewer agrees with the applicants position that ruxolitinib is an unlikely inducer of CYP1A2, CYP2B6 and CYP3A4 enzymes at clinically relevant concentrations.

2.4.3.4 Is the drug and/or metabolites a substrate and/or an inhibitor of P-glycoprotein transport processes?

No. Ruxolitinib is an unlikely substrate for the P-gp transporter (see Section 2.2.5.3).

To determine if ruxolitinib is a P-gp inhibitor in vitro, the B-A/A-B ratio of digoxin in Caco-2 cells was examined in the presence of ruxolitinib. The B-A/A-B ratio of digoxin (5 μM), a sensitive P-gp substrate, decreased in the presence of ruxolitinib in a concentration-dependent manner with an IC_{50} of 21 μM. The reviewer agrees with the applicant's position that, since the clinical steady state plasma Cmax value of ruxolitinib following 25 mg bid is 1.2 μM (total drug) yielding a Cmax/IC50 ratio of <0.1, it is unlikely that ruxolitinib at therapeutic concentrations will substantially inhibit the P-gp mediated transport of concomitant drugs that are P-gp substrates.

To determine if the M18 metabolite is a P-gp inhibitor in vitro, the transport of 3H-digoxin (1 μM) was assessed in the presence of varying concentrations of M18 (0 to 3 μM) using MDR1 over-expressing. No inhibition of digoxin uptake was observed by M18 at any of the concentrations tested. The reviewer agrees with the applicant's position that, since the mean plasma Cmax for M18 in humans after an oral 25 mg dose of ruxolitinib is 0.14 μM the approximate Cmaxss value is estimated to be 0.20 μM, it is unlikely that M18 at therapeutic concentrations will inhibit the transport of concomitant drugs that are P-gp substrates.

2.4.3.5 Are there other metabolic/transporter pathways that may be important?

No. Ruxolitinib and M18 were also tested in vitro for inhibitory potential against a panel of human drug transporters (BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1 and OAT3) using individual cell lines that overexpress these transporters (Table 20). The reviewer agrees with the applicant's position that, since the Cmax at the highest proposed therapeutic dose for ruxolitinib in humans (25 mg bid) is 1.2 μM (0.04 μM unbound), the ratio of $Cmax/IC_{50}$ for BCRP, OATP tested are less than 0.1 and the $Cmax_{unbound}/IC_{50}$ for OCT and OAT tested are less than <0.1, it is unlikely that ruxolitinib at therapeutic concentrations will substantially inhibit the transport of concomitant drugs that are substrates of BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1 and OAT3.

The metabolite M18 did not inhibit any of these transporters at the highest concentration tested (3 μM). The reviewer agrees with the applicant's position that, since the mean plasma Cmax for M18 in humans after an oral 25 mg dose of ruxolitinib is 0.14 μM the approximate $Cmax_{ss}$ value is estimated to be 0.20 μM, it is unlikely that M18 at therapeutic concentrations will inhibit the transport of concomitant drugs that are BCRP or OATP substrates. Since the free fraction of M18 is unknown, a conclusion regarding its potential inhibition of the transport of concomitant drugs that are OCT or OAT substrates can not be made; however, it is deemed unlikely by the reviewer.

Table 20: IC_{50} values for Inhibition of Human Transporters by Ruxolitinib and M18

Transporter	Ruxolitinib/M18 concentration	Human cell line	Probe substrate (concentration)	Positive control (concentration)	IC_{50} (μM)	
					Ruxolitinib	M18
BCRP	0-225 μM (Rux)0-3 μM (M18)	MDCK-MXR	PHIP (1 μM)	Fumitremorgin C (50 μM)	**48.0**	**NI**
OATP1B1	0-55 μM (Rux) 0-3 μM (M18)	HEK Flp In-OATP1B1	Estradiol-17β-glucuronide (1 μM)	Atorvastatin (10 μM) and Rifamycin SV (20 μM)	**19.3**	**NI**
OATP1B3	0-50 μM (Rux) 0-3 μM (M18)	HEK OATP1B3	Estradiol-17β-glucuronide (1 μM)	Atorvastatin(10 μM) and Rifamycin SV (20 μM)	**20.5**	**NI**
OCT1	0-50 μM (Rux) 0-3 μM (M18)	HEK Flp In- OCT1	MPP+ (0.025μM)	Decynium (10 μM)	**9.1**	**NI**
OCT2	0-50 μM (Rux) 0-3 μM (M18)	HEK Flp In- OCT2	MPP+ (0.025μM)	Phenoxybenzamine (50 μM)	**9.8**	**NI**
OAT1	0-37.5 μM (Rux)0-3 μM (M18)	HEK Flp In-OAT1	Aminohyppuric acid (1 μM)	Probenecid (100 μM)	**NI**	**NI**
OAT3	0-37.5 μM (Rux)0-3 μM (M18)	HEK Flp In-OAT3	Estrone-3-sulfate (1 μM)	Probenecid (100 μM)	**6.5**	**NI**

NS: Not studied
NI: No inhibition at the highest concentration tested (50 μM for ruxolitinib; 3 μM for M18)
PHIP: 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine
MPP+: 1-methyl-4-phenylpyridinium
Source: Applicant's clinical pharmacology summary

2.4.3.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No.

2.4.3.7 What other co-medications are likely to be administered to the target patient population?

No expected co-medications.

2.4.3.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No.

2.4.3.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Not applicable.

2.4.3.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

No.

2.4.4 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

None.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Ruxolitinib solubility is pH dependent. The lowest solubility is 38 mg (free base)/250 mL at pH 7.5, and the highest solubility was > 130 mg/250 mL at pH 3.3 or lower. In Caco-2 cell monolayers, ruxolitinib exhibited an apparent permeability (Papp) of 21.5 x 10^{-6} cm/sec, which is greater than that of the high permeability model drug metoprolol (17.4 x 10^{-6} cm/sec). On July 30, 2009, the Office of New Drug Quality Assessment (ONDQA) of the FDA issued a letter to the applicant stating "The BCS committee reviewed the solubility, permeability, and dissolution information provided in the [IND] amendment and concluded that INCB018424 phosphate [Ruxolitinib phosphate] can be classified as a BCS Class 1 compound."

2.5.2 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal trial formulation in terms of comparative exposure?

The composition of the to-be-marketed formulation and formulation used in the pivotal trials are the same. The applicant did not conduct a formal bioavailability trial of the proposed to-be-marketed formulation. The applicant reported that ≥ 95% of radio-labeled ruxolitinib was absorbed following an oral dose of 25 mg delivered as a solution in the mass balance and metabolism study that was conducted in healthy volunteers with ^{14}C-ruxolitinib. In addition, on 12/22/10 ONDQA issued a letter to the applicant stating that "because we [FDA] already classified INCB018424 phosphate [Ruxolitinib phosphate] tablets as a BCS-Class 1 drug product, a waiver for the requirement to provide in vivo bioequivalence data comparing the disperse solution/suspension product and the intact tablet is appropriate." A request for such a waiver, in addition to a waiver for in vivo bioequivalence studies for ruxolitinib phosphate 10 mg, 15 mg, 20 mg and 25 mg tablets, was submitted with this application and is deemed acceptable by ONDQA in its 10/20/11 review of this NDA. Given this information the reviewer finds ≥ 95% estimate for bioavailability reasonable and no additional studies are required.

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

This issue will be reviewed by ONDQA per memorandum of understanding with OCP.

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Not applicable given the requested waivers are deemed acceptable by ONDQA in its 10/20/11 review of this NDA. Ruxolitinib is not considered a narrow therapeutic index drug. The major safety concern with increased exposure is cytopenia's and loss of symptomatic relief is the major efficacy concern with reduced exposure. Neither issue will likely occur immediately, and the intensive monitoring is built into the dose titration phase of therapy should minimize them.

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable given the requested waivers are deemed acceptable by ONDQA in its 10/20/11 review of this NDA.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Exposure from the tablet formulation of ruxolitinib (25 mg strength) was evaluated following an overnight fast or immediately following a high-fat meal in a two period cross-over study in 12 healthy, primarily male subjects. The tablet formulation evaluated was not the to-be-marketed formulation. Administration of the 25 mg ruxolitinib tablet with a high-fat, high-calorie meal prolonging the median (range) Tmax from 1 (0.25 - 3) to 2.5 (0.25 - 6) hours, and lowered the mean (CI_{90}) Cmax by 24% (76% (63% - 91%)) compared to fasting administration. The AUC appeared unaffected (104% (97 – 113%)). Pharmacodynamic parameters were not evaluated.

Given the CI_{90} for the relative Cmax was outside of the 80-125% equivalence criteria, a food effect can not be ruled out; however, the 24% reduction in Cmax alone is unlikely to significantly impact efficacy (see Section 2.2.4.1). Not using the to-be-marketed formulation of Ruxolitinib is a limitation, but is acceptable given requested waivers are deemed acceptable by ONDQA in its 10/20/11 review of this NDA. Therefore, the reviewer agrees with the applicant's proposal that Ruxolitinib may be administered without regard to meals.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

This issue will be reviewed by ONDQA per memorandum of understanding with OCP.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Not applicable given the requested waivers are deemed acceptable by ONDQA in its 10/20/11 review of this NDA.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

The suitability of delivering the tablet as a suspension in Sterile Purified Water, USP through a NasoGastric (NG) tube was investigated in vitro (INCYTE-CMC-11.11.1). Studies were carried out with 5 mg and 25 mg tablets through three commercially available NG tubes immediately following preparation and after 6 hours storage at ambient temperature. No degradation was observed in NG tube compatibility or stability samples. Assay values of all samples were in the range of 90.0-110.0% of label claim. One important limitation is the applicant did not assess whether tube feeding products affect NG administration of ruxolitinib. We defer to CMC and ONDQA regarding the validity of these results. The lack of stability information with tube feeding products should be noted in labeling.

As stated above ONDQA issued a letter to the applicant stating ruxolitinib can be classified as a BCS Class 1 compound. On 12/22/10 ONDQA issued another letter to the applicant stating that a waiver for the requirement to provide in vivo bioequivalence data comparing the disperse solution/suspension product and the intact tablet is appropriate. A request for such a waiver is

included in this submission. Given that ruxolitinib has a BCS Class 1 classification, the requested waivers are deemed acceptable by ONDQA (see 10/20/11 ONDQA review), and is deemed suitable for administration of drug in aqueous suspension through a nasogastric tube to patients who have difficulty swallowing by the CMC reviewer (see 10/20/2011 CMC review) we find that the impromptu creation of a tablet suspension from the tablet formulation is not expected to significantly impact bioavailability from a clinical pharmacology perspective.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

In submitted clinical studies the turbo ion spray LC/MS/MS method in the applicant's report DMB-07.111.1 was used to quantify ruxolitinib in human plasma with K_3EDTA as the anticoagulant. Ruxolitinib was extracted from 50 µL of human plasma by a liquid/liquid extraction procedure using methyl t-butyl ether (MTBE), with INCB028452 as the internal standard. The LC/MS/MS assay conditions are listed in Table 21.

Table 21: LC/ MS/MS Conditions for Assay DMB-07.111.1

System Controller	Shimadzu SCL-10Avp
HPLC pump:	Shimadzu LC-20AD
HPLC column:	Phenomenex, Synergi 4µ Polar-RP 80A, (30 x 2mm)
Isocratic Elution:	MPA (45%): 2 mM ammonium acetate
	MPB (55%): 100% acetonitrile
Flow Rate:	300 µL/min
Injection Volume:	5 µL
Retention Times:	INCB018424; 0.58 min
	INCB028452; 0.58 min
Autosampler:	Leap Technologies, CTC ANALYTICS PAL system
	Flush solvent 1: 50% methanol in 0.1% formic acid
	Flush solvent 2: 80% acetonitrile in water
LC/MS Instrument:	API-3000
Software version:	Analyst 1.4.1 (Build 6880)
Interface:	Turbo Ion Spray @ 450°C
Mode:	INCB018424, m/z 307.3⇨186.2 (Positive, MRM)
	INCB028452, m/z 311.3⇨190.2 (Positive, MRM)

Source: Applicant's report # INCYTE-DMB-07.111.1

Experimental results from the validation of this bioanalytical method are listed in Table 22. This validation appears consistent with the guidance "Bioanalytical Method Validation." This validation is acceptable.

Table 22: Summary of Validation Parameters for Assay DMB-07.111.1

Parameter[1]	**Experimental Results**
Calibration Curve[2]	All of standards within ± 15% of nominal concentration
Intra-Day Accuracy	Overall Range 90.9% to 108%
Inter-Day Accuracy	Overall Range 96.3 – 100%
Intra-Day Precision	Overall Range 1.8 – 6.0%
Inter-Day Precision	Overall Range 4.7 – 7.1%
Sensitivity	Mean Conc. Range 98.1 – 106% % CV Range 2.9 –4.6%
Selectivity	
Blank Matrix	No interference observed
Selectivity at LLOQ	%CV 2.9% with mean concentration 94.6% of nominal

Matrix Effect	Mean matrix effect 0.96
Extraction Efficiency	Mean extraction efficiency ranged from 87.2% to 92.7%
Chromatographic Carryover	No carryover detected
Stability	
Stock Solution	-0.7% difference from fresh solution after 82 days
Room Temperature	Mean ranged from -5.0% to 1.0% difference of original results
Freeze / Thaw (3 cycles)	Mean ranged from -0.6% to -1.4% difference of original results
-70°C Storage (372 days) Conc. Range: 4 - 900 nM	Percent difference -1.9 - 0.6%
Reinjection Reproducibility	Mean ranged from 96.4% to 101%
Dilution of Samples	Mean concentration 4685 nM Mean accuracy 93.7% with %CV 2.4%

1 The QC samples were prepared at concentrations of 1.00 (LLOQ), 3.0, 50.0, 800 and 1000. In addition, a dilution QC (QC6) was prepared at a concentration of 5000 nM
2 The calibration curve standard sample concentrations were 1.0, 2.5, 5.0, 10, 25, 50, 100, 250, 500, and 1000 nM
Source: Applicant's report # INCYTE-DMB-07.111.1

The applicant's cross validation DMB-08-151-1 using of this assay using K_2EDTA in place of K_3EDTA as the anticoagulant in human plasma ruxolitinib sample was also within these limits and deemed acceptable.

In submitted clinical studies where metabolites were evaluated the turbo ion spray LC/MS/MS method in the applicant's report DMB-10.14.1 was used to quantify ruxolitinib and selected active metabolites in human plasma with K_3EDTA as the anticoagulant. Ruxolitinib and the selected active metabolites were extracted from 100 µL of human plasma by a liquid/liquid extraction procedure using methyl t-butyl ether (MTBE), with INCB028452 as the internal standard. The LC/MS/MS assay conditions are listed in Table 23.

Table 23: LC/ MS/MS Conditions for Assay DMB-10.14.1

System Controller	Shimadzu CBM-20A
HPLC pump:	Shimadzu LC-20AD
HPLC column:	Waters, Atlantis T3 3µm (2.1x100mm)
Gradient Elution:	MPA: 10 mM ammonium formate pH 3.0
	MPB: 100% methanol
Flow Rate:	350 µL/min
Injection Volume:	5 µL
Retention Times:	INCB018424: 12.9 min, m/z 307.4→186.2
	INCB025257: 2.9 min, m/z 323.3→186.2
	INCB025258: 3.6 min, m/z 323.3→186.2
	INCB041092: 4.0 min, m/z 323.3→186.2
	INCB025264: 4.5 min, m/z 323.3→186.2
	INCB025262: 5.0 min, m/z 323.3→186.2
	INCB027598: 8.5 min, m/z 323.3→186.2
	INCB025256: 3.2 min, m/z 321.3→186.2
	INCB025255: 4.0 min, m/z 321.3→186.2
	INCB028452: 12.5 min, m/z 311.4→190.2
Autosampler:	Shimadzu, SIL-5000
	Flush solvent 1: 50% methanol in 0.1% formic acid
	Flush solvent 2: water
LC/MS Instrument:	API4000_GLP2 (Software: Analyst 1.4.1 (6880))
Interface:	Turbo Ion Spray @ 500°C
Mode:	Positive, MRM

Source: Applicant's report # INCYTE-DMB-10.14.1

Experimental results from the validation of this bioanalytical method are listed in Appendix 4.1. This validation appears consistent with the guidance "Bioanalytical Method Validation" with the exception that 1) long-term frozen stability (653 days) of the minor metabolites INCB025257 and INCB041092 were outside ±15% range for % diff from day 0, 2) the extraction recovery was consistent but low for the metabolites, and 3) cross-validation was not conducted for K_2EDTA samples actually collected in the metabolite studies. Despite these limitations this validation is considered adequate for quantification of the active metabolites. The applicant's states that concentrations of ruxolitinib in the metabolite studies that were above the limit of quantification (ULQL of 1000 nM) for DMB-10.14.1 were not reanalyzed because DMB-10.14.1 was not considered the primary assay quantification of ruxolitinib. Therefore, quantification of ruxolitinib by assay DMB-07.111.1 was used preferentially in the review of these metabolite studies.[1] The applicant did not cross validate assay DMB-10.14.1 to DMB-07.111.1.

2.6.2 Which metabolites have been selected for analysis and why?

Metabolites INCB025255 (IC_{50}= 0.43 μM), INCB025256 (IC_{50}= 0.97 μM), INCB025257 (IC_{50}= 1.5 μM), INCB025258 (IC_{50}= 0.78 μM), INCB025262 (IC_{50}= 0.66 μM), INCB025264 (IC_{50}= 1.25 μM), INCB027598 (IC_{50}= 1.5 μM), and INCB041092 (IC_{50}= 1.5 μM) are considered active based on their comparative pSTAT3 IC_{50} to ruxolitinib (IC_{50}= 0.28 μM). Combined these account for approximately 18% to the pharmacodynamic activity relative to ruxolitinib in healthy subjects. Active metabolites play a greater role in subjects with renal impairment (see Section 2.3.2). Therefore these eight metabolites were selected for analysis in Studies INCB 18424-138 (Healthy volunteers), INCB 18424-135 (rifampin DDI), INCB 18424-137 (hepatic impairment), INCB 18424-142 (renal impairment). Metabolites from these studies were not analyzed as part of each respective study, but rather *en masse* in a separate metabolite report. This split presentation is unorthodox and less than ideal for comprehensively reviewing the impact of metabolites on exposure and safety with the various intrinsic and extrinsic factors studied and recommending dosing adjustments. These data were ultimately deemed acceptable following extensive additional analysis by FDA.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total drug was measured for all moieties. The applicant reported that although determination of ruxolitinib's unbound fraction of was part of the PK analysis plan for both the renal and hepatic impairment studies, these samples were not actually collected and do not exist.[2] The applicant states that given 1) ruxolitinib binds primarily to albumin, 2) in vitro studies suggest that the mean fraction unbound of ruxolitinib increases 2.9%, 3.8%, 5.3%, 7.9% and 14.8% at human serum albumin concentrations of 50, 40, 30, 20 and 10 mg/mL, respectively, and 3) the mean albumin concentrations reported in the hepatic and renal studies were > 30 mg/mL (Table 24) a theoretical change in free fraction of less than 2-fold anticipated.

