CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202192Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	202192
Priority or Standard	Priority
Submit Date	June 3, 2011
Received Date	June 3, 2011
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Reviewer Name	Albert B Deisseroth, MD, PhD
Review Completion Date	October 27, 2011
Established Name	Ruxolitinib Phosphate
Proposed Trade Name	JAKAFI™
Therapeutic Class	JAK2 Inhibitor
Applicant	Incyte Corporation
Formulation	Tablets (5, 10, 15, 20, and 25 mg)
Dosing Regimen	15 mg po bid
Indication	Treatment of Patients with Myelofibrosis
Intended Populations	Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, and Post-essential Thrombocythemia Myelofibrosis

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AD	Abdominal Discomfort
AE	Adverse Event
AML	Acute Myelogenous Leukmia
ASS	Abdominal Symptom Score
AUC	Area Under Curve
BAT	Best Available Therapy
CAT	Computerized Axial Tomography
CMC	Chemistry Manufacturing Control
CMH	Cochran Mantel Haenszel
CTCAE	Common Toxicity Criteria
DC	Discontinuation of Therapy
DHP	Division of Hematology Products
DLT	Dose Limiting Toxicities
DOR	Duration of Remission
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group
eCTD	Electronic Common Technical Document
ET	Essential Thrombocythemia
FF	Feeling Fullness
GI	Gastrointestinal
Hb	Hemoglobin
IPSS	International Prognostic Scoring System
IS	Itching Symptoms
ISS	Integrated Safety Summary
IWG	International Working Group
IWG MRT	International Working Group for Myelofibrosis Research and Treatment
JAK	Janus Associated Kinase
LFS	Leukemia Free Survival
MF	Myelofibrosis
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NDA	New Drug Application
NOAEL	No Observed Adverse Effect Level
NR	No Response
NS	Night Sweats
OS	Overall Survival
PC	Platelet Count
PET-MF	Post Essential Thrombocythemia Myelofibrosis
PFS	Progression Free Survival
PMC	Post Marketing Commitment

PMN	Neutrophil Count
PV	Polycythemia Vera
PPV-MF	Post Polycythemia Vera Myelofibrosis
pSTAT3	Phosphorylated STAT3
PUR	Pain Under Ribs
RBC	Red Blood Cell
SAE	Serious Adverse Advent
SEALD	Study Endpoints and Label Development
STAT3	Signal Transducers and Activators of Transcription Protein 3
SV	Spleen Volume
SVR	Spleen Volume Reduction
TEAE	Treatment Emergent Adverse Event
TSS	Total Symptom Score
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that ruxolitinib be granted Full Approval for patients with intermediate-2 and or high-risk myelofibrosis (MF), including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPVMF), and post-essential thrombocythemia myelofibrosis (PETMF).

Because the follow-up of the patients on the two phase III trials (INCB-351 and INCB-352) is insufficient to establish the durability of responses or aspects of the safety of long-term administration, I recommend the following post-marketing requirement:

1. Submit a protocol/plan to provide safety information on myelosuppression for up to 144 weeks of therapy following randomization in patients entered on INCB-351 and INCB-352 who are continuing on therapy past 24 and 48 weeks respectively.

I also recommend the following post-marketing commitments:

1. Commit to provide safety findings related to the interval of drug discontinuation in at least 150 patients previously entered onto INCB-351 and INCB-352 to determine if specific cautions are appropriate to describe discontinuation strategies.
2. Commit to provide longer-term efficacy and safety outcomes of current clinical trials (INCB-351 and INCB-352) to provide at least 3 year follow-up data.

1.2 Risk Benefit Assessment

Benefit-Risk Summary and Assessment:

Conclusions Concerning Potential Benefits: Two prospectively randomized trials have been carried out in the treatment of patients with high risk or intermediate-2 risk MF (including PMF, PPVMF, and PETMF) in patients with anemia, splenomegaly and with symptoms that justified therapy. The first trial (INCB-351) that was the pivotal trial randomized patients with MF who were intolerant/refractory/ineligible for available therapy to receive continuous ruxolitinib therapy or to receive placebo (1:1 randomization). The second supporting trial (INCB-352) randomized patients with MF 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), in a 2:1 randomization.

The primary endpoint in both trials was a statistically significant difference (as assessed by the Chi-square test in INCB-351 and by the Cochran-Mantel-Haenszel test stratified by prognostic category in INCB-352) 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% spleen volume reduction (SVR) as measured by MRI. The results for these primary endpoints in the two trials are presented below in Table 1.

Table 1-Primary Endpoint Results in Phase III Trials

Trial	Ruxolitinib	Placebo	P value
INCB-351	41.9% (N=155)	0.7% (N=154)	P<0.0001
Trial	Ruxolitinib	Best Available Therapy	
INCB-352	29.0% (N=146)	0.0% (N=73)	P<0.0001

The key secondary endpoint in the pivotal trial (INCB-351) was a statistically significant difference (as assessed by Chi-square testing) between the two arms in the percent of patients who displayed a ≥50% reduction in the "total symptom score" (TSS) after 24 weeks on treatment (the average of the last 7 days before the 24th week, as compared to the same score computed as an average of that recorded in the 14 days preceding randomization). The symptom inventory rated the severity (on a scale from 1 to 10) of the following 7 symptom categories: night sweats score, itchiness symptoms score, bone or muscle pain score, feeling of fullness (early satiety) score, pain under ribs score, abdominal discomfort score, or total abdominal system score. The results of INCB-351 for this key secondary endpoint are presented in Table 2.

Table 2-Percent of Patients With ≥50% Decrease in the TSS at 24 Weeks in INCB-351

Trial	Ruxolitinib	Placebo	P value
INCB-351	45.9% (N-148)	5.3% (N=152)	P<0.0001

The key secondary endpoint in INCB-352 was a statistically significant difference (as assessed by the Cochran-Mantel-Haenszel test stratified by prognostic category) between the two arms in the percentage of patients who by 24 weeks that achieved a ≥35% SVR as measured by MRI. The result for this key secondary endpoint in the INCB-352 trial is presented below in Table 3.

Table 3-Percent of Patients With ≥35% SVR at 24 Weeks in INCB-352

Trial	Ruxolitinib	Best Available Therapy	P value
INCB-352	32% (N=146)	0.0% (N=73)	P<0.0001

There are two aspects of these efficacy results which are impressive: 1. The reproducibility of the very significant differences between the treatment and comparator arms in the two randomized trials in terms of a clinically significant decrease in the volume of the spleen, which is a primary hall-mark of this disease, and is a cause of most of the symptoms which disrupt quality of life of these patients, in the patients who had no other therapeutic options; 2. In the INCB-351 trial, there was a ≥50% reduction in the TSS using a validated patient reported outcome instrument, for the other hall-mark of the disease: symptoms which disrupt the quality of life in patients with no other available therapy.

Conclusions Concerning Risks: Available for the analysis of safety were over 617 patients with exposure to ruxolitinib, 455 of whom had MF, and most of whom had failed other available therapies for MF. In addition, as presented below in Tables 4A, 4B, and 4C, there are data available from two prospectively randomized well controlled trials for the comparison of the toxicities of the 301 patients on the ruxolitinib arms as compared to the 224 patients on the comparison arms of the two randomized trials (INCB-351 and INCB-352).