Table 24: Baseline Serum Albumin Concentrations from Intrinsic Factor Studies 137 and 142

Study	Mean±SD Serum Albumin Concentration (mg/mL)				
	Normal	Mild	Moderate	Severe	ESRD
Hepatic Impairment (study 137)	40 ± 2	40 ± 3	37 ± 4	33 ± 10	NA
Renal Impairment (study 142)	43 ± 2	41 ± 5	40 ± 1	37 ± 5	38 ± 3

Source: Applicants reports INCB 18424-137 and INCB 18424-142

Based on this theoretical change in the unbound fraction of ruxolitinib, the applicant decided further analysis of free ruxolitinib was not warranted. The applicant's decision to only evaluate total concentrations is not ideal because albumin concentrations alone may not fully explain the

[1] This information was received on August 1, 2011, in response to an information request by FDA for clarification regarding the discrepancy in ruxolitinib concentrations reported by the applicant using DMB-07.111.1 and DMB-10.14.1 in Study 137 and the associated metabolite report DMB.10.55.1.

[2] This information was received on July 12, 2011, in response to an information request by FDA for clarification of the absence of free concentration data despite inclusion the PK analysis plan for studies 137 and 142.

changes in protein binding observed in the setting of hepatic or renal impairment; however, is deemed adequate.

2.6.4 What bioanalytical methods are used to assess concentrations?

See Section 2.6.1

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

See Section 2.6.1 for the range of the standard curves. This range is adequate for the clinical studies given the validation of the dilution method in both assays.

For assay DMB-07.111.1, the calibration curves were fit by a weighted ($1/x^2$) linear regression and met all acceptance criteria. Coefficients of determination (r^2) were > 0.9932 for ruxolitinib in human plasma.

For assay DMB-10.14.1, the calibration curves were fit by a weighted ($1/x^2$) linear regression and met all acceptance criteria. Coefficients of determination (r^2) were > 0.9910 for ruxolitinib and its metabolites in human plasma.

2.6.6 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The LLOQ and ULOQ for both the DMB-07.111.1 and DMB-10.14.1 is 1.00 to 1000 nM for ruxolitinib and the selected metabolites.

2.6.7 What are the accuracy, precision, and selectivity at these limits?

See Section 2.6.1

2.6.8 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

See Section 2.6.1.[3]

2.6.9 What is the QC sample plan?

For both assay DMB-07.111.1 or DMB-10.14.1quality control samples, with at least two replicates, at a minimum of three concentrations (one within 3x of the LLOQ (low QC), one in the midrange (middle QC), and one approaching the high end of the range (e.g., 3.0, 50.0, 800)) were incorporated into each run. The results of the QC samples provide the basis of accepting or rejecting the run. At least 67% of the QC samples must be within 15% of their respective nominal (theoretical) values; 33% of the QC samples (< 50% at each concentration) can be outside the ±15% range of the nominal value. In addition the minimum number of samples (in multiples of three) should be at least 5% of the number of unknown samples or six total QCs, whichever is greater. This plan is acceptable.

2.6.10 How are PD Biomarkers identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

STAT3 phosphorylation was used as a pharmacodynamic (PD) marker for JAK activation and inhibition. The STAT3[pY705] ELISA is a commercially available solid phase sandwich ELISA (Biosource STAT3[pY705] ELISA kit, catalog# KHO0481) used to detect and quantify the level of STAT3 phosphorylation (STAT3p) in cytokine-stimulated human whole blood. Blood was stimulated with human IL-6 (R&D Systems, 50 µg/mL, stock concentration) or human thrombopoietin (TPO) (R&D Systems, 25 µg/mL stock concentration).

[3] Long term sample storage information was received on September 28 2011, in response to an information request by FDA regarding whether or not this parameter was assessed by the applicant.

ELISA Sensitivity was evaluated by comparing it to a Western Blotting analysis. Similar results were obtained from both assays using stimulated and unstimulated blood. Examination of whole blood samples from multiple donors in 30 individual experiments demonstrated induction of STAT3p levels in the range of 3 -16 fold following IL-6 stimulation (< 3 fold does not meet assay secifications).

Based on the linearity of the 8-point standard curve, the sensitivity of the STAT3p ELISA ranges from 0.9 Units/mL to 100 Units/mL (1 Unit is equivalent to 20 pg of phosphorylated STAT3 protein). Linear regression analysis of sample values versus the expected concentration yielded a correlation coefficient of 0.99.

In order to assess intra-assay variability, eight replicates of the same samples were run in a single assay. These samples included unstimulated, IL-6 stimulated and IL-6 stimulated in the presence of various concentrations of INCB018424. The calculated % CV values were less than 30% except for the highest concentration of INCB018424 (%CV = 86%) where many of the samples (6 of 8) had STAT3p levels near the lower limit of detection in the assay.

To assess intra-subject and inter-assay variability, 7-8 replicates of unstimulated and IL-6 stimulated whole blood samples from different donors were tested in separate assays on multiple days. Over multiple assays using multiple donors, the calculated % CV values were all less than 30%. The average unstimulated STAT3p levels were 22 U/mL (9 – 42 U/mL) and the average IL-6 stimulated levels were 103 U/mL (48 – 293 U/mL), giving an average 5-fold stimulation index (3 – 16).

Optimal stimulation concentration was at 100 ng/mL regardless of lot for IL-6, and 50-100 ng/mL for TPO depending on the lot used. The optimal time of cytokine stimulation required to achieve maximal stable levels of STAT3p was 15 minutes. The potency of INCB018424 in blocking IL-6 induced STAT3p in human whole blood was similar for both western analysis (IC50 = 300 nM) and ELISA (IC50 = 282 ± 54 nM).

Stability of the whole blood and optimal storage conditions was assessed. The whole blood cells retain the capacity to respond to IL-6 stimulation for at least 24 hours at room temperature (RT) or at 4^{o}C and potentially up to 3 days if stored at RT. INCB018424 remains stable when present in whole blood for at least 24 hours at RT.

This ELISA method and validation are acceptable.

3 DETAILED LABELING RECOMMENDATIONS

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 APPENDICES

4.1 Summary of Validation Parameters for Assay DMB-10.14.1

Parameter	ruxolitinib	INCB025255	INCB025256	INCB025257	INCB025258	INCB025262	INCB025264	INCB027598	INCB041092
Calibration Curve[1]	within ± 15%	within ± 15%	within ± 15%	within ± 15%	within ± 15%	within ± 15%	within ± 15%	within ± 15%	within ± 15%
Intra-Day Accuracy (Range)	94.6% – 100%	85.7% – 104%	89.0% – 102%	85.6% – 101%	88.1% – 104%	88.9% – 102%	86.8% – 98.6%	91.1% – 98.8%	88.4% – 101%
Inter-Day Accuracy (Range)	96.4 – 98.9%	93.2 – 98.6%	90.6. – 98.5%	95.1 – 96.3%	94.3 – 98.0%	94.5 – 97.4%	94.1 – 96.5%	93.9 – 97.1%	90.6 – 97.8%
Intra-Day Precision (Range)	0.8 – 6.3%	1.9 – 7.7%	1.4 – 6.6%	0.7 – 5.6%	1.9 – 6.0%	1.4 – 6.0%	0.6 – 6.0%	0.9 – 5.7%	1.6 – 6.3%
Inter-Day Precision (Range)	1.8 – 5.3%	4.7 – 7.6%	3.1 – 5.4%	3.8 – 8.5%	3.7 – 8.3%	3.6 – 6.9%	3.6 – 6.7%	2.8 – 4.6%	3.5 – 5.1%
Sensitivity mean %CV)	 95.6 – 98.7% 4.5 – 6.3%	 85.7 – 97.1% 2.3 – 7.7%	 90.4 – 97.7% 1.8 – 6.6%	 85.6 – 101% 3.6 – 5.2%	 88.1 – 104% 3.5 – 5.2%	 88.9 – 102% 2.8 – 3.7%	 86.8 – 97.8% 0.6 – 5.4%	 91.1 – 97.0% 2.4 –4.5%	 90.9 – 100% 1.6 –4.4%
Selectivity (6 Lots of Matrix)									
Blank Matrix[2]	Criteria Met	Criteria Met	Criteria Met	Criteria Met	Criteria Met	Criteria Met	Criteria Met	Criteria Met	Criteria Met
Selectivity at LLOQ (mean/%CV)	101%/ 4.5%	95.4%/ 3.7%	97.4%/ 5.3%	100%/ 4.0%	100%/ 2.9%	101%/ 3.5%	101%/ 5.2%	92.4%/ 4.4%	99.0%/ 4.6%
Matrix Effect (mean)	– 1.06	– 1.05	– 1.04	– 1.03	– 1.07	– 1.06	– 1.02	– 1.05	– 1.07
Extraction Efficiency (Range)[3]	86.6% to 99.7%	55.5% to 75.0%	57.9% to 67.3%	45.3% to 53.4%	44.7% to 52.5%	52.8% to 61.4%	58.0% to 66.9%	84.5% to 96.9%	71.5% to 81.6%
Chromatographic Carryover[4]	Criteria Met	Criteria Met	Criteria Met	Criteria Met	Criteria Met	Criteria Met	Criteria Met	Criteria Met	Criteria Met
Stability Stock Solution[5]	4.1%	-4.90%	-2.40%	4.50%	-0.10%	-9.40%	-6.10%	-4.80%	2.50%
Plasma Stability Room Temp. (Range % diff)	-1.7% to 1.5%	-0.7% to 14.2%	-7.1% to 10.9%	7.7% to 12.9%	6.9% to 11.6%	3.4% to 13.8%	3.0% to 13.0%	0.1% to 14.6%	1.9% to 14.1%
Plasma Freeze / Thaw (3 Cycles) (Range % diff)	-2.5% to 0.4%	-7.7% to -4.6%	-5.0% to 0.3%	-3.0% to 0.4%	-5.9% to 0.5%	-3.9% to -1.8%	-5.0% to -2.7%	-3.3% to -2.7%	-3.9% to -2.8%
-70 C Storage (653 days) (Range % diff)		-12.6 to 6.2%	0.1 to 8.2%	18.5 to 20.1%	13 to 15.2%	5.4 to 7.7%	6.1 to 10.6%	6.9 to 10.1%	13.3 to 19.2%
Reinjection Reproducibility (Range % diff)	-1.2% to 1.5%.	0.7% to 6.1%.	-2.1% to 6.8%.	-0.8% to 2.4%.	-2.2% to 1.7%.	-0.9% to 3.6%.	-4.0% to 5.3%.	-1.5% to 2.1%.	-3.9% to 4.9%.
Dilution of Samples (10 X) (mean/%CV)	99.7%/ 1.7%	99.1%/ 4.3%	98.8%/ 2.9%	99.9%/ 4.9%	100%/ 2.2%	99.5%/ 2.1%	100%/ 4.1%	102%/ 2.7%	98.9%/ 3.3%

1 The calibration curve standard sample concentrations were 1.0, 2.5, 5.0, 10, 25, 50, 100, 250, 500, and 1000 nM for INCB018424 and metabolites.
2 Criteria: No interference > 20% of LLOQ
3 QC concentration for Extraction Efficiency: 3.0, 50.0, 800 nM
4 Criteria: Peak area of blank ≤ 20% of mean LLOQ peak area
5 stored 391 days at 2 – 8 C.

Source: Applicant's report # INCYTE-DMB-10.14.1

4.2 Proposed labeling (Original and Annotated)

- See FDA EDR: \\Cdsesub1\evsprod\NDA202192\0000\m1\us\114-label\1141-draft-label

4.3 Consult Reviews

4.3.1 IRT

See the 09/06/2011 IRT consult available in DARRTS

4.3.2 Pharmacometrics

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

Application Number	NDA 202192
Submission Number (Date)	June 3, 2011
Compound (Dosing regimen)	Ruxolitinib phosphate tablets (INCB018424) Starting dose: 15 mg given orally BID, with an initial platelet count between 100,000 and 200,000/μL and 20 mg BID with an initial platelet count of > 200,000/μL. (b) (4) [redacted]
Clinical Division	DHP
Primary PM Reviewer(s)	Satjit Brar, Pharm.D., Ph.D., Jian Wang, Ph.D.
Secondary PM Reviewer	Christine Garnett, Pharm.D.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there evidence of exposure-response relationship for efficacy endpoints?

Yes, there is evidence of exposure-response for both spleen volume reduction and total symptom score for ruxolitinib in trials 351 and 352.

Evaluation of % spleen size reduction as a function of average daily total dose (Figure 1) yields a clear relationship with the maximal effect on the primary endpoint being at daily doses >40 mg (>20 mg BID). Patients with average daily doses of >20 mg (>10 mg BID) yielded a clinically relevant benefit of spleen volume reduction. Of note, patients administered average daily doses ≤10 mg (≤5 mg BID) did not yield a clinically meaningful benefit of 35% reduction in spleen volume.

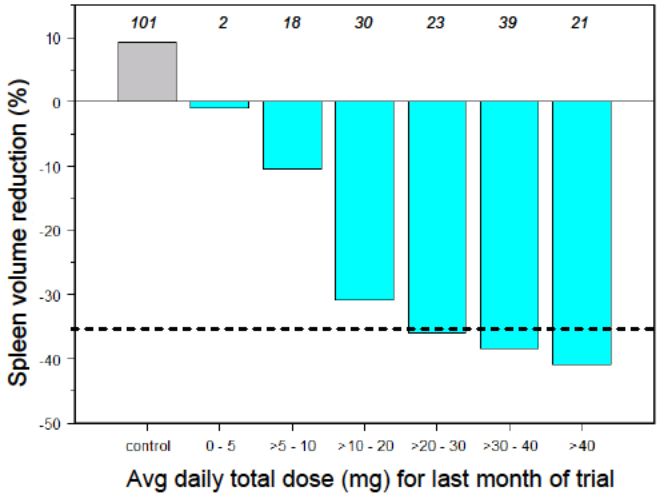


Figure 1. FDA analysis of spleen volume reduction as a function of average daily total dose for trial 351. Grey bar represents the placebo arm and the lighter grey bars represent the ruxolitinib average daily doses ranging from 0-5 mg to >40 mg. The dashed line represents the clinically relevant effect of 35% reduction. Number above bars represents the number of subjects in each dosing category.

With regard to exposure-response for spleen volume reduction and total symptom score, patients with pharmacokinetic samples from trial 351 (N=309) were divided into quantiles based on their model predicted steady state concentrations and the % of patients achieving a ≥35% spleen volume reduction and ≥50% total symptom score reduction were determined for each quantile (**Figure 2**).

Spleen volume reductions of ≥35% are observed in the patients with higher drug exposure in the upper quantiles (74%) compared to in the lower quantiles (9%). However, the difference in spleen volume reduction may not only be due to ruxolitinib concentrations but is also

likely due to other factors that are not balanced between the quantiles. For example, it was shown from the PK/PD model for spleen volume reduction that female, JAK 2V617F positive patients have more response compared to male JAK 2V617F negative patients (Figure 7).

To account for these confounding factors, the proportion of patients who achieved a ≥35% reduction in spleen volume from baseline to last observation was analyzed using a multivariate logistic regression model, including baseline factors (Table 9). The step-wise logistic regression analysis identified average ruxolitinib steady state concentration, sex and mutation status as significant predictors of ≥35% SVR in trial 351. The final model parameters are in Table 1 below. As the titration of ruxolitinib is primarily based on SVR and safety (i.e., platelet count), dose adjustment is not proposed.

Table 1. Parameter Estimates from Logistic regression Analysis for Responders (≥35% spleen volume reduction)

Predictors (Reference / comparator)	Parameter Estimate	Std Error	p-value	Odds ratio	Lower 95%CI	Upper 95%CI
Sex (Female / Male)	-0.798	0.328	***0.032***	1.72	1.24	2.51
V617F Mutation (Positive / Negative)	-0.636	0.311	***0.041***	2.14	1.48	6.22
Average Css (log transformed)	2.29	0.446	***0.029***	3.99	1.53	8.52

For total symptom score, greater proportion of patients who achieved >50% reduction were observed in the upper quantiles (64%) compared to the lower quantiles (40%). No covariates were observed in the response rates of total symptom score using logistic regression analysis.

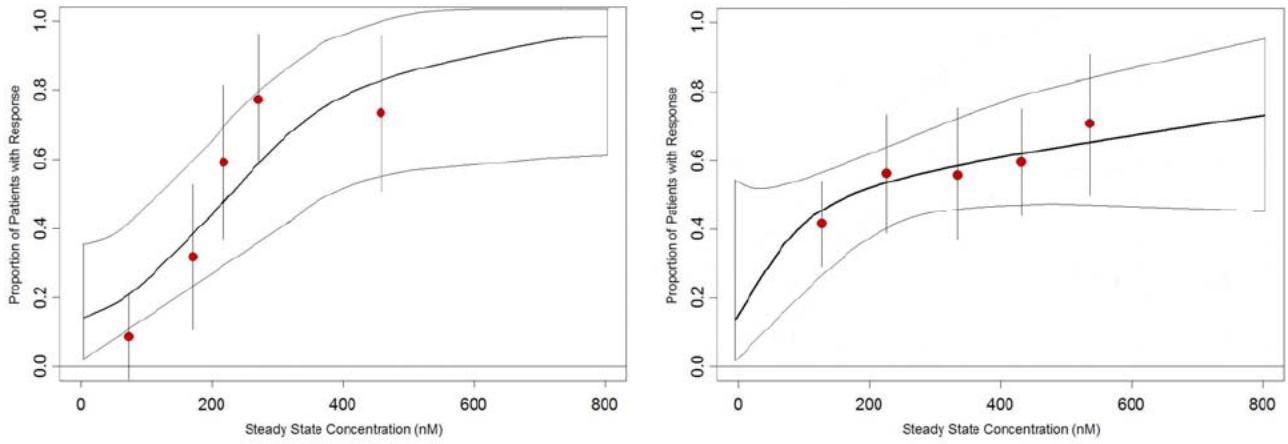


Figure 2. Proportion of patients achieving ≥35% spleen volume reduction (left) and ≥50% reduction in total symptom score (right) versus average steady state concentrations of ruxolitinib in trial 351. Solid round symbols represent the observed efficacy measure in each $C_{ss\ average}$ quantile. The vertical black bars represent the 95% confidence interval. The logistic regression is denoted by the solid black line along with the 95% confidence interval for the regression.

1.1.2 Is there evidence of exposure-response relationship for safety measures?

Yes, there is evidence of exposure-response for safety measures including platelet count and hemoglobin.

As the case for efficacy, the evaluation of exposure-response for platelet count and hemoglobin incorporated patients with pharmacokinetic samples from trial 351 (N=309) Observations were divided into quantiles based on their model predicted steady state concentrations and the platelet count and hemoglobin were determined for each quantile (Figure 3).

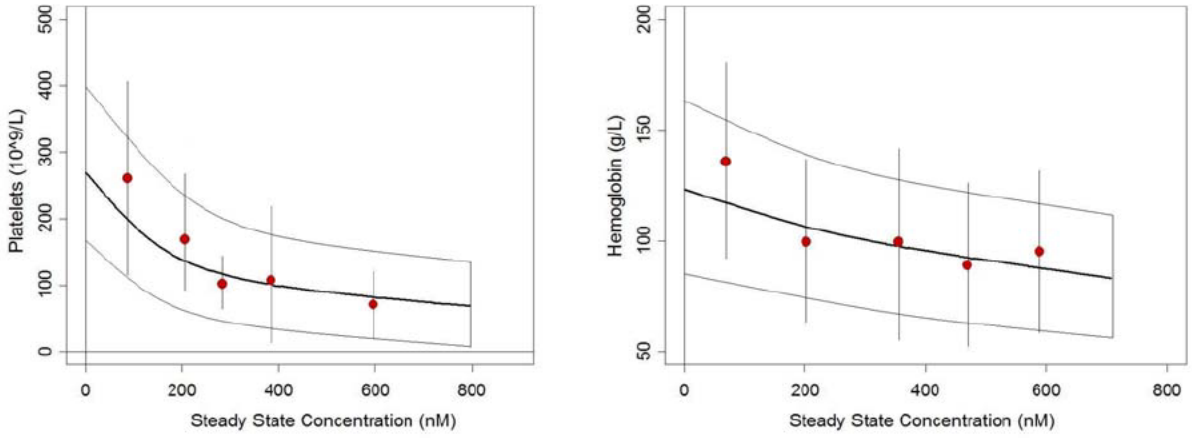


Figure 3. FDA Analysis of platelet count (left) and hemoglobin (right) versus average steady state concentrations of ruxolitinib in trial 351. Solid round symbols represent the observed efficacy measure in each $C_{ss\ average}$ quantile. The vertical black bars represent the 95% confidence interval. The model predicted relationship is denoted by the solid black line (with 95% confidence interval).

The exposure-response relationship depicts a decrease in platelet count with increasing ruxolitinib exposure. Approximately a 2.7 fold-difference in platelet count is observed between the lowest quantile ($C_{ss\ average}$ ~78 nM) and the highest quantile ($C_{ss\ average}$ ~588 nM). The exposure-response relationship for changes in platelet counts was also evaluated and no covariates, including baseline platelet count, could predict response.

This indicates that subjects with lower platelet counts are not likely to be inherently more sensitive to ruxolitinib, but rather, that they may be more prone to thrombocytopenia as their platelet counts decrease from a lower baseline value.

For hemoglobin measures, the exposure-response relationship depicts a gradual decrease in hemoglobin with increasing ruxolitinib exposure. Based on graphical analysis of binned quantiles, approximately a 20 g/L difference in hemoglobin is observed between the lowest quantile ($C_{ss\ average}$ ~51 nM) and all other quantiles. Further assessment of the exposure-response relationship for hemoglobin yielded no other covariates for predicting response.

1.1.3 Does the exposure-response relationship for efficacy and safety support the proposed dosing?

The exposure-response relationship for efficacy (i.e., SVR and TSS) and safety *does support* the recommended initial dose based on platelet count, as proposed in the label. The PK/PD model for platelet count over time was utilized to perform simulations for the continual dosing of 15 mg BID for those patients with an initial platelet count at 100 $x10^9$/L and 20 mg BID with an initial platelet count of $200x10^9$/L (Figure 5). On average, platelet counts were above the threshold of $50x10^9$/L for both dosing groups, further supporting the Sponsor's dosing justification for initial platelet count.

The exposure-response relationship for efficacy and safety *does support* the titration of ruxolitinib to 25 mg BID, as proposed in the label. Based on the dose-response analysis for the reduction in spleen volume (Figure 1) the maximal effect was observed at daily doses >40 mg (>20 mg BID). Moreover, 81% of the patients who were titrated to an average daily dose of >40 mg had reached a clinically relevant effect of >35% reduction in spleen volume and >50% reduction in total symptom score (Table 2).

Table 2. Percent of Responders Who Reached Both Efficacy Endpoints in Each Average Daily Dose Group

Average daily dose (mg)	>40	>30-40	>20-30	>10-20	>5-10	0-5
% reaching both TSS and SPV	81%	39%	8%	0%	0%	0%

On the other hand, patients on average daily doses ≤10 mg (≤5 mg BID) did not yield a clinically meaningful benefit for spleen volume and total symptom score. (b) (4) [redacted] Importantly, if a patient were to be maintained at a dose of 5mg BID, a high risk of thrombocytopenia (platelet < 50 g/L) would be present with minimal, if any, benefit in spleen volume reduction and total symptom score. Using the exposure-response relationship for platelet count, simulations

for a typical patient with a baseline platelet count of 50 g/L, maintained at a 5 mg BID dose, was performed (Figure 4). Results show that an individual, with low platelet count, maintained on a dose of 5 mg BID would be at risk from thrombocytopenia.

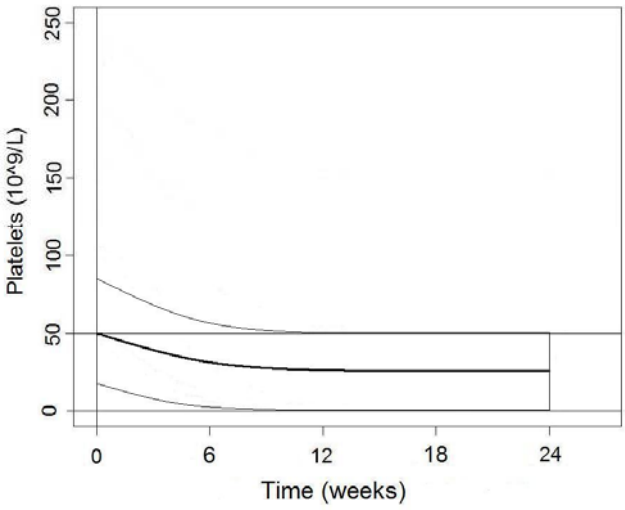


Figure 4. Simulated average platelet count over time for maintaining a starting dose of 5 mg BID for a baseline platelet count of 50 x 10^9/L. Dark line represents model prediction along with 95% prediction interval. The minimum threshold for platelet count is denoted by the solid black line at 50 g/L.

1.2 Recommendations

Dose-response for efficacy and safety does not support maintenance dose of 5 mg BID, based on the following:

1) No clinical benefit in spleen volume reduction or total symptom score is observed for average total daily doses of ≤10 mg per day.
2) The combined effect of low baseline platelet count and ruxolitinib's deleterious effect on platelets increase the risk of thrombocytopenia.
3) This dose has not been evaluated in clinical trials.

Patients with baseline platelet counts < 100x 10^9/L should not be maintained on 5 mg twice daily.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

2. DOSAGE AND ADMINISTRATION

2.2 Monitoring and Dose Modification Guidelines

(b) (4)

[redacted]

2 PERTINENT REGULATORY BACKGROUND

This application is under consideration for an accelerated approval for the treatment of patients with myelofibrosis (including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis). Efficacy and safety of ruxolitinib were evaluated in two Phase 3 registration trials (pivotal trial 18424-351 and supportive trial CINC424A2352). Type B meetings with FDA were held in December of 2008 and November of 2009. Orphan drug status was granted in September 2008. Fast track designation was granted on October 2009.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Exposure-Response Analysis for Effectiveness

The sponsor conducted exposure-response analysis for spleen volume and total symptom score.

3.1.1 Data

Data from studies INCB 18424-251 (Study 251), INCB 18424-351 (Study 351), and INCB 18424-352 (Study 352) were used in this analysis.

3.1.2 Methods and Results

Exposure-Response Analysis for Spleen Volume:

The final population PK/PD model for spleen volume changes was an indirect response model that characterized the effect of INCB018424 through an inhibitory E_{max} model applied to the production rate (k_{in}) of spleen volume. The final model for the spleen volume at 24 weeks is as follows:

$$\frac{dSV}{dt} = k_{in} \times I(C_{ss}^{ave}) - k_{out} \times SV$$

$$I(C_{ss}^{ave}) = 1 + E_{plc} - \left(\frac{I_{\max} \cdot C_{ss}^{ave}}{IC_{50} + C_{ss}^{ave}} \right)$$

Where the covariate effects on IC_{50} were described using the following equation:

$$IC_{50\,j} = \left(414 \times (1 - JAK_j) + 206 \times JAK_j\right) \times (1 - 0.41 \times SEXF_j)$$

Gender and JAK2V617F mutation status were both significant predictors of IC_{50}. Females exhibit a 41% reduction in IC_{50} compared to males. No statistically significant influence was found on spleen volume for the other covariates tested.

Table 3. Parameters of the Final Indirect Response PK/PD Model for Changes in Spleen Volume

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV[a])	
	Population Mean	%SEM[b]	Final Estimate	%SEM
E_{plc}[c] (cm^3)	0.0505	32.9	0.111 SD[d]	23.0
k_{out}[e] (hr^{-1})	0.00145	16.2	63.7	34.0
I_{max}[f]	0.765	9.14	NE[g]	NE
IC_{50}[h] for subjects with negative JAK[i] V617F mutation status (nM)	414	17.0	54.3	43.7
IC_{50} for subjects with positive (or unknown) JAK2V617F mutation status (nM)	206	14.5		
Proportional shift in IC_{50} for female subjects	-0.410	25.9		
RV[j] (%CV)	9.18	17.1	NA[k]	NA

[a] %CV= percent coefficient of variation, [b] %SEM = percent standard error of the mean, [c] E_{plc} = placebo effect, [d] SD=standard deviation, [e] k_{out}=first-order spleen volume removal rate constant, [f] I_{max}= maximum fractional inhibition in spleen volume, [g] NE=not estimated, [h] IC_{50} = $Css_{(ave)}$ producing 50% of maximal inhibition (nM), [i] JAK = Janus kinase, [j] RV=residual variability, [k] NA=not applicable.

(Source: Table 30 from Sponsor's Population PK/PD Modeling Analysis Report - dmb-11-05-1, page 159)

Reviewer's comments:

Sponsor's population PK/PD analysis is generally adequate and acceptable. The sponsor's conclusion that there is an exposure-response relationship for spleen volume is consistent with reviewer's conclusion.

Exposure-Response Analysis for MFSAF Total Symptom Score (TSS):

The population PK/PD model for total symptom score was developed using only data collected in Study 351. The final population PK/PD model for the time course in TSS was an indirect response model that characterized the effect of INCB018424 through an inhibitory E_{max} model applied to the total symptom score equilibration rate constant (k_{out}). The final model for the time course of TSS is as follows:

$$\frac{dTSS}{dt} = k_{out} \times (UTSS - TSS)$$

$$UTSS_{logit} = \log it(TSS_{BL}) + E_{plc} - \left(\frac{I_{max} \cdot (C_{ss(ave)})^{\gamma}}{IC_{50}{}^{\gamma} + (C_{ss(ave)})^{\gamma}} \right)$$

$$\log it(TSS_{BL}) = \log \left(\frac{\frac{TSS_{BL}}{60}}{1 - \frac{TSS_{BL}}{60}} \right)$$

$$UTSS = 60 \times \left[\frac{\exp^{UTSS_{logit}}}{1 + \exp^{UTSS_{logit}}} \right]$$

Where, TSS is the total symptom score (0 to 60), k_{out} is the first-order TSS equilibration rate constant, UTSS is the ultimate TSS, TSS_{BL} is the baseline TSS, $Css_{(ave)}$ is the average daily steady state concentration for the 4-week time period prior to the PD observation, E_{plc} is the placebo effect, I_{max} is the maximum inhibition of TSS production, and γ is the Hill coefficient describing the steepness of the exposure-response relationship. Of note, baseline total symptom score and blood transfusion status (eight weeks prior to screening) were each statistically significant predictors of E_{plc}. No covariates were found to be statistically significant predictors of drug effect parameters (I_{max}, γ).

Table 4. Parameters of the Final Indirect Response PK/PD Model for 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] E_{plc} = placebo effect, [d] SD=standard deviation, [e] k_{out}=first-order TSS equilibration rate constant, [f] I_{max}= maximum inhibition in TSS, [g] IC_{50} = $Css_{(ave)}$ producing 50% of maximal inhibition (nM), [h] NE=not estimated, [i] NA=not applicable, [j] RV=residual variability.

(Source: Table 41 from Sponsor's Population PK/PD Modeling Analysis Report - dmb-11-05-1, page 170)

Reviewer's comments:

Sponsor's population PK/PD analysis is generally adequate and acceptable. The sponsor's conclusion that there is an exposure-response relationship for Total Symptom Score is consistent with reviewer's conclusion.

3.2 Exposure-Response Analysis for Safety

The sponsor conducted exposure-response analysis for platelet count, hemoglobin levels and absolute neutrophil count.

3.2.1 Data

Data from studies INCB 18424-251 (Study 251), INCB 18424-351 (Study 351), and INCB 18424-352 (Study 352) were used in this analysis.

3.2.2 Methods and Results

Exposure-Response Analysis for platelet count:

Three separate semi-mechanistic PK/PD models were constructed to characterize the time course of platelet counts in response to INCB018424 exposure. These three models were developed using different subsets of subjects from the study population, including (A) a per protocol population (majority of study participants) regardless of dose changes and blood transfusions, (B) study participants that did not receive any blood transfusions during the entire course of study enrollment, and (C) study participants that received a consistent dose amount throughout the study duration (e.g., no dose escalations or reductions occurred). The assessment of model A is presented here.

The final population PK/PD model for the time course in platelet counts in the per protocol population was an indirect response model that characterized the effect of INCB018424 through an inhibitory E_{max} model applied to the production rate (k_{in}) of platelets. 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 base (and final) model for the time course of platelets is as follows:

$$\frac{dPLT}{dt} = k_{in} \times I(C_{ss}^{ave}) - k_{out} \times PLT$$

$$I(C_{ss}^{ave}) = 1 - \left(\frac{I_{max} \cdot C_{ss(ave)}}{IC_{50} + C_{ss(ave)}} \right)$$

Where, PLT is the platelet count (10^9/L), k_{in} is the is the zero-order platelet count formation rate constant (10^9/L/hr), k_{out} is the first-order platelet removal rate constant, $Css_{(ave)}$ is the average daily steady state concentration for the time period between the PD observation, I_{max} is the maximum inhibition of platelet count production, IC_{50} is the $Css_{(ave)}$ producing 50% of maximal inhibition of platelet count formation.

Table 5. Parameters of the Final Indirect Response PK/PD Model for Platelet Count (Per-protocol)

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV[a])	
	Population Mean	%SEM[b]	Final Estimate	%SEM
Baseline Platelet Count (10^9/L)	276	3.95	56.7	7.80
k_{out}[c] (hr^{-1})	0.00130	10.3	112	11.2
I_{max}[d]	1.00	FIXED	NE[e]	NE
IC_{50}[f] (nM)	204	7.60	98.2	18.9
RV[g] (SD[h], log_e units)	0.239	5.95	NA[i]	NA

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

(Source: Table 43 from Sponsor's Population PK/PD Modeling Analysis Report - dmb-11-05-1, page 173)

Reviewer's comments:
Sponsor's population PK/PD analysis is generally adequate and acceptable. The sponsor's conclusion that there is an exposure-response relationship for platelet count is consistent with reviewer's conclusion.

3.3 Population PK Analysis

3.3.1 Methods

Sponsor performed population PK modeling utilizing data from one phase 1/ 2 (Study 251) and two phase 3 studies (Studies 351 and 352). Primary objective of the population PK analysis was to characterize the population pharmacokinetics of INCB018424 and to quantify sources of variability in INCB018424 exposure.

Detailed descriptions of all data stratified by studies are provided in Table 6.

Table 6: Studies Used for the Population PK Model

Protocol	Study Design	Population	Number of Subjects	Treatment Groups	Dosing Duration
251	Open-label Phase 1/2	PMF or PPV-MF, or PET-MF	154	Part 1: 25 mg and 50 mg twice daily. Part 2: 10 mg and 25 mg twice daily; 25 mg, 50 mg, and 100 mg once daily. Part 3: 10 mg, 15 mg, and 25 mg twice daily; 50 mg, 100 mg, and 200 mg once daily.	Up to 33 cycles (cycle = 28 days)
351*	Randomized, double-blind, placebo-controlled Phase 3	PMF, PPV-MF, or PET-MF	309	Subjects with baseline platelet count > 200,000/μL: begin dosing at 20 mg twice daily. Subjects with baseline platelet count of 100,000- 200,000/μL: begin dosing at 15mg twice daily.	24 weeks
352 *	Randomized, controlled, compared to best available therapy Phase 3	PMF, PPV-MF, or PET-MF	219	Subjects with baseline platelet count > 200,000/μL begin dosing at 20 mg twice daily. Subjects with baseline platelet count of 100,000-200,000/μL begin dosing at 15mg twice daily.	48 weeks

* Standardized dosing paradigm used to determine dose adjustments for safety and efficacy.