Table 4A-Toxicity on INCB-351 and INCB-352

Study	INCB-351	INCB-351	INCB-352	INCB-352
Treatment	Ruxolitinib N=155	Placebo N=151	Ruxolitinib N=146	BAT N=73
Grade 3-4 AEs	47%	44%	42%	25%
Grade 5 <28days	5%	7%	3%	4%
SAEs	28%	35%	30%	29%
AEs → discontinuation	11%	11%	8%	8%
AEs→ decreased dose	51%	26%	64%	15%

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Table 4B-Serious Adverse Events >1% on INCB-351 and INCB-352

Study	INCB-351	INCB-351	INCB-352	INCB-352
Number	N=155	N=151	N=146	N=73
Therapy	Ruxolitinib	Placebo	Ruxolitinib	BAT
Preferred Term	n (%)	n (%)	n (%)	n (%)
Any	43 (27.7%)	53 (35.1%)	44 (30.1%)	21 (28.8%)
Anemia	5 (3.2%)	3 (2.0%)	7 (4.8%)	3 (4.1%)
Pneumonia	10 (6.5%)	5 (3.3%)	1 (0.7%)	4 (5.5%)
Thrombocytopenia	3 (1.9%)	1 (0.7%)	0 (0.0%)	1 (1.4%)
Bleeding	7 (3.7%)	7 (4.1%)	6 (4.2%)	0 (0.0%)
GI Bleed	2 (1.3%)	2 (1.3%)	2 (1.4%)	0 (0.0%)
CNS Bleed	0 (0.0%)	0 (0.0%)	2 (1.4%)	0 (0.0%)
Post Proc Bleed	1 (0.6%)	1 (0.7%)	1 (0.7%)	0 (0.0%)
UGI Bleed	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)

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Table 4C-Common Adverse Events (≥1%) on INCB-351 and INCB-352

Study	INCB-351	INCB-351	INCB-352	INCB-352
Number	N=155	N=151	N=146	N=73
Therapy	Ruxolitinib	Placebo	Ruxolitinib	BAT
Preferred Term	n (%)	n (%)	n (%)	n (%)
Thrombocytopenia	53 (34%)	14 (9%)	65 (45%)	7 (10%)
Epistaxis	6 (4%)	8 (5%)	12 (8%)	5 (7%)
Anemia	48 (31%)	21 (14%)	59 (40%)	9 (12%)
Neutropenia	4 (2.6%)	1 (1%)	5 (3%)	1 (1%)
Headache	23 (15%)	8 (5%)	15 (10%)	3 (4%)

Confusion	22 (15%)	8 (5%)	3 (2%)	1 (1%)
Dizziness	23 (15%)	10 (7%)	10 (7%)	4 (6%)
Pneumonia	13 (8.4%)	9 (6%)	3 (2%)	5 (7%)

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The data summarized above in Tables 4A, 4B and 4C lead to the following conclusions:

1. The on study deaths (≤28 days from last therapy) were lower in the ruxolitinib arm than in the other arm (placebo in INCB-351, and BAT in INCB-352);

2. There was no increase in SAEs on the ruxolitinib arms vs the comparison arms on INCB-351 or on INCB-352;

3. There was no increase in overall AEs on the ruxolitinib arms vs the comparison arms on INCB-351 or INCB-352.

3. The discontinuations due to adverse events on the ruxolitinib arms were equal to and no higher than those on the comparison arms in the two randomized trials;

4. Although the incidence of thrombocytopenia (including Grade 3 and Grade 4) was increased on the ruxolitinib arms of the two randomized trials vs the comparison arms, there was no increase in the incidence of bleeding on the ruxolitinib arms vs the comparison arms of INCB-351 and a minor increase in INCB-352. This was primarily the result of the dose adjustment schedule for thrombocytopenia (both prior to the commencement of therapy and during therapy). It is apparent that such dose adjustments to prevent severe thrombocytopenia did not prevent an impressive result in terms of efficacy.

5. The only adverse event (besides thrombocytopenia) for which there were clinically significant increases of Grade 3 and Grade 4 adverse events was anemia, for which significant increases occur on the ruxolitinib arms on INCB-351(from 5 to 10% for Grade 3 and from 0 to 5% for Grade 4) and for which significant increases occur on the ruxolitinib arm on INCB-352 (3 to 11% for Grade 3, but no increase for Grade 4). Anemias were not seen to be a cause of discontinuations on the ruxolitinib arms of either INCB-351 or INCB-352 (see Table 54).

6. The other adverse events which were increased with ruxolitinib (diarrhea, nausea, confusion, headache, and dizziness) were grade 1-2 adverse events.

Final Benefit-Risk Summary and Assessment: Two well designed well controlled randomized trials of ruxolitinib in MF patients who for the most part had no other available therapy, showed that clinically significant benefit was generated by ruxolitinib, and that the major side effect (thrombocytopenia) could be limited by dose adjustments which did not prevent the benefit otherwise generated by ruxolitinib. I recommend that ruxolitinib be granted Full Approval for patients with intermediate-2 and high-risk myelofibrosis (MF), including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPVMF), and post-essential thrombocythemia myelofibrosis (PETMF).

Because the follow-up of the patients on the two phase III trials (INCB-351 and INCB-352) is insufficient to establish the durability of responses, I recommend the following post marketing requirement:

1. Submit a protocol/plan to provide safety information on myelosuppression for up to 144 weeks of therapy following randomization in patients entered on INCB-351 and INCB-352 who are continuing on therapy past 24 and 48 weeks respectively.

I also recommend the following post-marketing commitments:

1. Commit to provide safety findings related to the interval of drug discontinuation in at least 150 patients previously entered onto INCB-351 and INCB-352 to determine if specific cautions are appropriate to describe discontinuation strategies.
2. Commit to provide longer-term efficacy and safety outcomes of current clinical trials (INCB-351 and INCB-352) to provide at least 3 year follow-up data.

Below is a separate analysis which was carried out using the Benefit-Risk Assessment Framework Tool. This analysis is provided below in Table 5.

Table 5-Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition: MF Clinical Manifestations Median Survival (all groups) Survival high risk Survival intermediate-2 Approved available therapy	 Splenomegaly and symptoms which disrupt quality of life 57 months 27 months 48 months No Approved therapy	MF is a serious, life-threatening condition in which death is due to evolution into AML (12%), bleeding (11%), portal hypertension (7%), and liver insufficiency (9%).
Unmet Medical Need: Therapy: Off label use of interferon-alpha, anagrelide, dexamethasone, hydroxyurea, erythropoietin, thalidomide, splenic radiation, and allografts.	Allograft is the only curative therapy (7 yr survival is 60%). Only a fraction of patients with MF are eligible. All other therapies are palliative and have significant side effects.	For most patients, there is no curative therapy, and no effective treatment which reduces symptoms and splenomegaly for a long time. There is an unmet medical need in MF.
Clinical Benefit: 2 randomized well controlled trials were conducted with reproducible results.	42% and 29% of ruxolitinib treated patients in the two trials displayed ≥35% reduction of splenic volume. In the pivotal phase III trial, 46% of patients experienced ≥50% reduction in total symptom score. Long term benefit and toxicity unknown	Two large well controlled and well designed trials met efficacy endpoints when measured at 24 and 48 weeks of therapy. Uncertain is the how long enefits will last beyond the 24 and 48 week and what will be toxicity of long term treatment
Risks: Early deaths (≤28 days) SAEs AEs	Ruxolitinib Arms Not increased Not increased	Thrombocytopenia was successfully managed by a dose adjustment schedule. Anemia was managed by RBC

↓platelets (Grade 3) ↓platelets (no Grade 4) Bleeding Anemia (Grade 3) Anemia (Grade 4) Infections AEs leading to discontinuation AEs leading to dose reduction	Increased Not increased Not increased Increased Increased Not increased Not increased Increased	transfusions. The risks of long term therapy have not been characterized.
Risk Management: Need for studies for toxicity of long term therapy.	Two phase III trials showed significant benefit and minimal risks for up to 48 weeks of treatment. Need PMC for longer term follow-up of response duration and toxicity.	PMR for follow-up (for 3 years after randomization) of phase III trial populations for myelosuppression PMC for post marketing followup of efficacy and safety outcomes of current randomized trials and to report on discontinuation of at least 150 patients previously entered onto the randomized trials to determine if specific cautions are appropriate to describe discontinuation strategies.

1.3 Recommendations for Postmarket Risk Management Activities: None

1.4 Recommendations for Postmarket Studies/Clinical Trials

1. Postmarketing Requirement: Submit a protocol/plan to provide safety information on myelosuppression for up to 144 weeks of therapy following randomization in patients entered on INCB-351 and INCB-352 who are continuing on therapy past 24 and 48 weeks respectively.

2. Post-marketing commitments:

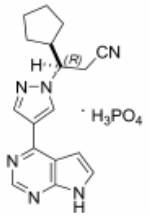
a. Commit to provide safety findings related to the interval of drug discontinuation in at least 150 patients previously entered onto INCB-351 and INCB-352 to determine if specific cautions are appropriate to describe discontinuation strategies.

b. Commit to provide longer-term efficacy and safety outcomes of current clinical trials (INCB-351 and INCB-352) to provide at least 3 year follow-up data.

2 Introduction and Regulatory Background

2.1 Product Information

Figure 1-Structure of Ruxolitinib



The chemical structure of ruxolitinib is shown above in Figure 1. The molecular formula is $C_{17}H_{21}N_6O_4P_2$. The molecular weight is 404.36 g/mol and its chemical name is (R)-3-(4-(7H-purrolo[2,3-d] pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate. All doses, regardless of form, are expressed as the free base equivalent. All GLP toxicology studies utilized the monophosphate salt form of ruxolitinib (correction factor of 1.32).

The drug is supplied as tablets of 5, 10, 15, 20 and 25 mg. The tablets contain the active ingredient and may include the following commonly used excipients: microcrystalline cellulose, lactose, (b) (4) magnesium stearate, colloidal silicone dioxide, sodium starch glycolate, povidone and hydroxyl propyl cellulose. All excipients are of USPh and EUPh compendial grade.

The established drug name is ruxolitinib and the proposed commercial name is JAKAFI™. Ruxolitinib has been referred to as INCB 424 or INCB 018424 in the past.

2.2 Tables of Currently Available Treatments for Proposed Indications

The proposed indication is " for the treatment of patients with myelofibrosis (MF), including patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPVMF), and post-essential thrombocythemia myelofibrosis (PET-MF)."

MF is comprised of three types: PMF, PPVMF and PETMF. The incidence is 1/100,000 and the age of onset of PMF is 65 years. The hallmarks of the disease include clonality of hematopoietic cells, splenomegaly, marrow fibrosis and atypical megakaryocytes with extramedullary hematopoiesis, thrombosis, bleeding, fatigue, fever, night sweats, rash, itching, left upper quadrant pain, early satiety, and abdominal fullness. The peripheral blood contains nucleated red cells, tear drops, immature myeloid cells (blasts), fragments of megakaryocytes, and levels of CD34+ cells that are 360 times normal. Prediction of the risk of dying with myelofibrosis is based on the number of the following factors in the International Prognostic Scoring System

(IPSS): age >65, anemia, constitutional symptoms, leukocytosis, and circulating blasts. Four survival risk categories are identified in IPSS as shown in Table 6 below.

Table 6-Survival in IPSS Prognostic Categories

Risk Category	Number of Factors	Median Survival Months	Median Survival Months
Low	0	135	11.3 years
Intermediate-1	1	95	7.9 years
Intermediate-2	2	48	4.0 years
High risk	≥3	27	2.3 years

A median survival of a series of 60 patients was reported recently to be 57 months (Sangre 35: 13, 1990) and 50 months (Blood 115: 4350, 2010). The causes of death in these two series of 60 and 172 patients with MF respectively, are presented in Table 7.

Table 7-Causes of Death in MF

	Percent of Patients (N=60)	Percent of Patients (N=172)
	Sangre 35: 14, 1990	Blood 115: 4350, 2010
Median Survival	4.75 years	3.27 years
AML at a median of 19 months	12%	14.5%
Septic shock	11%	0.0%
Hepatic insufficiency	9%	0.0%
Portal vein hypertension	7%	14.0%
Heart failure (hemochromatosis)	5%	16.0%
Bone marrow failure	0%	19.8%
Intracranial hemorrhage	2%	0.0%
Hemoperitoneum	2%	0.0%
Acute renal failure	2%	0.0%
Cachexia	0%	3.5%
Unclear cause of death	12%	23.8%
Total Died	61%	90.7%

There are no treatments for MF that have received full FDA approval. There is only one curative therapy for MF: allogeneic stem cell transplantation. The median age of patients transplanted is 42-45. The average age of diagnosis of MF is 65 (most patients are diagnosed between 50 and 69 years of age). Thus, the majority of patients are excluded from eligibility for allografts. The 5 year probability of treatment failure due to relapse or persistent disease after transplantation was 36%. Failure of sustained engraftment is in the 10% range.

The 7 year survival in the Seattle series is 61%. Common chemotherapies used in the community for the palliative treatment of MF include: busulfan, 6-thioguanine, chlorambucil with prednisone, interferon-alpha, melphalan, thalidomide, lenalidomide, erythropoietin, anagrelide, dexamethasone, and hydroxyurea. Splenic irradiation has been used for the relief of symptoms associated with massive splenomegaly.

Heterozygosity for the JAK2V617F activating mutation is found in 50% of MF and homozygosity for this mutation is found in 13% of PMF. A mutation of the transmembrane domain of the thrombopoietin receptor (MPLW515) has been found in 9 percent of patients with MF who are negative for the JAK2V617F mutation. Thirty percent of the patients with MF positive for the MPLW515 mutation are also positive for the JAK2V617F mutation. Patients with MF who are negative for the JAK2V617F and MPLW515 mutations still exhibit clonal hematopoiesis, suggesting the presence of other yet undiscovered mutations that play a role in the development of MF. In support of this observation, many authorities feel that the natural histories of patients with MF who are positive or negative for the JAK2V617F mutation are similar.

2.3 Availability of Proposed Active Ingredient in the United States

Incyte has provided information in NDA 202192 about the availability of the drug product in the 5, 10, 15, 20 and 25 mg strengths (see Table 8 below). The prevalence of MF in the United States is between 18,000 and 20,000 patients. Approximately one-half of these are sufficiently symptomatic as to need treatment. Assuming that only 10-20% of these patients will elect to be treated immediately following the announcement of the approval, Table 8 suggests that there are sufficient supplies of the drug to support the clinical demand.

Table 8-Drug Availability

Strength	Lot Number	Number Tablets	Manufacturing Date
5 mg	A53228	(b) (4)	November 18, 2009
10 mg	A65538A		November 18, 2009
15 mg	A65538B		January 24, 2011
20 mg	A64438C		January 24, 2011
20 mg	A65538C		January 24, 2011
25 mg	A51522		October 6, 2010
25 mg	A51342A		October 6, 2010
25 mg	A51341A		October 6, 2010

2.4 Important Safety Issues With Consideration to Related Drugs

Ruxolitinib is the first in its class and so there are no important safety issues with related drugs.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The regulatory history of ruxolitinib is outlined in Table 9.

Table 9-Regulatory History

Date	Event
03/30/07	Submission of IND 77456 by Incyte
03/04/08	Meeting with FDA for drug development plan
09/05/08	Orphan drug designation
09/18/08	Meeting with FDA for registration study
07/17/09	SPA agreement for INCB 18424-351 (MF)
07/30/09	BCA1 Classification for ruxolitinib
10/01/09	Fast track designation
09/02/10	SPA agreement for INCB 18424-356 (P Vera)
11/03/10	Pre-NDA meeting
06/03/11	Submission NDA

2.6 Other Relevant Background Information

Orphan drug status was given to ruxolitinib under FDA Act 526 for MF. Thus, there will be no requirement for a pediatric waiver request (see CFR316(d) Exemption for Orphan Drugs).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

NDA 202192 was submitted as an electronic Common Technical Document (eCTD) and is organized following the FDA Guidance for Industry. The eCTD was generated by Octagon Research Solutions, Inc., which filed an acceptable eCTD pilot with the FDA on June 2, 2004 (Pilot Number 9000024). All electronic files included in the NDA 202192 submission are on a single DLT Tape and the electronic submission is approximately 23.2 GB. All files were checked and verified to be free of viruses. All provisions outlined in the November 3, 2010 pre-NDA meeting were adhered to. The submission is acceptable for review.