PK data were evaluated using NONMEM Version 7.0 (Icon US, Hanover MD). The final model was evaluated for performance using several tests, including evaluation of an external validation database and visual predictive check (VPC) evaluation.

All exploratory data analyses and presentations of data were performed using S-Plus and SAS. NONMEM runs were executed using PDx-POP for NONMEM Version 4.0. Generalized additive model (GAM) analysis was performed using Xpose 3.10.S-Plus software was used for exploratory graphical analysis of covariates.

3.3.2 Results

Parameter estimates for fixed effect and random effects with standard errors are presented in Table 7 below. Basic goodness of fit plots from the sponsor's final model is presented in the Appendix.

Table 7 : Parameter Estimates and Standard Errors from the INCB018424 Final Population Pharmacokinetic Model – Sponsor's analysis

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] k_a = first-order absorption rate constant
[d] $ALAG_1$ = absorption lag time
[e] NE = not estimated
[f] CL/F = apparent oral clearance
[g] V_c/F = apparent volume of distribution for the central compartment,

$$V_c / F_j = 58.6 \times \left(\frac{WTKG_j}{72.9} \right)$$, where j represents the jth subject

[h] V_p/F = apparent volume of distribution for the tissue (peripheral) compartment
[i] Q/F = apparent intercompartmental clearance
[j] RV = residual variability
[k] NA = not applicable

(Source: Table 16 from Sponsor's Population PK Modeling Analysis Report - dmb-11-04-1, page 65)

3.3.3 Sponsor's Conclusions

- The PK of INCB018424 are well described by a 2-compartment disposition model with first-order absorption (with an absorption lag time) and linear elimination.

- Apparent oral clearance is 22.1 L/hr and 17.7 L/hr for a typical male and female subject, respectively, with 39.1 % CV unexplained IIV.
- The apparent central volume of distribution increases linearly with respect to body weight and is 58.6 L for a typical subject weighing 72.9 kg. The remaining unexplained variability in V_c/F is 28.0 %CV. The apparent total volume of distribution at steady-state is 69.8 L for a typical subject, with 102.0 %CV unexplained IIV in the apparent peripheral volume of distribution.
- Absorption of INCB018424 is rapid, with a short absorption lag time (approximately 3 minutes) and an estimated absorption half-life of approximately 10 minutes.
- Although gender and body weight were statistically significant predictors of INCB018424 PK, the geometric mean ratios in both cases fell within 50% to 200% bounds.
- No covariates were found to be statistically significant predictors of k_a or V_p/F.
- Based upon formal covariate analysis, no notable differences were observed between subjects with varying degrees of hepatic or renal dysfunction.
- Based upon 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 INCB018424 PK.
- The predicted typical value of the apparent terminal elimination half-life using the parameter estimates from the final population model was 3.76 hours and 4.07 hours for male and female subjects, respectively, weighing 72.9 kg. The individual estimates of the apparent terminal elimination half-life were moderately variable with means (%CV) of 4.72 hours (64.5%) and 4.12 (41.4%) for the Phase 1/2 and Phase 3 subjects, respectively.
- The study data did not allow for a conclusive assessment of dose proportionality, although based upon the available data and the analyses performed, the PK of INCB018424 appear dose proportional for doses ranging from 10 mg to 200 mg.

Reviewer's comments on Sponsor's Population PK Analysis:

- *Reviewer's analysis showed that log-transformed data produces better goodness-of-fit. The parameter estimates (e.g. CL) are comparable between reviewer's and sponsor's analysis. Please see reviewer's analysis in Section 3 for details.*

- *The effects of both sex and body weight was further explored as covariates for PK. Inclusion of sex as a covariate for CL resulted in the reduction in the objective function value (OFV) by 42. Inclusion of body weight as covariate for CL covariates resulted in the reduction in the objective function value (OFV) by 36. By using sex or body weight as the covariate, the inter-patient variability for CL are 40% and 42%, respectively. See the section of Reviewer's analysis for details.*

- *Sponsor's population PK analysis is generally adequate and acceptable.*

4 REVIEWER'S ANALYSIS

4.1 Objectives

The reviewer's analysis objectives are:

1. to determine if the exposure-response relationship for the efficacy endpoints: spleen volume reduction and total symptom score;
2. to determine is there is exposure-response relationship for safety endpoints, platelet count and hemoglobin;
3. to determine is the exposure-response relationship for efficacy and safety supports the proposed dosing recommendations;
4. to quantify sources of inter-patient variability in INCB018424 exposure.

4.2 Methods

4.2.1 Data Sets

Data sets used are summarized in Table 8.

Table 8. Analysis Data Sets

Study Number	Name	Link to EDR
INCB 18424-351 (Study 351)	aseff3.xpt	\\Cdsesub1\evsprod\NDA202192\0000\m5\datasets\incb-18424-351\listings
INCB 18424-352 (Study 352)	aseff3.xpt	\\Cdsesub1\evsprod\NDA202192\0000\m5\datasets\incb-18424-352\listings
pooled PK w/ phase 2 study INCB 18424-251 (Study 251)	pk_all.xpt	\\cdsesub1\EVSPROD\NDA202192\0000\m5\datasets \\cdsesub1\EVSPROD\NDA202192\0000\m5\datasets\dmb-11-04-1\analysis\programs\pk
pooled PK/PD	pd2votc.xpt pd2votw.xpt pd2mfsa.xpt pd2plta.xpt	\\Cdsesub1\evsprod\NDA202192\0000\m5\datasets\dmb-11-04-1\analysis\datasets

4.2.2 Software

S-PLUS, SAS and NONMEM were used for the reviewer's analyses. R 2.10.1 (www.r-project.org) was used in combination with the population PK tool library in order to generate diagnostic and pertinent covariate plots.

4.2.3 Models

For simulations, the models described in section 3.2.2 were used for both the efficacy measures (i.e., spleen volume and total symptom score) and safety measures (i.e., platelet count).

4.3 Results

4.3.1 Exposure-Response Analysis

Dose and exposure-response relationship was conducted for the reduction in spleen volume (SPV) and total symptom score (TSS) for the efficacy the pivotal trial. Safety measures, including platelet counts and hemoglobin, were also assessed for an exposure-response relationship.

For the dose-response relationship the exposure measure used was the average daily total dose for the last month of the trial. For the exposure-response relationships, the exposure measure used for the analysis was the average steady state ruxolitinib ($C_{ss\ average}$), calculated for each subject from the average daily dose and the individual estimate of apparent drug clearance derived from the population PK model.

The PK/PD model was further utilized to perform simulations for the proposed dosing of 15 mg BID for patients with platelet count between 100 and 200 $x10^9$/L and 20 mg BID with an initial platelet count of > 200 $x10^9$/L (Figure 5). In addition and simulation was performed evaluating 5 mg BID for those patients with low platelet counts (patients with platelet counts between 50 $x10^9$/L and 100 x 10^9/L) (Figure 4).

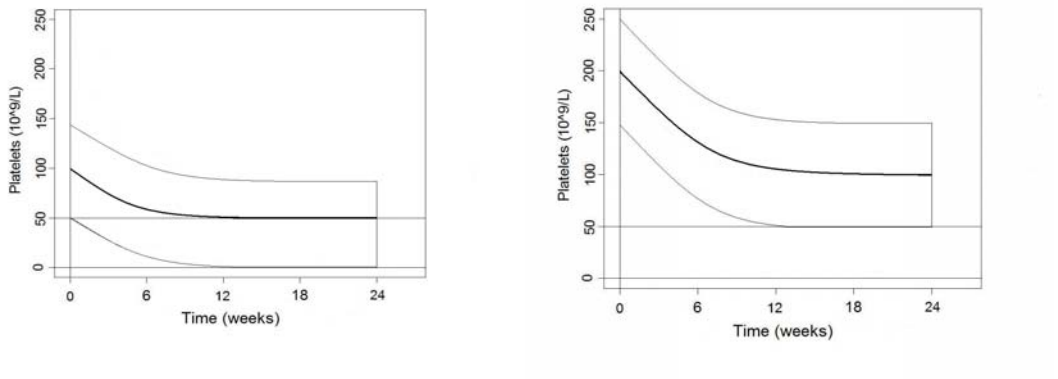


Figure 5. Simulated average platelet count over time for a maintenance dose of 15 mg (left) and 20 mg (right). Dosing varied according to baseline platelet count, and simulations

represent the worst-case scenario for the platelet range. The minimum threshold for platelet count is denoted by the solid black line at 50 x10^9/L.

4.3.2 Subgroup Analysis

A differential response in spleen volume reduction was observed with sub group populations within the registration trials. Response rates in trial 351, for different population subgroups, are shown in the figure below.

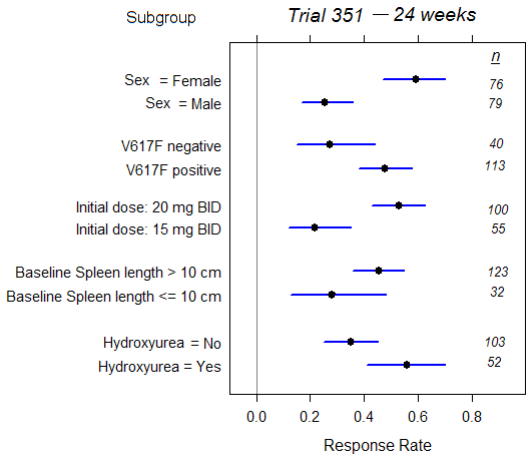


Figure 6. Forest plot evaluating the individual covariate effects on response rates in spleen size reduction for the pivotal trial.

Sex differences in response rates differed in trial 351 with females having a response rate of ~ 60% while males ~25%. Moreover, 47% of JAK2V617F mutation status positive patients were responders compared to the ~27% mutation negative patients. To further explore the response rates of sex and mutation status, simulations were performed to assess the time course of spleen volume reduction.

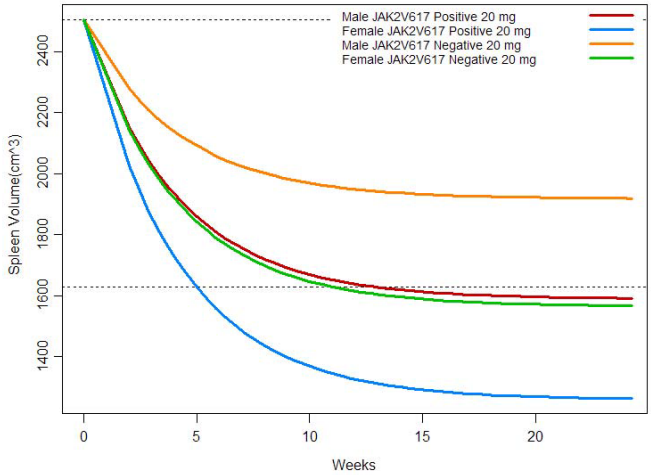


Figure 7. Simulated spleen volume vs. time for both mutation status and sex differences. Females respond more than males and mutation positive patients more than negative patients. PK differences in exposure between females and males, these differences only explain a minor portion of the overall difference in response rates between males and females, suggesting a PD difference between sexes. Based on the PK/PD model for spleen volume, IC50 for women is ~59% of that for men.

To account for these confounding factors, the proportion of subjects who achieved a ≥35% reduction in spleen volume from baseline to last observation was analyzed using a logistic regression model, including factors such as ruxolitinib exposure (average steady state concentration), baseline spleen volume, age, prior hydroxyurea use, gender and JAK 2V617F mutation. The step-wise logistic regression analysis identified average ruxolitinib steady state concentration, as well as V617F mutation and gender, as significant predictors of response in trial 351. All factors deemed as significant were tested for interaction between the factors. No significant interactions were observed in the analysis.

Table 9. Parameter Estimates from Multivariate Logistic regression Analysis for Responders (≥35% spleen volume reduction)

Predictors (Reference / comparator)	Parameter Estimate	Std Error	p-value	Odds ratio	Lower 95%CI	Upper 95%CI
Sex (Female / Male)	-0.856	0.414	***0.037***	1.61	1.18	2.23
Age (≤65 / >65)	0.42	0.391	0.643	0.791	0.215	2.74
Baseline Spleen-Volume (≤median / >median)	0.000314	0.00022	0.066	1.46	1.02	2.12
Prior hydroxyurea use (No / Yes)	0.161	0.192	0.526	1.14	0.436	1.95
V617F Mutation (Positive / Negative)	-0.724	0.382	***0.043***	2.27	1.37	7.83
Average Css (log transformed)	3.42	0.510	***0.027***	4.21	1.48	9.13
Sex : V617F Mutation interaction	0.167	0.056	0.081			

4.3.3 Dose-response and Achieving Both Spleen Volume Reduction and Total Symptom Score

A discordance was observed with the proportion of patients who achieved both clinically relevant spleen volume reduction (SVR ≥35%) and a clinically relevant reduction in total symptom score (TSS≥50%) (see Table 10 below). Graphical exploration of the dose-

response relation for both endpoints was performed to determine if average daily dose was a determining factor for clinically relevant achievement of both endpoints.

Table 10. Percent of Responders Who Reached Both Efficacy Endpoints

	Reduction in SVR≥35%	Reduction in TSS≥50%
Evaluable patients	155	148
Responders	65	68
Patients reaching both	35/65	35/68
% reaching both	54%	51%

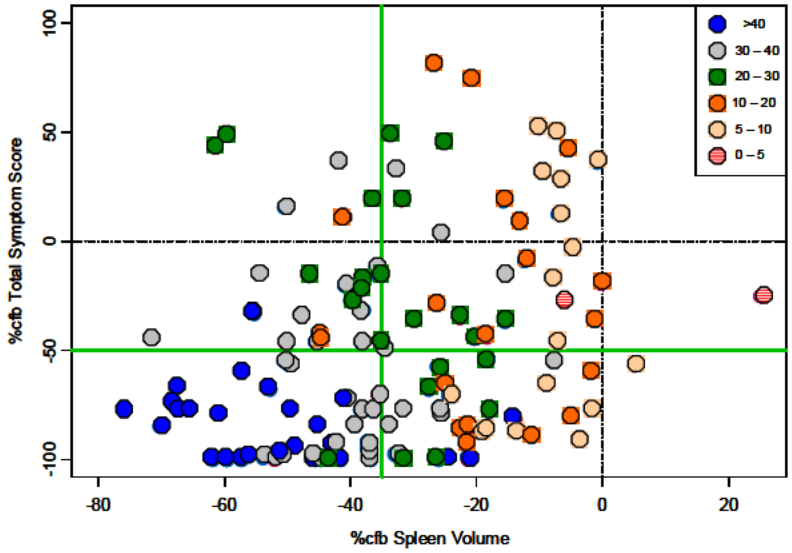


Figure 8. Individual level data for % change from baseline (cfb) in total symptom score and spleen volume reduction for all active arm patients in trial 351. The solid lines represent the clinically beneficial effect of 35% spleen volume reduction and 50% reduction in symptom score. Each individual is categorized by average total daily dose with the highest average daily total dose being 40 mg (>20 mg BID).

Table 11. Percent of Responders Who Reached Both Efficacy Endpoints in Each Average Daily Dose Group

Average daily dose (mg)	>40	>30-40	>20-30	>10-20	>5-10	0-5
% reaching both TSS and SPV	81%	39%	8%	0%	0%	0%

4.3.4 Population Pharmacokinetic Analysis

An independent analysis for population pharmacokinetics was conducted. Reviewer's analysis showed that log-transformation of the PK data improves the model fit. The difference of the parameter estimates (e.g. CL) are slightly different between reviewer's analysis and sponsor's analysis (see Table 12).

Table 12. Summary of Ruxolitinib population PK model parameter estimates.

	Fixed-Effects Parameters	Estimate	RSE(%)	CI95
1	CL/F (Clearance (L/hr))	23.1	3.506	(21.51-24.69)
2	V2/F (Central volume of distribution	59.1	2.792	(55.87-62.33)
3	Q (Q)	1.74	13.68	(1.274-2.206)
4	V3 (V3)	14.3	25.59	(7.127-21.47)
5	KA (KA)	3.56	5.421	(3.182-3.938)
6	ALAG1 (ALAG1)	0.057	4.632	(0.05183-0.06217)
7	CLFE	18.1	3.536	(16.85-19.35)
8	PROP	0.451	5.455	(0.4028-0.4992)
9				
10	Inter-Individual Variability	Estimate	RSE(%)	Shrinkage(%)
11	CL/F	40.74	5.151	9.604
12	Corr(CL-V2)	0.7297	9.051	-
13	V2/F	26.57	12.61	29.89
14	V3	125.7	31.65	-
15	KA	108.6	8.178	-
16				
17	Intra-Individual Variability	Estimate	RSE(%)	Shrinkage(%)
18	PRO	1	-	11.14

Goodness-of-fit

Goodness-of-fit plots for ruxolitinib population PK final model are shown in Figure 9 .