DSI inspections for data audits have been carried out at two of the sites for INCB-351 as outlined in Table 10. No significant deficiencies have been uncovered by DSI at these sites.

Table 10-DSI Audit Sites for INCB-351

Site Number	Name of PI	Institution	Location	Number of Patients

023	Jason Gotlib	Stanford U	Sanford, CA	15
046	Carole Miller	St. Agnes Health Care, Inc.	Baltimore, MD	8

3.2 Compliance with Good Clinical Practices

This study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization and laws and regulatory requirements of all countries in which the trial was carried out.

3.3 Financial Disclosures

A FDA Financial Disclosure Form 3454 dated May 20, 2011 and signed by Dr. Ron C. Falcone of Incyte, was submitted on behalf of all the investigators at all of the clinical trial sites.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Incyte has provided information in NDA 202192 about the availability of drug product in the 5, 10, 15, 20 and 25 mg strengths. This data, which is summarized in Table 8 above, suggests that there are sufficient supplies of the drug to support the clinical demand if indeed ruxolitinib is approved for MF. CMC did not have issues with the NDA as the manufacturing site inspections showed no deficiencies.

4.2 Clinical Microbiology

The analysis of the Clinical Microbiology studies is summarized in the CMC section of the Review of NDA 202192. There were no significant deficiencies noted in the manufacturing site inspections.

4.3 Preclinical Pharmacology/Toxicology

Ruxolitinib was not carcinogenic in a 26 week study in transgenic mice (Tf.rasH2) as outlined in Module 2.4. A two year oral carcinogenicity study in rats was initiated on April 27, 2009 and the results from this study are pending.
[ISS, p. 193]

Testing did not reveal mutagenicity or clastogenic potential in human peripheral blood lymphocytes (see Module 2.4).
[ISS, p. 193]

Increases in post-implantation loss were noted in the rat (NOAEL, 10 mg/kg) see Module 2.4, and therefore the use of ruxolitinib during pregnancy is not recommended.
[ISS, 187]

The results of the detailed analysis of the Pre-clinical Pharmacology/toxicology studies are summarized in the Pharmacology Toxicology Section of the Review of NDA 202192.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The drug is a member of the new class of Janus kinase (JAK) inhibitors. JAKs are associated with cytokine or growth factor receptors which lack intrinsic tyrosine kinase activity. Binding of the ligand triggers oligomerization of the receptor subunits which then leads to activation of one or more members of the JAK family of kinases which are associated with these receptors. Once activated, the JAKs phosphorylate the growth factor receptors as well as a family of downstream signals called the "signal transducers and activators of transcription" (STATs). These STATs then dimerize and translocate to the nucleus where they bind to promoter regulatory regions of target genes leading to their transcription.

Ruxolitinib is a potent ATP competitive inhibitor of JAK1 (IC_{50} =3.3 $\pm$ 1.2 nM) and JAK2 (IC_{50} =2.8 $\pm$ 1.2 nM). Ruxolitinib has modest inhibitory activity for the TYK2 (IC_{50} =19 $\pm$ 3.2 nM) and for JAK3 (IC_{50} =428 $\pm$ 243 nM) when assessed at 1 mM ATP concentration. Ruxolitinib exhibited no inhibitory activity against a broad panel of 30 other kinases when tested at 200 nM.

When tested in cell based assays, ruxolitinib inhibited erythroid colony formation from polycythemia vera donors (who are positive for the V617F activating mutation) at an IC_{50} of 223 nM compared to an IC_{50} of 407 nM for normal donors. Cells bearing the JAK2V617F mutation were not more sensitive to ruxolotinib compared to cells from healthy volunteers with respect to colony formation in the presence of optimal concentrations of erythropoietin. Ruxolitinib inhibits

STAT3 phosphorylation in response to stimulation of whole blood cells with thrombopoietin or IL-5 (IC_{50} of 281 nM).

JAK2 is required for signaling through receptors for erythropoietin, thrombopoietin, G-CSF, IL-3, prolactin, IL-5 and interferon alpha. JAK1 is required for signaling through G-CSF, IL-4, IL-5, IL-10, IL-11, IL-12 and interferon alpha and beta. These data, and the fact that ruxolitinib inhibits both normal as well as mutant JAKs, suggests that the toxicity of ruxolitinib will include thrombocytopenia, anemia, neutropenia, and infections. In fact, the only DLT encountered in the initial phase I trials of ruxolitinib was thrombocytopenia. Other non-DLT adverse events included anemia and infections. Ruxolitinib appears to display equivalent activity in patients with MF who have the V617F activating mutation of JAK2 as in those who are negative for this mutation. This suggests that other activating mutations of JAK2 in other parts of the molecule than the ATP binding site to which ruxolitinib binds (that are not identified by the current assay for V617F), are over-ridden by the inhibition of the ATP binding by ruxolitinib.
[Module 2.4 Non-clinical overview, pp. 7-8].

There was evidence for a ruxolitinib induced decrement in the level of the V617F JAK2 mutant allele positive cells during long term ruxolitinib therapy (see Section 6.1.5.f and Table 34 for INCB-351 and Section 6.1.16 and Table 46 in INCB-352).

4.4.2 Pharmacodynamics

The analysis of the pharmacodynamics of ruxolitinib is outlined in the sections of the review that pertain to Clinical Pharmacology and Pharmacology Toxicology.

4.4.3 Pharmacokinetics

The analysis of the pharmacokinetics of ruxolitinib is outlined in the sections of the review that pertain to Clinical Pharmacology. The parent unchanged compound, ruxolitinib, has a plasma half life of 3.1 hours. The active metabolites have a plasma half-life of 5.8 hours. Only 1% of the parent compound is excreted unchanged. This drug is metabolized by CYPC3A4. One of the issues discovered was that the response rate range was higher in women than in men in INCB-351 (non-overlapping ranges in the forest plot analysis which is presented in Figure 9 on page 49 of this report). The one remaining explanation is the well known antagonism of JAK2 by estrogens in women. This effect of estrogens could have made women with MF more sensitive to the effects of ruxolitinib.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

As shown below in Table 11, Incyte's study of the efficacy of ruxolitinib is based on two large well controlled randomized comparisons of ruxolitinib with either a placebo (INCB-351) or Best Available Therapy (INCB-352). Together, these two trials provide the efficacy outcome on 301 individuals with MF who predominantly were in need of therapy.

Incyte's safety analysis of ruxolitinib is based on 455 patients with MF treated with ruxolitinib, and an additional 162 patients with other diseases (prostate cancer, myeloma, polycythemia vera, and essential thrombocythemia) who were exposed to ruxolitinib.

Table 11-Completed Clinical Trials

Number of Patients	Trial Number	Type of Trial	Type of Patients
155	INCB-351 (Pivotal)	Phase III	MF
146	INCB-352 (Supporting)	Phase III	MF
154	INCB-251	Phase I/II	MF
22	INCB-254	Phase II	Prostate Cancer
13	INCB-255	Phase II	Myeloma
73	INCB-256	Phase II	Polycythemia Vera
617	Total Treated	Phase I, II, III	
455	MF Patients Treated	Phase II and III	

5.2 Review Strategy

Incyte completed two phase III randomized comparisons of ruxolitinib with either a placebo (INCB-351) or Best Available Therapy (INCB-352). These patients support the analysis of efficacy for ruxolitinib. There are a total of 301 patients with MF for this efficacy comparison with 227 patients on the non-ruxolitinib arms. The primary endpoint for both trials was the percent of patients on both arms who have experienced ≥35% SVR by MRI during the 24 weeks treatment period in INCB-351 and during the 48 week treatment period in INCB-352.

In addition, in INCB-351, the key secondary endpoint was the percent of patients on both arms who have experienced ≥50% reduction of the Total Symptom Score (TSS) following 24 weeks of treatment, which was derived from a patient reported outcome (PRO) instrument. This was a key secondary endpoint for efficacy on INCB-351. The key secondary endpoint in INCB-352 was the percent of patients on both arms who experienced ≥35% SVR by MRI during the 24 weeks of treatment.

The safety analysis was restricted to the 455 patients with MF who have been treated with ruxolitinib. The safety analysis focused on patients entered onto INCB-351 and INCB-352, because the randomized nature of these trials provides the opportunity to test whether adverse

events observed on the ruxolitinib arms of these trials can be attributed to ruxolitinib or not. Fortunately, there were 301 patients treated with ruxolitinib on both of these trials, and 227 patients on the non-ruxolitinib arms.

5.3 Discussion of Individual Studies/Clinical Trials

The clinical trials of ruxolitinib in neoplastic disorders which have been completed are summarized below in Table 12. The phase III randomized comparisons of ruxolitinib with placebo (INCB-351) or with Best Available Therapy (INCB-352) were submitted in support of the efficacy analysis. The patients treated with ruxolitinib on these phase III (301 patients with MF) trials, along with the patients treated with ruxolitinib on the other trials form the basis of the Integrated Summary of Safety (617 patients).

Table 12-Patients Included in Integrated Safety Summary

Study #	Efficacy	ISS	Type Trial	Schedule	Disease	# Ruxolitinib Treated patients
INCB-351	+ (Pivotal)	+	Phase III	15 mg po bid	MF	155
INCB-352	+ (Supportive)	+	Phase III	15 mg po bid	MF	146
INCB-251	Not considered	+	Phase I/II	Dose Escalation	MF	154
INCB-254	Not considered	+	Phase II	25 mg po bid	Pros Ca	22
INCB-255	Not considered	+	Phase II	25 mg po bid	Myeloma	13
INCB-256	Not considered	+	Phase II	10, 25, 50 mg bid	P Vera, ET	73
Total						617
Total MF						455

Phase I/II Trials of MF

INCB-251: Phase I/II Single Arm Study of Ruxolitinib in PMF, PPVMF and PETMF.
The goal of this trial was to characterize the safety and tolerability of ruxolitinib in MF. The most common adverse events were anemia and thrombocytopenia. The most frequently reported SAE was pneumonia (7%).

Part 1: The goal in this classic 3+3 dose escalation trial of ruxolitinib in patients with PMF, PPVMF or PETMF that required therapy due to symptoms or splenomegaly who were either refractory/relapsed, or treatment naïve but ineligible for allograft, and high risk or intermediate-2 risk, was to determine the DLTs and the MTD when ruxolitinib was given bid continuously for a single 28 day cycle. The DLT at 50 mg po bid was Grade 4 thrombocytopenia. The MTD for this schedule was set at 25 mg po bid.

Part 2: The goal was to study three schedules:

Schedule A: Patients were give a single daily dose (not bid) continuously. The MTD for this schedule was 100 mg po qd (twice that of the bid schedule). This makes sense in

view of the fact that the half life of the unmetabolized parent compound is 3.1 hours and of all the active metabolites is 5,8 hours.

Schedule B: Tolerability of low dose bid regimen given continuously without stopping at 10 mg po qd was greater in terms of thrombocytopenia. There were no cases of Grade 4 thrombocytopenia on this regimen, and the incidence of Grade 3 thrombocytopenia was less than on higher bid doses of ruxolitinib.

Schedule C: Using an induction schedule with 25 mg po bid for two 28 day cycles followed by maintenance at 10 mg po bid, thrombocytopenia leading to dose adjustments occurred most frequently during the first cycle.

Part 3: This study examined the effect of adjustment of the beginning dose of ruxolitinib on the intensity of symptoms of patients with MF requiring therapy due to symptoms, to 15 mg po bid if the pre-treatment platelet count was >200,000/microliter, or to 10 mg po bid if the pre-treatment platelet count was ≤200,000/microliter.

Efficacy Results of INCB-251: Among patients participating in spleen volume evaluation, 40.7% (11/27) had ≥35% SVR and the responses for 7/11 of these patients were maintained through week 72. The median percent change of the spleen was greater in the groups receiving 10-20 mg po bid, than in the groups receiving 5-10 mg po bid. At week 24, there was an improvement in the symptom score for night sweats, abdominal discomfort/pain, itching, and bone pain.
[CSR INCB-251, pp. 3-6]

Reviewer Comment*: The results of this carefully designed phase I/II study of ruxolitinib in MF led to the provisions in the phase III trials (INCB-351 and INCB-351) for a starting dose of 20 mg po bid if the pre-treatment platelet count was >200,000/dL, and the provisions in these trials for reduction of the starting dose of 20 mg po bid to 15 mg po bid if the pre-treatment platelet count was >100,000/microliter, and <200,000/microliter.*

These starting dose rules (along with dose adjustments on the basis of thrombocytopenia following initiation of therapy) may have played an important role in the result observed (see below) for the two phase III trials (INCB-351 and INCB-352): impressive responses in terms of reduction of spleen volume and reduction of symptoms without any increase on the ruxolitinib arms of clinically significant bleeding associated with thrombocytopenia. These dose adjustments clearly led to a favorable efficacy outcome without a disruption of the quality of life by serious adverse events.

Phase III Trials of MF: There were two phase III prospectively randomized trials of ruxolitinib in patients with MF completed by the Sponsor:

1. **INCB-351 (Pivotal Trial)**. This was a double-blind, prospectively randomized, placebo-controlled phase III trial, which is the pivotal trial for the NDA that was carried out in the USA, in which 309 patients with MF who had failed available therapy and who needed treatment due to symptoms were randomized 1:1 to ruxolitinib or to placebo. The primary endpoint was a statistically significant difference (as assessed by the Chi-square test) between the

ruxolitinib arm and the placebo arm in terms of the percent of patients who achieved ≥35% SVR by week 24 of treatment (2-sided alpha of 0.05).

Secondary endpoints were planned to be analyzed if the study reached the efficacy objective in the primary endpoint. The secondary endpoints were to be analyzed in a fixed-sequence-testing procedure in the order indicated below with each at the alpha level of 0.05.

a. The primary endpoint and the key secondary endpoint were a statistically significant difference (by the Chi-square test) between the ruxolitinib arm and the placebo arm in terms of the percent of patients who 1. achieve ≥35% SVR and 2. achieve ≥50% reduction in the TSS as assessed by a validated patient related outcomes instrument.
b. A comparison between the ruxolitinib and placebo arms for the percent change from baseline in the Week 24 total symptom score using the Wilcoxon Rank-Sum test and the analysis of covariance methods.
c. Survival for each treatment group (estimated with 95% confidence intervals) using the log-rank test to test for an effect of treatment effect on survival.
d. Another secondary endpoint was the duration of ≥35% SVR using the Kaplan-Meier method. No comparative analysis was performed for this endpoint.
[CSR INCB-351, pp. 3-10]

2. **INCB-352 (Supportive Trial).** This was a open-label prospectively randomized trial carried out in Europe in which patients with MF who had failed available therapy and who were in need of treatment due to symptoms, or if previously untreated were ineligible for allograft, and who were high risk or intermediate-2 risk patients, were randomized 2:1 to ruxolitinib or to Best Available Therapy (BAT).