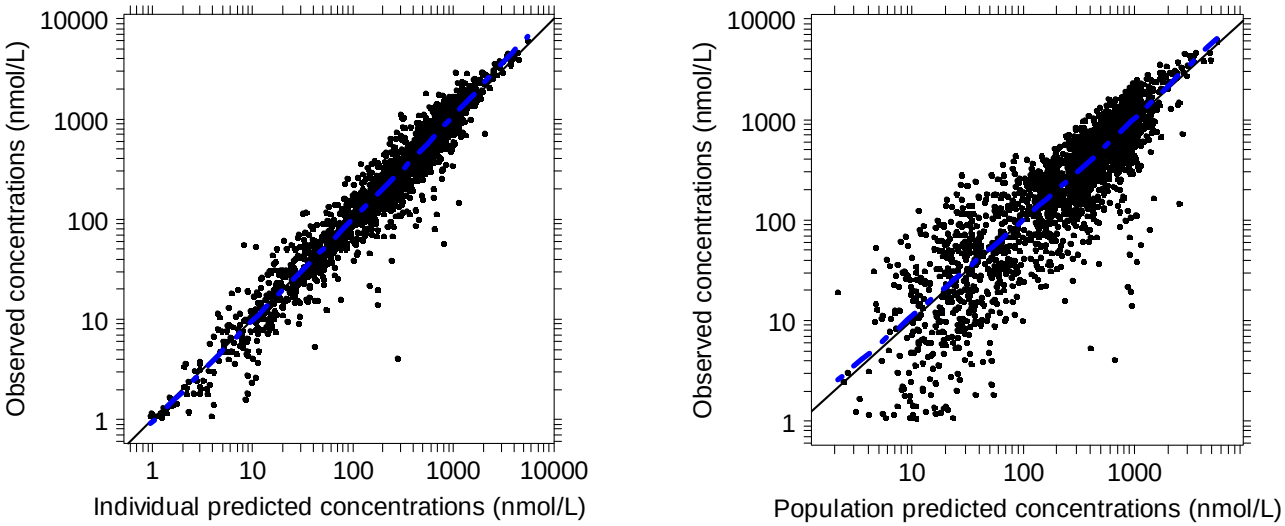


Figure 9. The goodness-of-fit graphs for Ruxolitinib population PK model

CL vs Body Weight or Sex

The effects of sex and body weight on clearance were examined by the reviewer. Inclusion of sex or body weight as covariate for clearance covariates resulted in the reduction in the objective function value (OFV) by 42 and 36, respectively (Figure 10). Sex explains ~8% of inter-subject variability on ruxolitinib clearance.

The sex difference in pharmacokinetics can be primarily explained by the difference of body weight between males and females. Males have higher body weight and lower exposure at steady state compared to female patients (Figure 11). After replacing sex with body weight in the final model, no trend was observed regarding inter-patient variability of clearance vs. sex (Figure 12). After including sex or body weight as the covariate, the inter-patient variability for clearance are 40% and 42%, respectively.

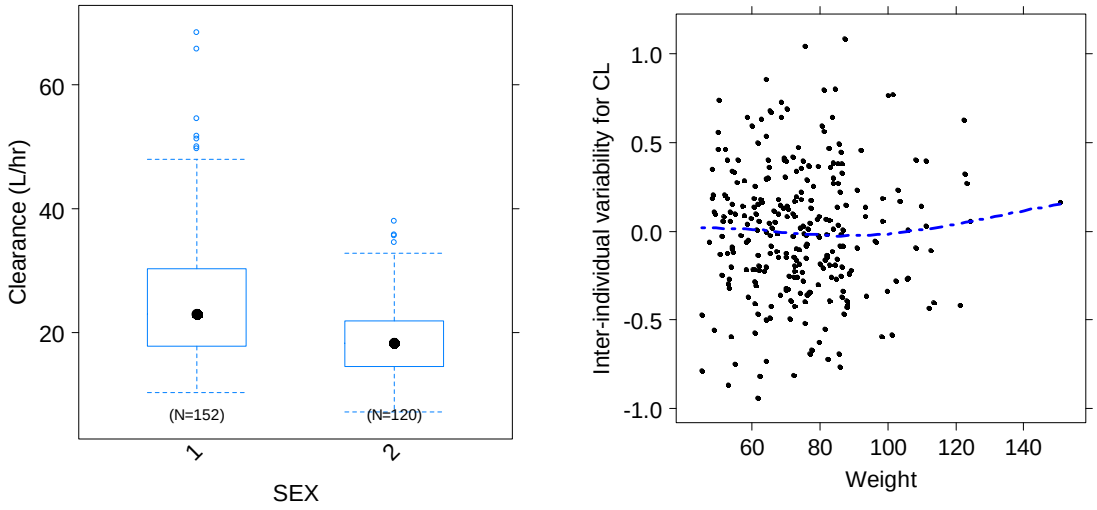


Figure 10. Plots of CL/F vs sex (left) and Inter-individual variability of CL/F vs. body weight (right) under the final model with sex as a covariate for clearance.

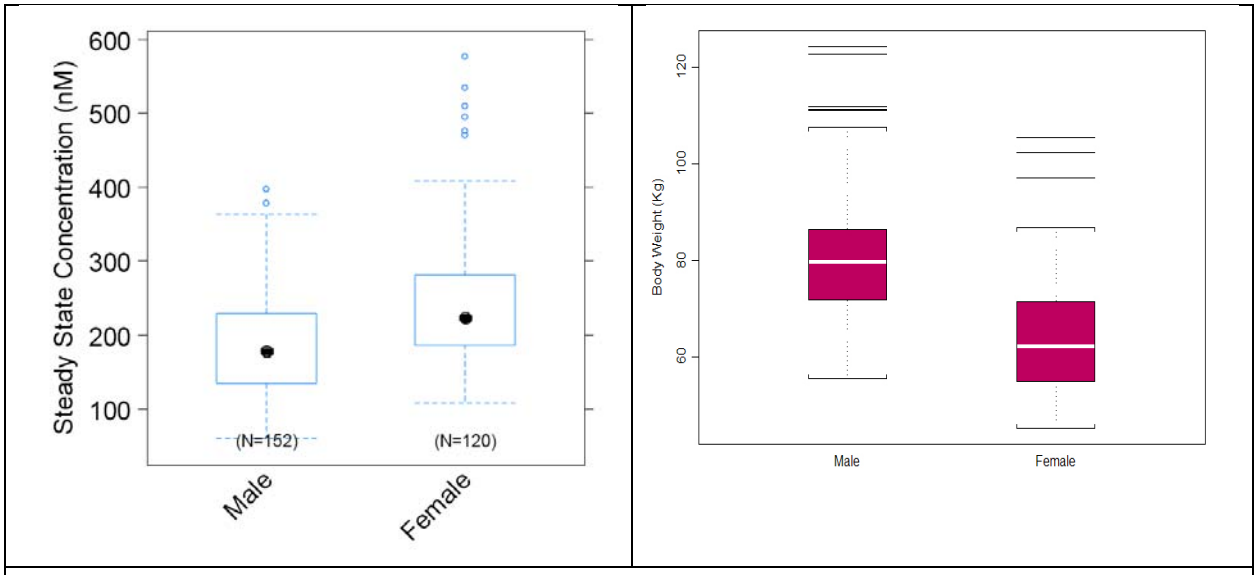


Figure 11: Comparisons of steady state concentration at 15 mg daily dose (left) and the body weight (right) between male and female patients.

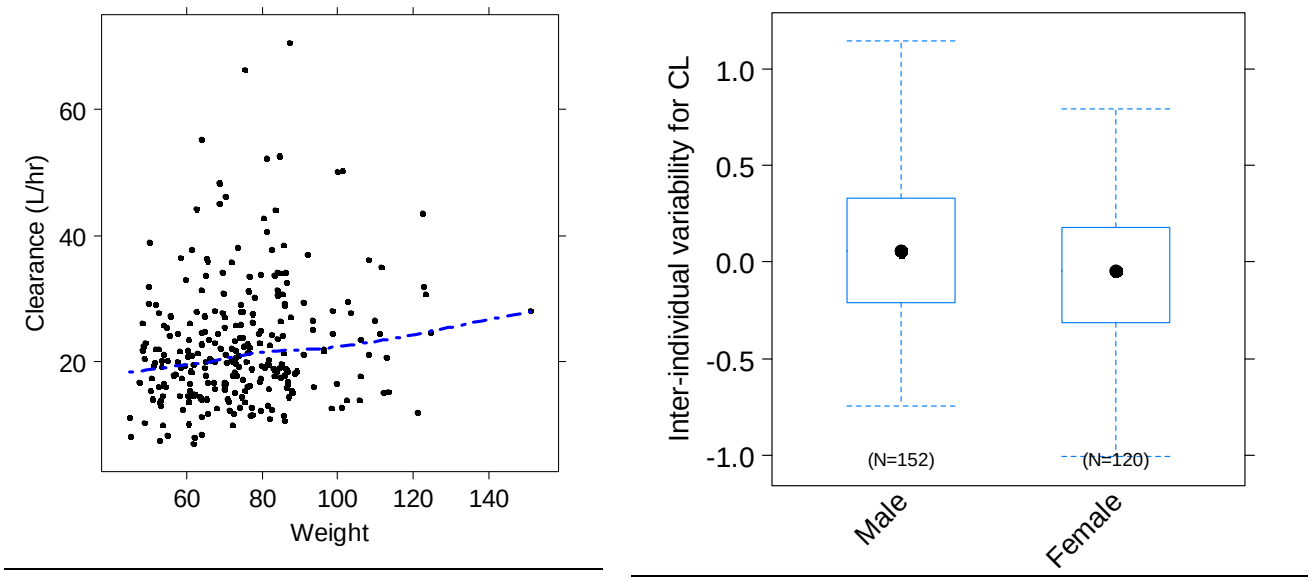


Figure 12: Plots of CL/F vs weight (left) and Inter-individual variability of CL/F vs sex (right) under the final model with body weight as a covariate for clearance.

CYP Inducers and Inhibitors

Ruxolitinib is a CYP3A4 substrate. In presence of moderate or strong CYP inhibitors, patients have a lower median CL of ruxolitinib as compared in absence of CYP inhibitors, indicating higher drug exposure are expected for patients co-administrated with moderate or strong CYP inhibitors.

A slight trend is observed between inter-individual variability on clearance and CYP inhibitors (CIH, Figure 13). Population PK results support the findings of a dedicated CYP inhibitor study where increased exposures were observed in subjects when ruxolitinib was administered in combination with ketoconazole as compared to ruxolitinib administered alone. However, caution should be taken as only one patient received a strong CYP inhibitor and the dose and the timings for the administration of inducers are unclear. A dedicated study for CYP3A4 inducers and inhibitors were conducted by the sponsor. Please see review by Dr. Joe Grillo for details.

Patients taking CYP3A4 weak and moderate inducers showed a slightly increased ruxolitinib clearance. A slight trend is observed between inter-individual variability on clearance and CYP inducers (CID, Figure 6). No strong CYP3A4 inducers are included in the PopPK analysis. A dedicated study was conducted for CYP3A4 inducers. Please see review by Dr. Joe Grillo for details.

The PopPK finding provides supportive evidence for the effects of CYP inducers on drug exposure.

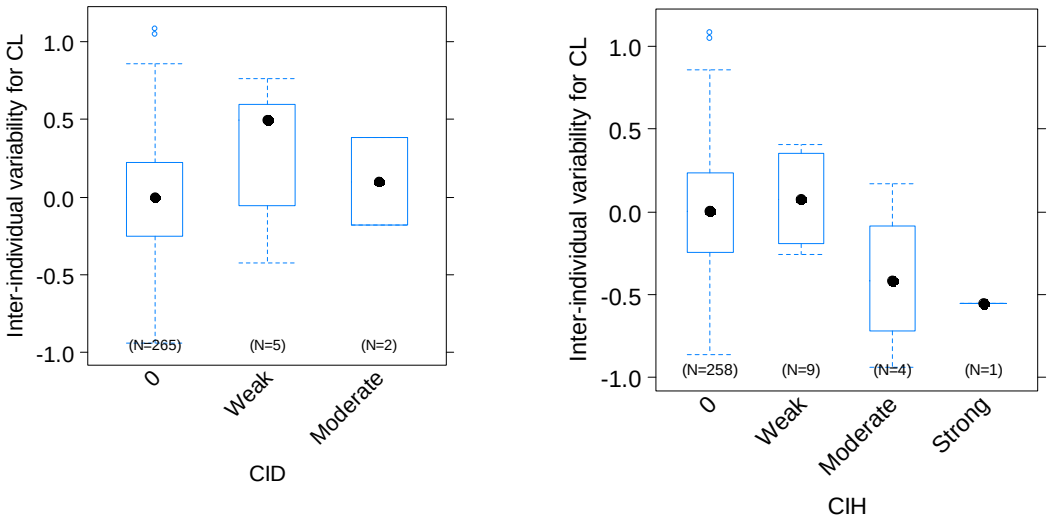


Figure 13: Inter-individual variability on clearance vs. concomitant use of CYP3A4 inducers(left) and inhibitors (right).

Renal and hepatic impairment

A slight trend is observed between inter-individual variability on clearance and renal function. Figure 14 shows that the median CL for subjects with severe renal impairment was lower (16.0 L/hr) compared to normal subjects (25.6 L/hr). Thus, a 0.6-fold increase in median dose-normalized AUC is expected for subjects with severe renal impairment. This analysis is limited because of the low patient number in the severe impairment group (N=2), but does imply that a stronger relation is likely to exist for patients with severe renal impairment and thus needs to be further explored by a dedicated study. This result provided supportive evidence for the necessity of dose adjustment for patients with renal impairments.

Boxplot of the inter-individual variability on clearance show that there is no systematic trend between inter-individual variability on clearance and hepatic function. Similarly, no trend is observed for aspartate aminotransferase (AST) or Modification of Diet in Renal Disease (MDRD) levels.

Note*: The NCI Organ Dysfunction Working Group (ODWG) criteria for hepatic impairment were used to identify subjects with varying degrees of hepatic impairment. Subjects were classified as normal (bilirubin ≤ 1.0 ULN and AST ≤ 1.0 ULN (ULN, upper limit of normal)), mild impairment B1 (bilirubin ≤ 1.0 ULN and AST >1.0 ULN), mild impairment B2 (bilirubin > 1.0 to ≤ 1.5 ULN), moderate impairment (bilirubin > 1.5 to ≤ 3 ULN) and severe impairment (bilirubin > 3 ULN). The mild B1 and B1 are combined together in reviewer's covariate analysis.*

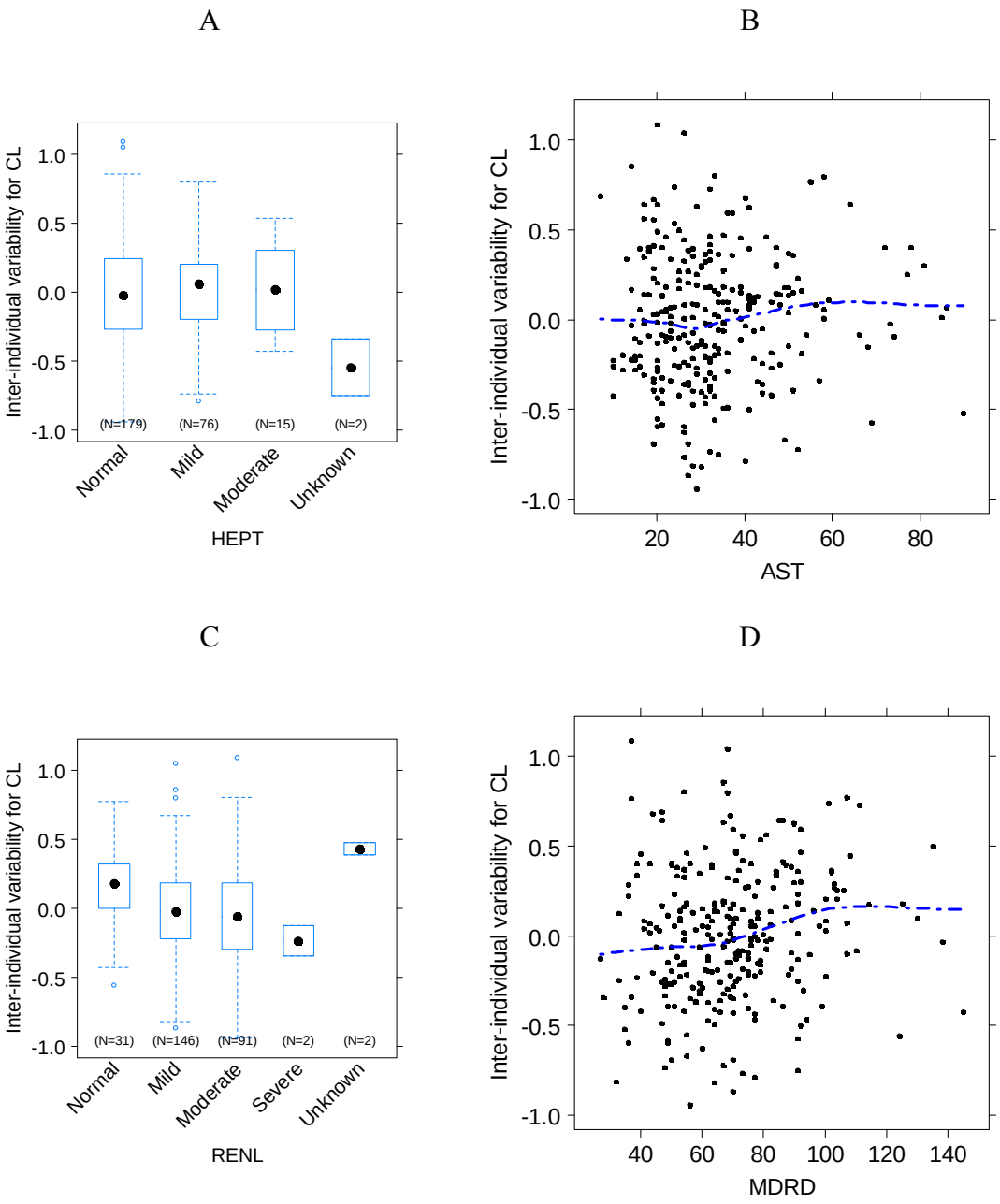


Figure 14: Plots of Inter-individual variability on clearance vs. hepatic impairment (A), AST levels (B), renal impairment (C) and MDRD levels (D)

4.4 Summary

Reviewer's summary is below:

1. *The relatively small effect of body weight on exposure does not support body-size based dosing. The exposure difference between males and females explains 26% of the difference of spleen volume reductions between male and female patients. With regard to PD, IC_{50} for spleen volume reduction in women is ~59% of that in men. Although there are additive PK and PD differences between males and females, ruxolitinib will be titrated to a maximal dose tolerated, therefore gender-based dose adjustment is not necessary.*
2. *The exposure-response relationship for efficacy and safety does support the titration of ruxolitinib to 25 mg BID. Based on the dose-response analysis for the reduction in spleen volume the maximal effect was observed at daily doses >40 mg (>20 mg BID).*
3. *Average daily doses ≤10 mg (≤5 mg BID) did not yield a clinically meaningful benefit of 35% reduction in spleen volume. Patients maintained at a dose of 5mg BID would be at a high risk of thrombocytopenia (platelet < 50 g/L) with minimal, if any, benefit in spleen volume reduction.*
4. *Sex explains ~8% of inter-subject variability on ruxolitinib clearance. The sex difference in pharmacokinetics can be mainly explained by the difference of body weight in males and females. After including sex or body weight as the covariate, the inter-patient variability for clearance are 40% and 42%, respectively. Body weight was found to be a significant covariate for central volume of distribution (Vc).*
5. *Log-transformation of the PK data improves the model fit. The difference of the parameter estimates (e.g. clearance) are slightly different between reviewer's analysis and sponsor's analysis.*