The primary endpoint was a statistically significant difference as assessed by the Cochran-Mantel-Haenszel (CMH) test stratified by prognostic category (intermediate -2 or high risk) between the ruxolitinib arm and the BAT arm in terms of the percent of patients who achieve ≥35% SVR by week 48 of treatment.

The key secondary was a statistically significant difference between the ruxolitinib arm and the BAT arm in terms of the percent of patients who achieve ≥35% SVR by week 24 of treatment as assessed by the CMH test.

Other secondary endpoints included: duration of maintenance of ≥35% SVR, leukemia–free survival, overall survival, transfusion dependency, and a change in bone marrow histomorphology. There was no pre-specified order of analysis.
[CSR INCB-352, pp. 3-8]

These two phase III trials are summarized below in Table 13.

Table 13-Design of Phase III Trials

	INCB-351	INCB-352
Design	Double blind	Open label
Location	USA	Europe
High risk or intermediate-2	Yes	Yes
Previously treated, relapsed/refractory	Yes	Yes
Previously untreated, ineligible for SCT	No	Yes
Need treatment due to symptoms or splenomegaly	Yes	Yes
Patients randomized	309	219
Randomization of ruxolitinib vs comparator	1:1 (155 pts: 154 pts)	2:1 (146 pts:73 pts)
Comparator Arm	Placebo	Best Available Therapy
Primary Endpoint: ≥35% ↓ SVR	Week 24 of treatment	Week 48 of treatment
Key Secondary Endpoint at week 24	% ↓ TSS ≥50%	% SVR ≥35%

6 Review of Efficacy

6.1 Indication for INCB-351 and INCB-352

The proposed indication is "for the treatment of patients with myelofibrosis (MF), including patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPVMF), and post-essential thrombocythemia myelofibrosis(PETMF)."

6.1.1 Methods for INCB-351

This section will describe design issues for INCB-351. For additional details, see Section 5.3 above.

Eligibility: This double blind placebo controlled trial prospectively randomized 309 patients with MF with the following eligibility characteristics (see Table 14):

Table 14-Eligibility for INCB-351

1. PMF, PPVMF or PETMF ≥18 years, ECOG PS=0-3
2. Resistant, refractory, or intolerant of available therapy
3. In need of treatment (see Table 15 below for definition)
4. Life expectancy ≥6 months
5. Spleen length ≥5cm below left costal margin
6. Intermediate-2 risk or high risk by IWG criteria
7. Hb <10 g/dL or dependency on red blood cell transfusions

[Clin Protocol, July 21, 2009]

The definition or criteria for patients who are in need of therapy is given below in Table 15.

Table 15-Definition of Patients with MF Who Need Treatment

IWG Category of high risk (≥3 factors) as outlined above in Table 6
Palpable spleen ≥10 cm below left costal margin
Active symptoms: one of the following symptoms which is ≥5/10 in severity or a score of ≥3 on ≥2 of the following: a. early satiety b. abdominal discomfort c. abdominal pain d. inactivity e. night sweats f. pruritis g. bone pain

Treatment: Patients on the treatment arm received daily oral ruxolitinib tablets, and patients on the control arm received daily placebo tablets that matched those on the treatment arm in appearance and number.

Pre-Treatment Dose Adjustments (Reductions): The patients were treated with a starting dose of 20 mg po bid if the pre-treatment platelet count was >200,000/microL. The dose of 20 mg po bid was reduced to 15 mg po bid if the pre-treatment platelet count was >100,000/microL, and <200,000/microL. The dose could be increased by 5 mg incremental intervals by the fourth week of therapy if the following 3 conditions were met:

a. The spleen length below the left costal margin had been reduced by ≤40% by 4 weeks as compared to baseline;

b. The platelet count at Week 4 was ≥150,000/microL and the platelet count had never been <150,000/microL from the time of baseline;

c. Absolute neutrophil counts (ANC) remained ≥1,000/microL since baseline.

[CSR INCB-351, p. 39]

Dose Adjustments Due to Reductions in the Platelet or Neutrophil Count During Treatment: During the 24 week treatment period, the CBC with differential count was done at weeks 1 and 2 and then every other week thereafter. The frequency of CBC determinations was increased to twice weekly if the platelet count falls less than <50,000/microL or if the ANC is <500/microL.

[INCB-351 Protocol Version December, 2008, Section 7, pages 54-55]

The procedure for reducing the dose of ruxolitinib, as outlined in the INCB-351 clinical protocol document was as is outlined in Table 16 below.

Table 16 Guide for Dose Reductions

Platelet Count at time of decline	Dose at time of decline: 25 mg BID	Dose at time of decline: 20 mg BID	Dose at time of decline: 15 mg BID	Dose at time of decline: 10 mg BID	Dose at time of decline: 5 mg BID
	New Dose	New Dose	New Dose	New Dose	New Dose
≥125K/μL	25 mg BID	20 mg BID	15 mg BID	10 mg BID	5 mg BID
100to<125K/μL	20 mg BID	20 mg BID	15 mg BID	10 mg BID	5 mg BID
75to<100K/μL	10 mg BID	10 mg BID	10 mg BID	10 mg BID	5 mg BID
50to<75K/μL	5 mg BID	5 mg BID	5 mg BID	5 mg BID	5 mg BID
<50 K/ μL	0	0	0	0	0

[INCB-351 Protocol Version December, 2008 Section 5.4.2, page 44]

Reviewer Comment*: Because of the dose adjustment system described above in Table 16, the incidence of adverse events leading to discontinuations of ruxolitinib due to thrombocytopenia, anemia and neutropenia in the combined experience of INCB-351 and INCB-352 are given below in Table 17.*

Table 17: Discontinuations of Ruxolitinib on INCB-351 and -352

Parameter	*Dose Discontinuation*	
	Percent	*(n/N)*
Thrombocytopenia	*0.7%*	*(2/301)*
Anemia	*0.3%*	*(1/301)*
Neutropenia	*0.3%*	*(1/301)*

[INCB-351 Protocol Version December, 2008, page 86]

Dose Increases Due To Failure to Achieve a Response: After the first four weeks of therapy, doses of ruxolitinib were subject to escalation by 5 mg BID for subjects who demonstrated inadequate efficacy, and who met all of the following conditions:

a. inadequate efficacy demonstrated by failure to achieve 35% SVR relative to baseline by CT or MRI;
b. Platelet count > 125,000/microL at 4 weeks and platelet count never been below 100,000/microL;
c. ANC levels have remained > 750/microL since enrollment in the study.

[INCB-351 Protocol Version December, 2008, Section 5.4.1, pages 42-43]

Cross-Over From Placebo to Ruxolitinib Arm: At week 24, patients on the control arm were eligible to be crossed over to ruxolitinib if the platelet count was ≥75,000/microL and the ANC ≥500/microL. The dose of initiation of ruxolitinib is determined by the platelet count as is indicated below in Table 18**:**

Table 18: Starting Dose of Ruxolitinib After Cross-Over

Starting Dose	**Platelet/ANC Count**
20 mg BID	Platelets ≥200,000/microL

15 mg BID	Platelets>100,000/microL but <200,000/microL
10 mg BID	Platelets ≥75,000/microL but <100,000/microL
Cannot Start	Platelets <75,000/microL, or ANC<500/microL

[INCB-351 Protocol Version December, 2008, page 40, Table 3]

Endpoints: The first and key secondary endpoints were a statistically significant difference (by the Chi-square test) between the ruxolitinib arm and the placebo arm in terms of the percent of patients who 1. achieve ≥35% SVR and 2. achieve ≥50% reduction in the TSS as assessed by a validated patient related outcomes instrument.

Additional secondary endpoints include:

a. A comparison between the ruxolitinib and placebo arms for the percent change from baseline in the Week 24 TSS using the Wilcoxon Rank-Sum test and the analysis of covariance methods.

b. Survival for each treatment group (estimated with 95% confidence intervals) using the log-rank test to test for an effect of treatment effect on survival.

c. Another secondary endpoint was the duration of the reduction of the spleen volume by ≥35% using the Kaplan-Meier method. No comparative analysis was performed.

Secondary endpoints were planned to be analyzed if the study reached the efficacy objective in the primary endpoint. The secondary endpoints were to be analyzed in a fixed-sequence-testing procedure in the order indicated below with each at the alpha level of 0.05.
[CSR INCB-351, pp. 3-10]

Statistical Analysis and Missing Data: This study had a single primary endpoint. The study was to achieve the efficacy objective if the primary endpoint showed a significant result at 2-sided alpha of 0.05 at final analysis (24 weeks). The secondary efficacy endpoints was analyzed only if the study reached the primary endpoint. The secondary efficacy variables were tested following a fixed sequence-testing procedure with each at the alpha level of 0.05 in the following order shown below: 1. The proportion of subjects who had a ≥50% reduction of TSS from Baseline in Week 24; 2. Percent change from Baseline in the TSS; and 3. OS. If the study achieved the primary endpoint but not the first 2 secondary endpoints, the p value resulting from the analysis of OS was considered as a summary statistic only. The duration of a ≥35% SVR at 24 weeks was analyzed only in subjects who were randomized to the active groups. There was no false positive error associated with the variable and there was no alpha spending associated with the analysis of this variable.
[CSR INCB-351, p. 62]

***Reviewer Comment**: Patients who left the trial, or for whom the response evaluations were missing were considered to be failure events. There were no imputations for missing data performed. [CSR INCB-351, p. 53]*

6.1.2 Demographics for INCB-351

The demographic features of patients entered onto each arm of INCB-351 at Baseline are presented below in Table 19A.

Table 19A-Demographic Features at Baseline for INCB-351

Feature	Ruxolitinib (N=155)	Placebo (N=154)
Female Gender	49.0%	42.0%
Primary Myelofibrosis (PMF)	45.0%	55.0%
PPV-MF	32.0%	31.0%
PET-MF	23.0%	14.0%
Years (median) since diagnosis (range)	2.1 (0.0, 30.1)	2.5 (0.0, 33.2)
Median Spleen Volume at Baseline(cm^3)	2,598 cm^3	2,566 cm^3
Range Spleen Volume at Baseline (cm^3)	478.1-7461.8 cm^3	521.0-8880.7 cm^3
ECOG PS≥2 vs <2	14.0%	22.0%
IWG High Risk vs Intermediate-2	58.0% vs 42%	65.0% vs 35%
% Patients Positive for V617F at Baseline	73.0%	80.0%

[CSR-351, pp. 70-72]

Prior treatment history for the patients on INCB-351 is shown below in Table 19B.

Table 19B-Prior Treatment History of Patients Entered onto INCB-351

Therapy	Ruxolitinib		Placebo	
Number of Patients	N=155		N=154	
	n	(%)	n	(%)
Hydroxyurea	104	(67.1%)	87	(56.5%)
Prior Splenic Radiation	1	(0.6%)	0	(0.3%)
Blood Transfusions	43	(27.7%)	44	(28.6%)

[CSR INCB-351, p. 74]

Reviewer Comment*: The data (Table 19A) suggest that the patients on both arms were well balanced with the exception for ECOG performance status ≥2 which was 8% higher on the placebo arm, and the percentage of patients who were high risk vs intermediate-2 risk (7% higher on the placebo arm). These differences do not explain the observed differences in SVR or reduction in TSS at Week 24. Listings of protocol violations and prohibited medications did not show significant differences between the two arms.*

6.1.3 Subject Disposition for INCB-351

The disposition of human subjects entered onto INCB-351 is summarized in Table 20 below.

Table 20-Disposition on INCB-351

Treatment Arm	Ruxolitinib	Placebo
Number Entered	N=155	N=154
Variable	n (%)	n (%)
Number of patients on study as of 11/02/10	134 (86.5%)	78 (52.7%)*

Number of subjects who crossed over	0 (0.0%)	36 (23.8%)
Number subjects withdrawn from study	21 (13.5%)	37 (24.5%)
Reasons for withdrawal from study		
a. Death	9 (5.8%)	9 (6.0%)
b. Adverse event	8 (5.2%)	8 (5.3%)
c. Disease progression	3 (1.9%)	12 (7.9%)
d. Consent withdrawn	1 (0.6%)	3 (2.0%)

*the percentage of patients who crossed over to ruxolitinib and who are still on study is 88.9%.
[CSR for INCB-351, pp. 67-69]

The number of patients evaluable for spleen volume reduction at week 24 was 155 on the ruxolitinib arm and 153 on the placebo arm (virtually all of them). On the ruxolitinib arm, as of the data lock of November 2, 2010, there were 134 of the original 155 patients (87%) originally randomized to ruxolitinib still on study (see Table 20 above). The number of patients on the placebo arm who were still evaluable at the time of the November 2, 2010 data lock was only 78 (53%) of the 154 patients originally randomized to the placebo arm (see Table 20 above).
[CSR INCB-351, pp. 86-87]

Reviewer Comment*: The data presented above in Table 20 shows that the number of patients who were still on study at the time of data lock in November 2, 2010 on the ruxolitinib arm was much greater than that on the placebo arm. In contrast, the number of subjects who withdrew from the study was greater on the placebo arm. In addition, as will be shown in the analysis of the safety data in the Integrated Summary of Safety (ISS), the number of adverse events in most categories (excluding anemia, thrombocytopenia, dizziness, headache and confusion) is not greater on the ruxolitinib arm than on the placebo arm. This evidence suggests that ruxolitinib may be having a desired therapeutic effect without increasing clinically significant toxicity.*

6.1.4 Analysis of Primary and Key Secondary Endpoints for INCB-351 at Week 24

The efficacy results for the primary efficacy endpoint and the key secondary endpoint at week 24 for INCB-351 is presented below in Table 21 below.

Table 21-Efficacy Results for INCB-351

Treatment Arm	Ruxolitinib	Placebo	P value
Patients Randomized	N=155	N=154	
Primary Endpoint	N=155	N=153	
% SVR ≥35% at week 24	41.9%	0.7%[#]	P<0.0001*
Key Secondary Endpoint	N=148[&]	N=154	
%↓TSS by ≥50% week 24	45.9%	5.3%	P<0.0001**

*By Fisher's exact test; ** by Chi-square test; [&]NR=data not recorded or available.
[#] This patient died (105-002) from disease progression 4 days after this measurement. It was not determined if this patient had a splenic infarct which could have accounted for the rapid reduction in the splenic volume in this patient.
[CSR-351, pp. 87 and 103]

Among the patients who qualified for cross-over from the placebo arm to the ruxolitinib arm, 36 of the 154 patients on the placebo arm crossed over (23.8%).

The waterfall plots presented below in Figure 2 show that the vast majority of patients on ruxolitinib displayed some degree of reduction of splenic volume (see Panel A of Figure 2) and TSS by week 24 (see Panel B of Figure 2). In each of these panels, the waterfall for the ruxolitinib (almost all below the line at 0) is on the left, and in each panel, the waterfall for the control arm (most of the entries are above the line 0% change line on the ordinate). These figures show that the vast majority of patients on the placebo arm displayed an increase during the treatment period of 24 weeks, and most of the patients on ruxolitinib showed decreases in the splenic volume and the TSS.