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
platelet_ER_BINS.ssc	Exposure-response evaluation and simulations for platelet count	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews \Ruxolitinib_NDA202192_SB \ER Analyses\Platelets
SPV_ER_BINS.ssc	Exposure-response evaluation, simulations and logistic regression for Spleen volume reduction (SVR)	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews \Ruxolitinib_NDA202192_SB \ER Analyses\SpleenVol
TSS_ER_BINS.ssc	Exposure-response evaluation and simulations for Total Symptom Score (TSS)	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews \Ruxolitinib_NDA202192_SB \ER Analyses\TSS
TSS_SVR.ssc	Dose-response evaluation for SVR and TSS	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews \Ruxolitinib_NDA202192_SB \ER Analyses\TSS_SVR

4.4 Cover sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	202192	Brand Name	Jakafi
OCP Division (I, II, III, IV, V)	5	Generic Name	Ruxolitinib Phosphate Tablets
Medical Division	DHP	Drug Class	
OCP Reviewer	Joseph Grillo	Indication(s)	Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis
OCP Team Leader	Julie Bullock	Dosage Form	Tablets
Pharmacometrics Reviewer	Jian Wang/ Satjit Brar	Dosing Regimen	(b) 20 mg PO bid start based on platelet count then titrate to a maximum of 25 mg PO bid
Date of Submission	June 3, 2011	Route of Administration	Oral
Estimated Due Date of OCP Review	9/9/11	Sponsor	Incyte
Medical Division Due Date	9/23/11	Priority Classification	Priority (4 month)
PDUFA Due Date	10/3/11		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	4		
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	3		
Blood/plasma ratio:	X			
Plasma protein binding:	X	2		
In vivo Metabolite Characterization & Quant	X	3		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	1		
Patients-				
single dose:				
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	3		
In-vivo effects of primary drug:				
In-vitro:	X	10		
Subpopulation studies -				
Weight:	X			Pop-PK
ethnicity:	X			Pop-PK
gender:	X			Pop-PK
pediatrics:				
geriatrics:	X			No PK, P3 safety/efficacy
renal impairment:	X	1		
hepatic impairment:	X	1		
PD -				
Phase 1:				
Phase 2/3:				
PK/PD -				
Phase 1 and/or 2 proof of concept:	X	1		
Phase 3 clinical trial:	X	2		
Population Analyses -				
Data rich:	X	1		
Data sparse:	X	2		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	X			ADME not compared to tab
alternate formulation as reference:	X	1		SR formulation
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X			Part of NHV SD
Bio-waiver request based on BCS	X			2 submitted
BCS class	X	3		
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	X			waiver
Literature References	X			4 submitted
ECG Monitoring	X	1		TQT
Biomarkers	X	1		pSTAT3 across studies
Immunogenicity Testing				
Metabolite activity	X	1		
Total Number of Studies		43		

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY
M/CHECKLIST FOR NDA/BLA or Supplement

On initial review of the NDA/BLA application for filing

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		Biowaviers submitted for 1) BE for 10 mg, 15 mg, 20 mg and 25 mg tabs 2) BE of dispersed sol/susp and tabs
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			EOP2 agreement
4	Did the sponsor submit data to allow the evaluation of	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N/A	Comment
	the validity of the analytical assay?				
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			Some errors
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		Will IR
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N/A	Comment
	provided in this submission?				

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1 Please provide a complete study report and raw data set in electronic format (i e , SAS transport files) for the Nasogastric tube study summarized in Section 1 4 of module 3 2 P 8

2 Please provide a table listing the different tablet formulations used in the various human clinical studies or affirm that the to-be-marketed image was used in all studies

3 (b) (4)

4 Please confirm that the formulation used in the food effect sub- study in study INCB 18424-131 was the to-be-marketed formulation

5 We note in both your hepatic impairment (INCB 18424-137) and renal impairment (INCB 18424-142) studies that the fraction unbound parameter was part of your PK analysis plan yet these data are not present in your report or your raw data sets Please provide your analysis of this parameter and the respective raw data set in electronic format (i e , SAS transport files) for each of these studies If this information has already been submitted please provide the location in the eCTD

6 Please provide the raw data set in electronic format (i e , SAS transport files) for each of the following studies:

- a DMB-10 43 1
- b DMB-10 55 1
- c DMB-06 168 1
- d IN VITRO-11 01 1

7 Please provide file definitions for the raw datasets associated with study INCB 18424-251

8 Please provide the Provide Bioanalytical Report(s) for studies DMB-10 43 1 and DMB-10 55 1

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

9 We noticed that you submitted the dataset for PopPK analysis and PK/PD analyses Please submit the each PK and PD datasets for each clinical study and the programs you used to support the individual PK analysis in each study

10 In PopPK dataset, please clarify the difference regarding the coding for the following variables:

a Variable "HEPCLS": both 2 and 3 are coded for "Mild impairment" in the Define PDF file

b Variable "CYPInd" both 3 and 4 are coded for "weak inducers" in the Define PDF file

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSEPH A GRILLO
10/26/2011

JIAN WANG
10/26/2011

SATJIT S BRAR
10/26/2011

CHRISTINE E GARNETT
10/27/2011

JULIE M BULLOCK
10/27/2011
I concur

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	202-192/N-000
Submission Date:	06/03/11, 07/07/11, 09/27/11, and 10/19/11
Related IND:	77,456
Brand Name:	Jakafi
Generic Name:	Ruxolitinib Phosphate
Formulation:	Immediate release (IR) oral tablets
Strength:	5, 10, 15, 20, and 25 mg
Applicant:	Incyte
Type of submission:	Original (Priority review; 6 months)
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Background:

Ruxolitinib phosphate was developed by Incyte for the treatment of myelofibrosis. The Applicant developed 5 strengths; 5, 10, 15, 20, and 25 mg IR oral tablets. The Applicant conducted the phase 3 clinical trials using only the 5 mg tablet strength. The phase 3 formulation is the same as the to-be-marketed (TBM) formulation. The TBM tablets are uncoated (b) (4)

NDA Submission:

On 06/03/11, the Applicant submitted a new NDA 202-192 for ruxolitinib phosphate IR tablets, 5, 10, 15, 20, and 25 mg. It is a new molecular entity (NME) and the first in its class of action for the unmet medical needs. Therefore, the above NDA was designated for a priority review (6 months). On 06/29/11 and 09/16/11, requests for additional information regarding CMC and Biopharmaceutics issues were sent to the Applicant. The Applicant responded on 07/07/11 and 09/27/11, respectively.

Relevant Communications Submitted Under the IND

- ***BCS Designation:*** The Applicant submitted *in vitro* and *in vivo* data on 02/27/09 to IND 77,456 (SN-082) and requested the Agency's Biopharmaceutical Classification System (BCS) Class 1 designation for ruxolitinib phosphate. The Agency reviewed the data and on 07/30/09 Ruxolitinib Phosphate Tablets were classified as a BCS-Class 1 drug substance.

- ***Biowaiver Requests:***
  - On 07/08/10, the Applicant submitted an amendment to IND 77,456 (SN-203) requesting a waiver for the CFR requirement to provide bioavailability (BA) data for the higher strengths, 10, 15, 20, and 25 mg, which were not tested clinically. The amendment included the supportive comparative dissolution data in three media (0.1 N HCI, pH 4.5 buffer and pH 6.8 buffer) for the 5 tablet strengths of ruxolitinib phosphate. The comparative dissolution data in three media were reviewed and found acceptable. The letter dated 11/04/10 indicated that the

Agency would formally review and provide their recommendation regarding the acceptability of the biowaiver proposal under the NDA submission.

- On 01/17/11, the Applicant submitted another amendment to their IND (SN-235) requesting a waiver for the requirement of conducting a bioequivalence (BE) study comparing the oral solution/suspension vs. the oral tablets. The amendment also included an *in vitro* study protocol designed to assess the stability and degradation of the dispersed solution/suspension. The overall information provided on 01/17/11 to support this biowaiver request and the protocol for the *in vitro* stability/degradation study was formally reviewed under the NDA.

- ***Proposed Dissolution Method and Acceptance Criterion:***
  The proposed method and acceptance criterion for the dissolution test evaluating Ruxolitinib Phosphate tablets are shown below.

  USP Apparatus: II (Paddle)
  Speed: 50 rpm
  Dissolution medium: 900 mL of 0.1 N HCI at 37± 0.5°C
  Sampling timepoints: 10, 15, 20, 30, and 60 min
  Acceptance Criterion: Q=(b) (4) at 30 min

The dissolution information/data supporting the proposed dissolution method was reviewed under the IND and the method was deemed acceptable. However, the Agency informed the Applicant that the evaluation of the overall dissolution data supporting the acceptability of the proposed acceptance criterion was a review issue under the NDA.

Biopharmaceutics Review:

Since the dissolution development report and the comparative dissolution data for the five strengths of ruxolitinib phosphate IR tablets were reviewed previously under the IND, the Biopharmaceutics review for the NDA would focus on the evaluation of the data supporting: **1)** the biowaiver requests, **2)** the proposed dissolution acceptance criterion, and **3)** the *in vitro* study evaluating the stability of ruxolitinib phosphate in oral solution after passing through the NG tubes, including the Applicant's 07/07/11 response to the Agency's 06/29/11 information request. Note that the recommendation regarding the acceptability of the stability/degradation data will be provided by the CMC reviewer.

The Applicant also included the updated 24-month stability data for the 25 mg tablet strength in the 09/27/11 submission. A teleconference was held on 10/18/11 between the Agency and the Applicant to discuss the Agency's proposed dissolution acceptance criteria. The Applicant responded on 10/19/11. These responses are reviewed here.

RECOMMENDATION

ONDQA-Biopharmaceutics has evaluated the overall information supporting the approval of this submission and has the following comments:

1. The BA waiver request for the 10, 15, 20, and 25 mg higher strengths that were not tested clinically and the waiver request for a BE study comparing the oral solution/suspension vs. the oral tablets are acceptable.

2. With respect to the dissolution acceptance criterion, the dissolution data from the bio-batch and registration stability batches clearly supported a tighter value. Therefore, the following revision for the dissolution acceptance criterion was recommended:

   From Q = (b) (4) at 30 minutes
   To Q = (b) (4) at 30 minutes

   The updated 24-month stability data submitted on 09/27/11 also support the dissolution acceptance criterion of Q= (b) (4) at 30 minutes. On 10/18/11, the Applicant agreed to implement Q = (b) (4) at 30 minutes as the specification criterion for the dissolution test of their product at release and on 10/19/11, the Applicant submitted the revised specifications for all five strengths to Section M32P51. Therefore, the final dissolution method and acceptance criterion for Ruxolitinib Phosphate Tablets are as follow:

   USP Apparatus: USP II (Paddle)
   Speed: 50 rpm
   Dissolution Medium: 900 mL of 0.1 N HCl at 37± 0.5°C
   Final Acceptance Criterion: Q = (b) (4) at 30 minutes for release (USP <711>)

Overall Assessment:

From the Biopharmaceutics viewpoint, NDA 202-192 for Jakafi (ruxolitinib phosphate) Tablets is recommended for approval.

10/19/11
Tien-Mien Chen, Ph.D. Date
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

10/19/11
Angelica Dorantes, Ph.D. Date
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

CC: NDA
Tien-Mien Chen, Scott Goldie

BIOPHARMACEUTICS QUALITY ASSESSMENT

1. BACKGROUND

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAK-STAT pathway has been associated with several cancers and increased proliferation and survival of malignant cells.

Ruxolitinib is indicated for the treatment of patients with myelofibrosis, including primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF), and post-essential thrombocythemia-myelofibrosis (PET-MF). The recommended dose is (b) (4) mg twice a day (BID) to 25 mg BID.

2. CURRENT SUBMISISON

On 06/03/11, Incyte submitted NDA 202-192 for Ruxolitinib Phosphate IR tablets, 5, 10, 15, 20, and 25 mg. It is an NME and the first in its class of action for the unmet medical needs. Therefore, it was designated for priority, a 6-month time review clock.

Ruxolitinib Phosphate has been developed by Incyte for five strengths, 5, 10, 15, 20, and 25 mg IR oral tablets. The TBM formulations are uncoated (b) (4) The Applicant conducted a phase 3 clinical trials using only the 5 mg tablet strength for the treatment of myelofibrosis. The phase 3 formulation is the same as the TBM formulation.

This NDA includes: **1)** The studies/reports that have been previously reviewed by the Biopharmaceutics team under the IND and **2)** The overall dissolution data supporting the proposed dissolution acceptance criterion, and **3)** the new data for the *in vitro* study assessing the stability and degradation of the dispersed solution/suspension.

3. PREVIOUS AMENDMENTS UNDER IND 77,456

The previous IND amendments and the Agency's responses are summarized here:

- On 02/27/09, the Applicant requested (SN-082) the BCS Class 1 designation for the ruxolitinib phosphate drug substance based on the supportive data consisting of
  (a) solubility of API (active pharmaceutical ingredient) in different pH conditions,
  (b) permeability in caco-2 cells,
  (c) lack of active transporter involvement in the oral absorption,
  (d) stability of drug substance in simulated gastric and intestinal fluid,
  (e) rapid dissolution of 5 mg and 25 mg tablets that were used in earlier clinical studies,
  (f) linear pharmacokinetics in healthy volunteers over a dose range of 5 mg to 200 mg administered as single doses, and
  (g) results from a ^{14}C mass balance study in healthy volunteers that indicated near-complete oral absorption.

- On 07/30/09, the Agency reviewed the submitted data and classified ruxolitinib phosphate as a BCS Class 1 drug substance.

- On 07/08/10, the Applicant requested (SN-203) the Agency's feedback for a biowaiver request and the review of the *in vitro* dissolution data for the 5 tablet strengths. The comparative dissolution data showed ≥ (b) (4) dissolved at 15 min for all 5 tablet strengths under all three dissolution conditions (pHs of 0.1 N HCl, pH 4.5 buffer and pH 6.8 buffer).

- In the 11/04/10 Advice letter, the Agency agreed with the biowaiver proposal and informed the Applicant that the recommendation regarding the acceptability of the biowaiver request will be done under the NDA.

- On 12/22/10, the Agency further agreed that it was appropriate to submit a biowaiver request for demonstrating *in vivo* BE between the intact tablet and the dispersed solution/suspension.

- On 01/17/11, the Applicant submitted (SN-235), the biowaiver request with an *in vitro* study protocol to assess the stability and degradation of the dispersed solution/suspension.

- The above biowaiver request and the *in vitro* protocol were reviewed and the Biopharmaceutics comments were conveyed to the Applicant on 05/27/11 and the Applicant responded on 07/07/11.

4. DRUG PRODUCT FORMULATIONS

The description/composition of the TBM formulations for the five commercial tablet strengths are summarized below.

Table 1. The Description/Composition of the Commercial Formulation of Ruxolitinib Phosphate IR Tablets

Component	5 mg Tablets (mg/tablet)	10 mg Tablets (mg/tablet)	15 mg Tablets (mg/tablet)	20 mg Tablets (mg/tablet)	25 mg Tablets (mg/tablet)
Tablet Formulation					
Ruxolitinib Phosphate[a]	(b) (4)				
Microcrystalline Cellulose, NF					
Lactose Monohydrate, NF					
Colloidal Silicon Dioxide, NF					
Hydroxypropylcellulose, NF					
Polyvinyl Pyrrolidone, USP					
Sodium Starch Glycolate, NF					
Magnesium Stearate, NF					
(b) (4)					
Total Tablet Weight					
Tablet Shape	Round	Round	Oval	Capsule-shaped	Oval
Size	7.5 mm diam.	9.3 mm diam.	0.589 x 0.278"	0.648 x 0.291"	0.689 x 0.328"
Lot Number Tested	A53228	1399-2644RD-3B	1399-2644RD-2B	1399-2493RD-Sublot 2	1399-2612 RD-18KP

(b) (4)

The formulations are [redacted] (b) (4) However, only the lowest strength, 5 mg, was tested clinically.

5. DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION

The proposed dissolution methodology and acceptance criterion for the five tablet strengths are shown below.

USP Apparatus: II (Paddle)
Speed: 50 rpm
Dissolution medium: 900 mL of 0.1 N HCI at 37± 0.5°C
Sampling timepoints: 10, 15, 20, 30, and 60 min
No. of Units: 12 tablets/test
Acceptance Criterion: Q [redacted] (b) (4) at 30 min

The details, the individual and mean dissolution data for all five strengths are included in Appendix 1.

Review Comments:

1. ***The data supporting the proposed dissolution test was reviewed under the IND and deemed acceptable (****see Dr. Tien-Mien Chen review in DARRTS****).***

2. ***With respect to the acceptance criterion, the dissolution data clearly support a tighter value. Therefore, it was recommended that the acceptance criterion be revised as follows:***

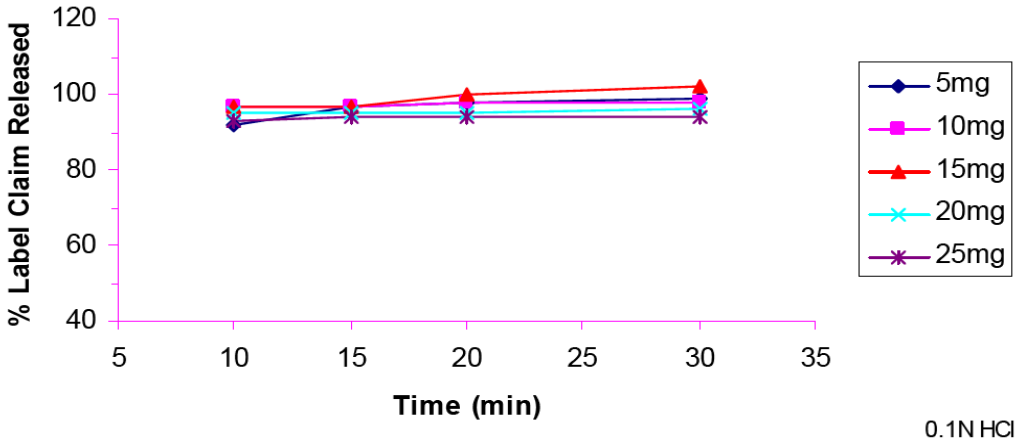
   From Q= [redacted] (b) (4) ***at 30 minutes***
   To Q [redacted] (b) (4) ***at 30 minutes***

- ***On 10/18/11, a teleconference was held to discuss the above recommendation and they agreed to implement Q =*** [redacted] (b) (4) ***at 30 minutes as the specification criterion for the dissolution test of their product at release.***

6. BIOWAIVER REQUESTS

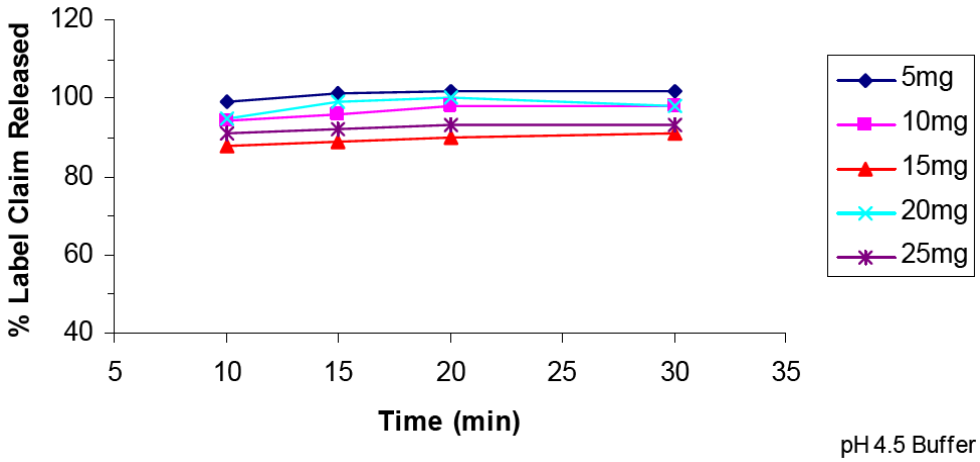
Biowaiver for Higher Strengths: To support the approval of the biowaiver request for the 10, 15, 20, and 25 higher strengths, the Applicant provided the supportive comparative dissolution profile data for the five tablet strengths in three media (0.1 N HCl, pH 4.5, and pH 6.8 using USP Apparatus 2 and 50 rpm).

Figure 1. Mean Dissolution Profiles of Ruxolitinib Phosphate IR Tablets (5 Strengths) in 0.1 N HCl Medium



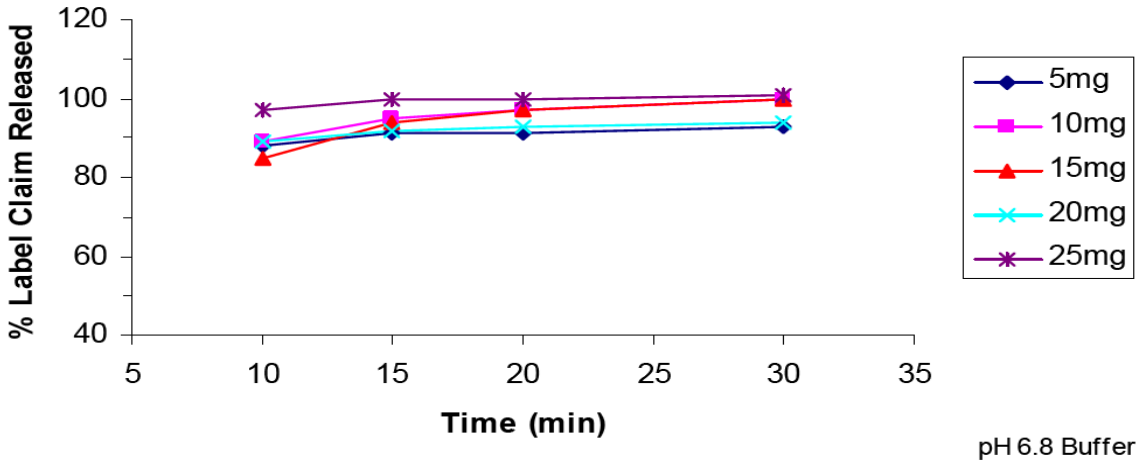
0.1N HCl

Figure 2. Mean Dissolution Profiles of Ruxolitinib Phosphate IR Tablets (5 Strengths) in pH 4.5 Buffer Medium



pH 4.5 Buffer

Figure 3. Mean Dissolution Profiles of Ruxolitinib Phosphate IR Tablets (5 Strengths) in pH 6.8 Buffer Medium



pH 6.8 Buffer

The above dissolution data showed ≥ 85% dissolved at 15 min for all five tablet strengths under all 3 dissolution conditions (pHs of 0.1 N HCI, pH 4.5 buffer and pH 6.8 buffer).

Upon request, on 07/07/11 the following manufacturing information for the rest of the 4 strengths employed in the above dissolution testing was provided.

Table 2. The Manufacturing Information for the Above Tested Tablets in the *In Vitro* Dissolution Study

Strength (mg)	Lot Number	Manuf. Date	Manuf. Site	Blend Batch Size (kg)
10	1399-2644-RD-3B	4/28/10	(b) (4)	(b) (4)
15	1399-2644-RD-2B	4/28/10		
20	1399-2493-RD-sublot 2	11/23/09		
25	1399-2612-RD-18KP	3/25/10		

Note: (b) (4)

The Applicant reported that they have been manufacturing ruxolitinib phosphate clinical supplies at (b) (4) since June 2008 (IND 77,456 SN0042, dated June 18, 2008).

Reviewer Comments:

The following issues were identified by this reviewer:

- ***The four higher strengths were made at*** (b) (4) ***(a site for the phase 2 formulations).***
- ***The*** (b) (4) ***is not the proposed commercial manufacturing site, DSM, (for the commercial formulation).***
- ***Three out of four batches*** (b) (4) ***were manufactured*** (b) (4) (b) (4)
- ***It was also noted that for the 5 mg tablet strength, the Phase 2 formulation (No. 18424-002-00) and Phase 3/commerical formulation (No. 18424-007-00) are slightly different as shown below.***

Table 3. Composition Comparison of Ruxolitinib Phosphate 5 mg IR Tablets Formulation Nos. 18424-002-00 (Phase 2) and 18424-007-00 (Phase 3/Commercial)

Component	Formulation 18424-002-00 (mg/tablet)	Formulation 18424-007-00 (mg/tablet)
Ruxolitinib Phosphate[a]	(b) (4)	
Microcrystalline Cellulose, NF		
Lactose Monohydrate, NF		
Colloidal Silicon Dioxide, NF		
Hydroxypropyl Ccellulose, NF		
Povidone, USP		

Sodium Starch Glycolate, NF		(b) (4)		
Magnesium Stearate, NF				
(b) (4)				
Total				

- ***The Applicant, however, provided comparative dissolution data for the 5 mg tablets (Tables 4 and 5 below), demonstrating similar dissolution characteristics, i.e., ≥ 85% in 15 min and therefore, supporting the equivalence between the Phase II and Phase III formulations of the 5 mg tablets manufactured at the two different sites.***

Table 4. Dissolution Data of 5 mg Tablets of Formulation 18424-002-00 (Phase 2); Lot No. 2008H085A

Time Point (Minutes)	Lot 2008H085A	% Dissolved (0.1N HCl)	% Dissolved (pH 4.5 Buffer)	% Dissolved (pH 6.8 Buffer)
10	Mean	93	89	90
	%RSD	2.8	12.0	8.0
15	Mean	94	92	92
	%RSD	2.8	10.8	6.7
20	Mean	95	94	93
	%RSD	3.1	9.5	3.7
30	Mean	97	96	95
	%RSD	3.5	8.1	3.6

Table 5. Dissolution Data of 5 mg Tablets of Formulation 18424-007-00 (Phase 3 and Commercial); Lot No. A53228

Time Point (Minutes)	Lot A53228	% Dissolved (0.1N HCl)	% Dissolved (pH 4.5 Buffer)	% Dissolved (pH 6.8 Buffer)
10	Mean	92	99	88
	%RSD	12.0	1.8	7.2
15	Mean	97	101	91
	%RSD	5.5	1.5	5.2
20	Mean	98	102	91
	%RSD	2.4	1.3	4.7
30	Mean	99	102	93
	%RSD	1.5	1.4	3.3

- ***It is also noted that the Phase 2 formulations for the four higher tablet strengths*** (b) (4) ***The comparison between the 5 and 25 mg Phase-2 tablet strengths is shown below.***

Table 6. Composition of Ruxolitinib Phosphate 5 mg and 25 mg Tablets, Phase 2 Clinical Supplies

Component (mg/tablet)	Formulation # 18424-002-00 5 mg tablet	Formulation # 18424-001-00 25 mg tablet
Ruxolitinib Phosphate		
Microcrystalline Cellulose		
Lactose Monohydrate		
Sodium Starch Glycolate		
(b) (4)		
Hydroxypropyl Cellulose		
Povidone		
Colloidal Silicon Dioxide		
Magnesium Stearate		
(b) (4)		
Total		

(b) (4)

(b) (4)

- ***Since no comparative dissolution profile data between the phase 2 formulation and the Phase 3 (TBM) formulation for the 25 mg tablets were provided (to encompass the entire 5-25 mg tablet strengths range), another Information request was sent out on 09/16/11. On 09/27/11, the Applicant provided the comparative dissolution data showing the similarity of the Phase 2 and Phase 3 formulations for the 25 mg tablets below. Please see the submitted mean dissolution data and profiles in Appendix 2 for details. Finally, the issue of three out of four batches*** (b) (4) ***that were manufactured*** (b) (4) ***of a full production batch size is less of a concern.***

Figure 4. Mean Comparative Dissolution Profiles of 25 Mg Tablets; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in 0.1 N HCl Medium

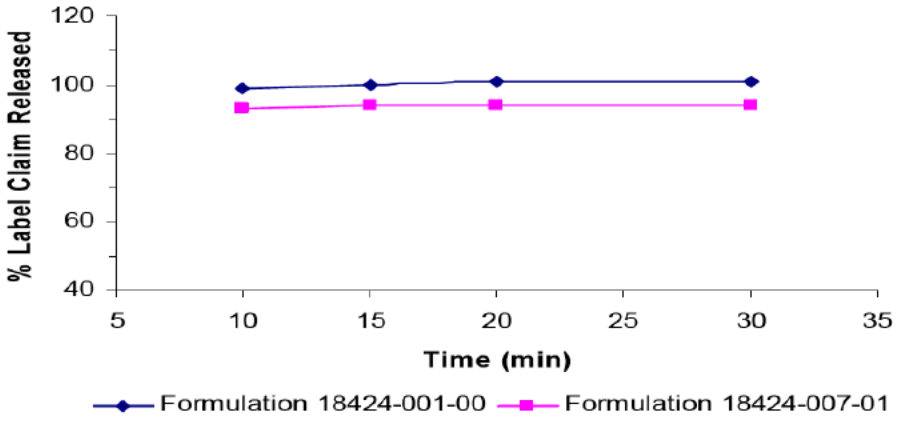


Figure 5. **Mean Comparative Dissolution Profiles of 25 Mg Tablets; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in Phosphate Buffer pH 4.5 Medium**

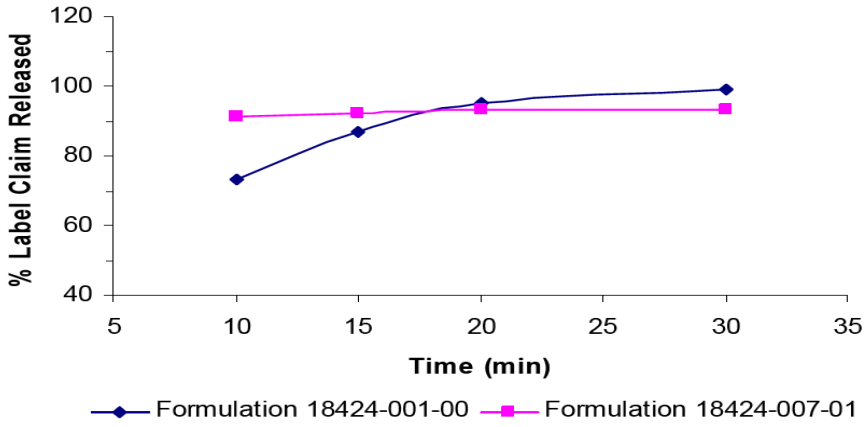
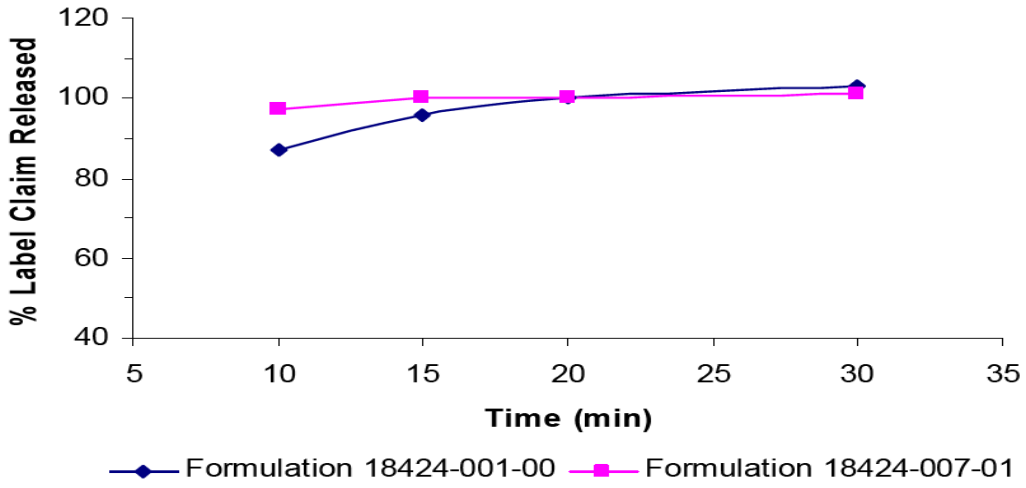


Figure 6. **Mean Comparative Dissolution Profiles of 25 Mg Tablets; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in Phosphate Buffer pH 6.8 Medium**



- ***<u>Overall Conclusion:</u> Although the above issues were identified, based on the fact that ruxolitinib phosphate has been classified as a BCS-Class 1 drug substance and the overall dissolution data support the similarity between the phase 2 and Phase 3 formulations and the fast dissolving characteristics of the product, ONDQA-Biopharmaceutics considers that the biowaiver request for Ruxolitinib 10, 15, 20, and 25 mg Tablets is appropriate and it is granted.***

7. *IN VITRO* STUDY TO EVALUATE THE STABILITY and DEGRADATION OF THE DISPERSED SOLUTION/SUSPENSION

On 01/17/11, the Applicant submitted an amendment (SN-235) to the IND including: **1)** a waiver request for the requirement of conducting a bioequivalence (BE) study comparing the oral solution/suspension vs. the oral tablets, and **2)** an *in vitro* study protocol evaluating the stability and degradation of the dispersed solution/suspension. The above biowaiver request and the *in vitro* protocol were reviewed and Biopharmaceutics comments asking for additional information were conveyed to the Applicant on 05/27/11 and the Applicant responded on 07/07/11. Please see Agency's comments and the Applicant's 07/07/11 response for details.

Summary of the In Vitro Stability and Degradation Study:

The *in vitro* stability study was conducted using 6 tablets of each strength (2 tablets for each of 3 different NG tubes) at two time points, i.e., the first time point is after shaking for 10 min (immediately after tablet dispersion) and the other timepoint is upon standing for 6 hrs at ambient temperature.

The Applicant showed the above *in vitro* study results:

I. The Control Samples (After immediate preparation, at 10 min timepoint without passing through NG tubes):

Control Samples – Two control samples were prepared for both the 5 mg and 25 mg tablets produced the following results:

- The 5 mg Controls produced a mean recovery of 99.1%
- The 25 mg Controls produced a mean recovery of 98.7%

II. The NG Tube Exposure (After immediate preparation, at 10 min timepoint and after passing through NG tubes)

NG Tube Exposure – Upon exposure to three types of NasoGastric feeding tubes, two INCB018424 Phosphate Suspensions per label strength produced results as follows:

- DOBBHOFF™ (8 Fr.)
  - 5 mg suspension demonstrated a mean recovery of 92.7%
  - 25 mg suspension demonstrated a mean recovery of 95.2%
- ENTRIFLEX™ (8 Fr.)
  - 5 mg suspension demonstrated a mean recovery of 93.3%
  - 25 mg suspension demonstrated a mean recovery of 94.9%
- ARGYLE™ (18 Fr.)
  - 5 mg suspension demonstrated a mean recovery of 97.0%
  - 25 mg suspension demonstrated a mean recovery of 98.4%

III. The stability study was conducted when tablets were upon standing for 6 hrs at ambient temperature. The combined results showed the recovery results in each of the three NG tube at these two timepoints as shown below.

Tablet Sample	Recovery (% Label Claim)		
	Dobbhoff Tube	Entriflex Tube	Argyle Tube
5 mg – tablet 1[a]	(b) (4)		
5 mg – tablet 2[a]			
5 mg – tablet 3[b]			
5 mg – tablet 4[b]			
Mean	93.4	93.8	97.4
%RSD	1.2	0.8	1.0
25 mg – tablet 1[a]	(b) (4)		
25 mg – tablet 2[a]			
25 mg – tablet 3[b]			
25 mg – tablet 4[b]			
Mean	95.2	94.7	98.3
%RSD	0.4	0.5	0.5

[a] Initial time point (average of 2 injections)
[b] 6 hour time point(average of 2 injections)

Note that the Applicant initiated the *in vitro* study on NG tubes before they received the Agency's comments requesting this in vitro study. ONDQA-Biopharmaceutics considers that the Applicant adequately addressed the Agency's comments and the study results and their justifications are acceptable.

For the specific details, please see the mean and individual stability/recovery data in Appendix 3 for details. Note that the recommendation regarding the acceptability of the stability/degradation data is been provided by the CMC Reviewer.

Reviewer's Comments:

- ***The results for the above in vitro study on the stability of ruxolitinib phosphate in oral solution after passing through the NG tubes showed the following similarities in stability: a) Between the two timepoints (10 min and 6 hrs) and b) Between the two strengths (5 and 25 mg). The results also showed similarity in recovery after passing through the three NG tubes; a mean recovery of greater than 93% (range: 92.7 to 98.5%) was observed.***

- ***Based on the BCS-Class 1 designation for ruxolitinib phosphate and the data showing stability of the dispersed solution/emulsion, the waiver request for the requirement to provide BE data comparing the dispersed solution/suspension vs. the oral tablets is acceptable.***

NDA 202-192 (N-000) for Ruxolitinib Phosphate IR Oral Tablets, 5, 10, 15, 20, and 25 mg

Appendix 1

In Vitro Mean and Individual Dissolution Data

Table 1. Mean and Individual Dissolution Profiles of Ruxolitinib Phosphate IR 25 mg Tablets

Time Point	25 mg Lot# 1399-2612-RD-18 KP	(b) (4)
10 Minutes	Average	(b) (4)
	Min	
	Max	
	%RSD	
15 Minutes	Average	
	Min	
	Max	
	%RSD	
20 Minutes	Average	
	Min	
	Max	
	%RSD	
30 Minutes	Average	
	Min	
	Max	
	%RSD	

Table 2. Mean and Individual Dissolution Profiles of Ruxolitinib Phosphate IR 20 mg Tablets

Time Point	20 mg Lot# 1399-2493-RD-Sub lot-2	(b) (4)
10 Minutes	Average	(b) (4)
	Min	
	Max	
	%RSD	
15 Minutes	Average	
	Min	
	Max	
	%RSD	
20 Minutes	Average	
	Min	
	Max	
	%RSD	
30 Minutes	Average	
	Min	
	Max	
	%RSD	

Table 3. Mean and Individual Dissolution Profiles of Ruxolitinib Phosphate IR 15 mg Tablets

Time Point	15 mg Lot# 1399-2644-RD- 2B	(b) (4)
10 Minutes	Average	
	Min	
	Max	
	%RSD	
15 Minutes	Average	
	Min	
	Max	
	%RSD	
20 Minutes	Average	
	Min	
	Max	
	%RSD	
30 Minutes	Average	
	Min	
	Max	
	%RSD	

Table 4. Mean and Individual Dissolution Profiles of Ruxolitinib Phosphate IR 10 mg Tablets

Time Point	10 mg Lot# 1399-2644-RD- 3B	(b) (4)
10 Minutes	Average	
	Min	
	Max	
	%RSD	
15 Minutes	Average	
	Min	
	Max	
	%RSD	
20 Minutes	Average	
	Min	
	Max	
	%RSD	
30 Minutes	Average	
	Min	
	Max	
	%RSD	

Table 5. Mean and Individual Dissolution Profiles of Ruxolitinib Phosphate IR 5 mg Tablets

Time Point	10 mg Lot# 1399-2644-RD- 3B	(b) (4)
10 Minutes	Average	(b) (4)
	Min	
	Max	
	%RSD	
15 Minutes	Average	
	Min	
	Max	
	%RSD	
20 Minutes	Average	
	Min	
	Max	
	%RSD	
30 Minutes	Average	
	Min	
	Max	
	%RSD	

NDA 202-192 (N-000) for Ruxolitinib Phosphate IR Tablets, 5, 10, 15, 20, and 25 mg

Appendix 2

Mean Comparative Dissolution Data on 25 mg Tablets Between Phase 2 and Phase 3 Formulations

Table 1. Mean Comparative Dissolution Data of 25 Mg Tablets; Phase-2 vs. Phase-3/Commerical (TBM) Formulation in 0.1 N HCl Medium

25 mg Tablet Strength	10 min	15 min	20 min	30 min
Phase-2 Formulation No. 18424-001-00 (Lot No. 2008H086A)	99	100	101	101
Phase-3 (TBM) Formulation No. 18424-007-01 (Lot No. 1399-2612-RD-18 KP)	93	94	94	94

Figure 1. Mean Comparative Dissolution Profiles of 25 Mg Tablets; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in 0.1 N HCl Medium

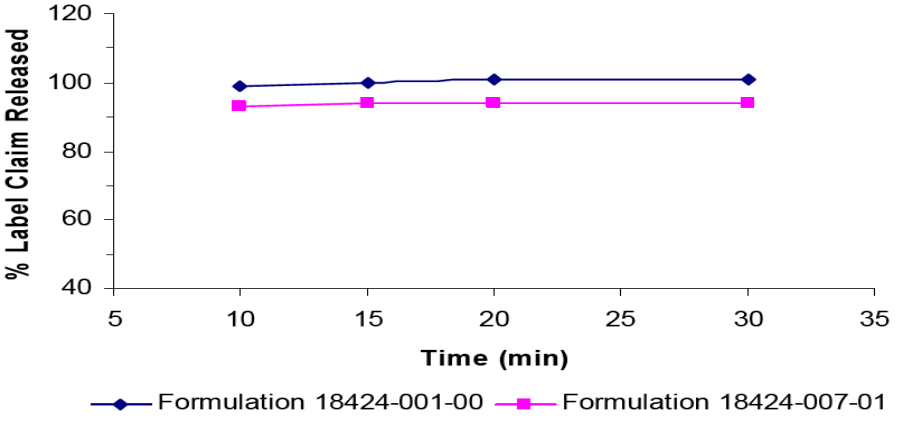


Table 2. Mean Comparative Dissolution Data of 25 Mg Tablet; Phase-2 vs. Phase-3/Commerical (TBM) Formulation in Phosphate Buffer pH 4.5 Medium

25 mg Tablet Strength	10 min	15 min	20 min	30 min
Phase-2 Formulation No. 18424-001-00 (Lot No. 2008H086A)	73	87	95	99
Phase-3 (TBM) Formulation No. 18424-007-01 (Lot No. 1399-2612-RD-18 KP)	91	92	93	93

Figure 2. Mean Comparative Dissolution Profiles of 25 Mg Tablets; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in Phosphate Buffer pH 4.5 Medium

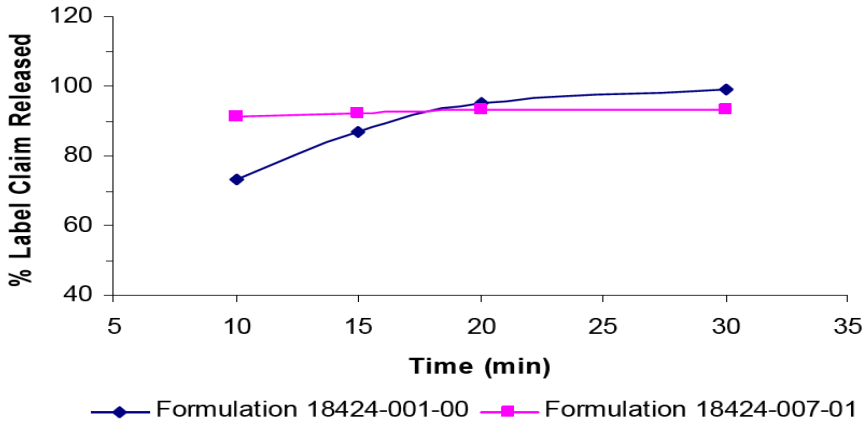
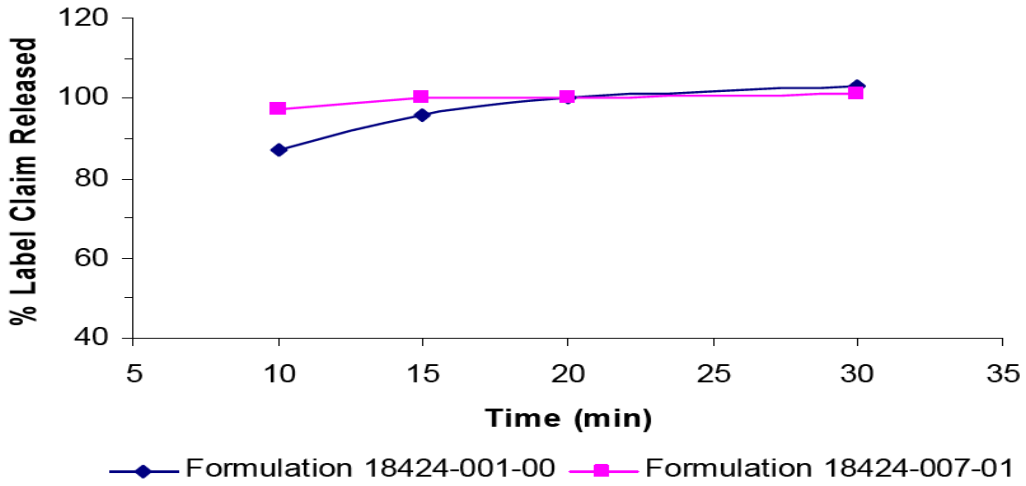


Table 3. Mean Comparative Dissolution Data of 25 Mg Tablet; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in Phosphate Buffer pH 6.8 Medium

25 mg Tablet Strength	10 min	15 min	20 min	30 min
Phase-2 Formulation No. 18424-001-00 (Lot No. 2008H086A)	87	96	100	103
Phase-3 (TBM) Formulation No. 18424-007-01 (Lot No. 1399-2612-RD-18 KP)	97	100	100	101

Figure 2-3. Mean Comparative Dissolution Profiles of 25 Mg Tablets; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in Phosphate Buffer pH 6.8 Medium



NDA 202-192 (N-000) for Ruxolitinib Phosphate IR Tablets, 5, 10, 15, 20, and 25 mg

Appendix 3

In Vitro Mean and Individual Stability/Recovery Data on NG Tubes

Control Samples – Two control samples were prepared for both the 5 mg and 25 mg tablets produced the following results:

- The 5 mg Controls produced a mean recovery of 99.1%
- The 25 mg Controls produced a mean recovery of 98.7%

Individual and Mean Data for Control Samples

Control Solutions: 5 mg	% Label Claim	Control Solutions: 25 mg	% Label Claim
5mg - 1	(b) (4)	25mg - 1	(b) (4)
5mg - 1		25mg - 1	
5mg - 2		25mg - 2	
5mg - 2		25mg - 2	
Mean	**99.1**	**Mean**	**98.7**
%RSD	**0.7**	**%RSD**	**0.1**

** Indicates Control Solution prepared to a final volume of 250 mL

NG Tube Exposure – Upon exposure to three types of NasoGastric feeding tubes, two INCB018424 Phosphate Suspensions per label strength produced results as follows:

- DOBBHOFF™ (8 Fr.)
  - 5 mg suspension demonstrated a mean recovery of 92.7%
  - 25 mg suspension demonstrated a mean recovery of 95.2%
- ENTRIFLEX™ (8 Fr.)
  - 5 mg suspension demonstrated a mean recovery of 93.3%
  - 25 mg suspension demonstrated a mean recovery of 94.9%
- ARGYLE™ (18 Fr.)
  - 5 mg suspension demonstrated a mean recovery of 97.0%
  - 25 mg suspension demonstrated a mean recovery of 98.4%

Nasogastric Tube Effects/Exposure on Ruxolitinib Recovery

		% Label Claim		
NG Tube Effects	**INJ**	**Dobbhoff Tube 8 Fr.**	**Entriflex Tube 8 Fr.**	**Argyle Tube 18 Fr.**
5mg Sample 1	1	(b) (4)		
	2			
5mg Sample 2	1			
	2			
Mean		**92.7**	**93.3**	**97.0**
%RSD		**0.2**	**0.5**	**1.2**
25mg Sample 1	1	(b) (4)		
	2			
25mg Sample 2	1			
	2			
Mean		**95.2**	**94.9**	**98.4**
%RSD		**0.4**	**0.3**	**0.5**

Suspension Stability - After approximately 6 hours at ambient laboratory conditions, two INCB018424 Phosphate Suspensions per label strength produced results as follows:

- DOBBHOFF™ (8 Fr.)
  - 5 mg suspension demonstrated a mean recovery of 94.1%
  - 25 mg suspension demonstrated a mean recovery of 95.0%

- ENTRIFLEX™ (8 Fr.)
  - 5 mg suspension demonstrated a mean recovery of 94.2%
  - 25 mg suspension demonstrated a mean recovery of 94.3%

- ARGYLE™ (18 Fr.)
  - 5 mg suspension demonstrated a mean recovery of 97.7%
  - 25 mg suspension demonstrated a mean recovery of 98.1%

The Recovery of the Suspension Stability Samples After 6 Hours

		% Label Claim		
Suspension Stability	**INJ**	**Dobbhoff Tube 8 Fr.**	**Entriflex Tube 8 Fr.**	**Argyle Tube 18 Fr.**
5mg Sample 1	1	(b) (4)		
	2			
5mg Sample 2	1			
	2			
Mean		94.2	94.2	97.7
%RSD		1.0	0.7	0.2
25mg Sample 1	1	(b) (4)		
	2			
25mg Sample 2	1			
	2			
Mean		95.0	94.3	98.1
%RSD		0.6	0.6	0.4

APPEARS THIS WAY ON ORIGINAL

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/s/

TIEN MIEN CHEN
10/20/2011

ANGELICA DORANTES
10/20/2011

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202192**	**Brand Name**	**Jakafi**
OCP Division (I, II, III, IV, V)	**5**	**Generic Name**	**Ruxolitinib Phosphate Tablets**
Medical Division	**DHP**	**Drug Class**	
OCP Reviewer	**Joseph Grillo**	**Indication(s)**	**Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis**
OCP Team Leader	**Julie Bullock**	**Dosage Form**	**Tablets**
Pharmacometrics Reviewer	**Jian Wang/ Satjit Brar**	**Dosing Regimen**	**(b) (4) 20 mg PO bid start based on platelet count then titrate to a maximum of 25 mg PO bid**
Date of Submission	**June 3, 2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**9/9/11**	**Sponsor**	**Incyte**
Medical Division Due Date	**9/23/11**	**Priority Classification**	**Priority (4 month)**
PDUFA Due Date	**10/3/11**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**4**		
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		
Isozyme characterization:	**X**	**3**		
Blood/plasma ratio:	**X**			
Plasma protein binding:	**X**	**2**		
In vivo Metabolite Characterization & Quant	**X**	**3**		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		
multiple dose:	**X**	**1**		
Patients-				
single dose:				
multiple dose:	**X**			
Dose proportionality -				
fasting / non-fasting single dose:	**X**			
fasting / non-fasting multiple dose:	**X**			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**3**		
In-vivo effects of primary drug:				

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In-vitro:	**X**	**10**		
Subpopulation studies -				
Weight:	**X**			**Pop-Pk**
ethnicity:	**X**			**Pop-Pk**
gender:	**X**			**Pop-Pk**
pediatrics:				
geriatrics:	**X**			**No PK. P3 safety/efficacy**
renal impairment:	**X**	**1**		
hepatic impairment:	**X**	**1**		
PD -				
Phase 1:				
Phase 2/3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**		
Phase 3 clinical trial:	**X**	**2**		
Population Analyses -				
Data rich:	**X**	**1**		
Data sparse:	**X**	**2**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	**X**			**ADME not compared to tab**
alternate formulation as reference:	**X**	**1**		**SR formulation**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**			**Part of NHV SD**
Bio-waiver request based on BCS	**X**			**2 submitted**
BCS class	**X**	**3**		
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**X**			**waiver**
Literature References	**X**			**4 submitted**
ECG Monitoring	**X**	**1**		**TQT**
Biomarkers	**X**	**1**		**pSTAT3 across studies**
Immunogenicity Testing				
Metabolite activity	**X**	**1**		
Total Number of Studies		**43**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		Biowaviers submitted for 1) BE for 10 mg, 15 mg, 20 mg and 25 mg tabs 2) BE of dispersed sol/susp and tabs
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			EOP2 agreement
4	Did the sponsor submit data to allow the evaluation of	X			

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	Content Parameter	Yes	No	N/A	Comment
	the validity of the analytical assay?				
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			Some errors
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		Will IR
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and			X	

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	Content Parameter	Yes	No	N/A	Comment
	provided in this submission?				

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Please provide a complete study report and raw data set in electronic format (i.e., SAS transport files) for the Nasogastric tube study summarized in Section 1.4 of module 3.2.P.8
2. Please provide a table listing the different tablet formulations used in the various human clinical studies or affirm that the to-be-marketed image was used in all studies.
3. [redacted] (b) (4)
4. Please confirm that the formulation used in the food effect sub- study in study INCB 18424-131 was the to-be-marketed formulation.
5. We note in both your hepatic impairment (INCB 18424-137) and renal impairment (INCB 18424-142) studies that the fraction unbound parameter was part of your PK analysis plan yet these data are not present in your report or your raw data sets. Please provide your analysis of this parameter and the respective raw data set in electronic format (i.e., SAS transport files) for each of these studies. If this information has already been submitted please provide the location in the eCTD.
6. Please provide the raw data set in electronic format (i.e., SAS transport files) for each of the following studies:
    a. DMB-10.43.1
    b. DMB-10.55.1
    c. DMB-06.168.1
    d. IN VITRO-11.01.1
7. Please provide file definitions for the raw datasets associated with study INCB 18424-251
8. Please provide the Provide Bioanalytical Report(s) for studies DMB-10.43.1 and DMB-10.55.1

9. We noticed that you submitted the dataset for PopPK analysis and PK/PD analyses. Please submit the each PK and PD datasets for each clinical study and the programs you used to support the individual PK analysis in each study.
10. In PopPK dataset, please clarify the difference regarding the coding for the following variables:
    a. Variable "HEPCLS": both 2 and 3 are coded for "Mild impairment" in the Define.PDF file
    b. Variable "CYPInd" both 3 and 4 are coded for "weak inducers" in the Define.PDF file

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Reviewing Clinical Pharmacologist	Date
Team Leader/Supervisor	Date

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/s/

JOSEPH A GRILLO
07/05/2011

JULIE M BULLOCK
07/06/2011