Reviewer Analysis and Comment*: On the basis of these results, it is clear that ruxolitinib is a highly active treatment for patients with MF and that both the primary and key secondary pre-specified endpoints of INCB-351 have been met. Importantly, as shown by the two waterfall plots shown in Figure 2A and Figure 2B, most patients on the ruxolitinib arm (the left hand waterfall in each panel) showed reduction (improvement) of spleen volume and TSS, while those on the comparator arms (the waterfall on the right of each panel) worsened (increased). Notably, the PRO data was complete for all but 7/155 patients, a major achievement for a trial.*

Figure 2-Waterfall Plots for A. SVR and B. Reduction of TSS at 24 Weeks

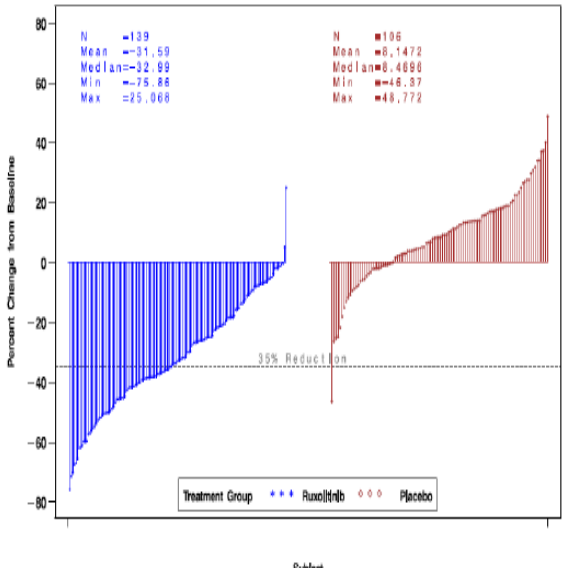


Figure 2A: SVR
[CSR INCB-351, page 90]

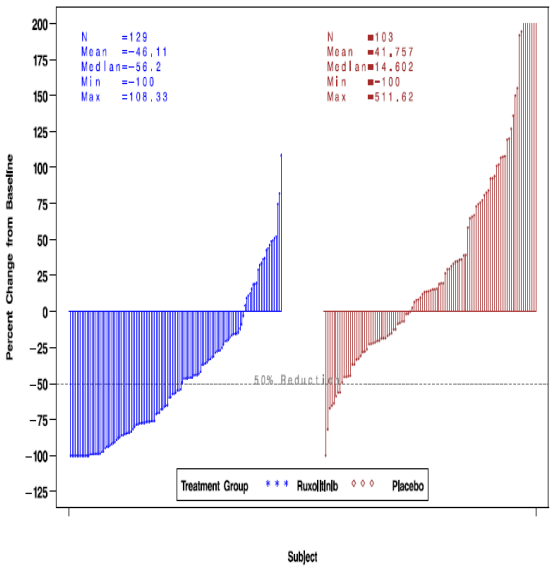


Figure 2B: TSS
[CSR INCB-351, page 106]

It was then of interest to test whether all patients who achieved the criterion for the primary endpoint of a ≥35% SVR on ruxolitinib by week 24 also displayed a ≥50% reduction of the TSS by week 24, and vice versa. As shown below in Table 22

a. *Only 54% (35/65) of the patients treated with ruxolitinib who exhibited ≥35% SVR by MRI at 24 weeks also exhibited ≥50% reduction in the TSS at 24 weeks;*
b. *Only 51% (35/68) of the patients treated with ruxolitinib who exhibited ≥50% reduction in the TSS also exhibit ≥35% in SVR at 24 weeks.*

Table 22-Number of Patients in Different Responder Subgroups

↓TSS without SVR	↓TSS and SVR both	SVR without ↓TSS	SVR, no TSS data
33 patients	35 patients	27 patients	3 patients

The relationship between these subgroups and the final results presented by the Sponsor for the primary and secondary endpoints of their pivotal trial INCB-351 is shown below in Table 23.

Table 23: Efficacy Results in Different Responder Subgroups

Patient subgroup	1^oEndpoint: SVR of ≥35%	2^oEndpoint: ↓TSS of ≥50%
Total number of responders	65	68
Number evaluable patients	155	148 (no data for 7 pts)
Final result for endpoint	41.9%	45.9%
% who reach both endpoints	54.0% (35/65)	51.0% (35/68)

That only one half of patients achieving each of the two endpoints (TSS and SVR) reached both endpoints by week 24 of ruxolitinib therapy is a surprising result and suggests that the patients belonging to the following three response groups:

a. *↓TSS of ≥50% and SVR of ≥35% double positives*
b. *↓TSS of ≥50% without SVR of ≥35%*
c. *SVR of 50% without ↓TSS of ≥50%*

may differ with respect to a number of pre-treatment baseline characteristics. A listing of the characteristics which could be different among the three groups of responding of patients is provided below in Table 24.

Table 24-Baseline Clinical Characteristics

Baseline spleen volume
V617F JAK2 mutation status
Risk category (high risk vs intermediate-2)
Primary MF vs Post PV MF vs Post ET MF
Per cent decrease of TSS by 24 weeks
Symptom specific decrease by 24 weeks
Per cent SVR by 24 weeks

The symptoms utilized by the Sponsor in computing the TSS score are listed below in Table 25.

Table 25-Individual Components of the TSS

	Symptom	*Abbreviation used in NDA*
Abdominal Related		
	Abdominal system score	*ASS*
	Feeling fullness score	*FF*
	Pain under ribs	*PUR*
	Abdominal discomfort	*AD*
Abdominal Unrelated		
	Bone or muscle pain	*BP*
	Night sweats	*NS*
	Itching symptoms	*IS*

The results of analysis of the three main groups of responders listed below in Table 26 for the features listed above in Table 25 are presented below in Tables 27, and Tables 26-30. The results of the analysis of the three main groups of responders listed below in Table 23 for the percent reduction of each of the individual symptom classes listed in above in Table 22 are presented below in Table 25.

Table 26-Responder Groups

Group 1	*↓TSS of ≥50% and SVR of ≥35% double positives*
Group 2	*↓TSS of ≥50% without SVR of ≥35%*
Group 3	*SVR of ≥35% without ↓TSS of ≥50%*

The pretreatment spleen volume (at baseline) was first examined in each of the responder groups listed above in Table 25. The results of this analysis are presented below in Table 27.

Table 27-Baseline Pre-treatment Splenic Volume

	↓TSS without SVR	*↓TSS and SVR both*	*SVR without ↓TSS*
Number in group	*N=33*	*N=35*	*N=27*
Mean	*2,883 cu mm*	*2,794 cu mm*	*2,610 cu mm*
Median	*2,685 cu mm*	*2,800 cu mm*	*2,451 cu mm*

Surprisingly, the responder group that developed a SVR of ≥35% without a decrease TSS of ≥50% had the smallest initial pre-treatment mean and median spleen volumes. However, the spleen volumes in all these three categories (↓TSS without SVR), (↓TSS and SVR both) and (SVR without ↓TSS) are huge. Therefore, baseline spleen volume probably is not the explanation for why some patients are achieving both endpoints of response (decreased TSS and SVR) whereas others are achieving either decreased TSS or SVR.

A second possibility that could explain these three response groups is that there are differences among the individual symptom categories in the TSS inventory in the three response categories.

To address this question, the percent change by week 24 for each of the individual symptoms listed above in Table 25 was analyzed in each of the three responder groups listed in Table 26. The results of this analysis are presented below in Table 28.

Table 28 Mean Percent Change in Individual Symptoms at Week 24

	Abdominal Unrelated				*Abdominal Related*			
	NS	*IS*	*BP*		*ASS*	*AD*	*PUR*	*FF*
↓TSS and SVR both	*-88%*	*-92%*	*-74%*		*-85%*	*-67%*	*-88%*	*-84%*
↓TSS without SVR	*-85%*	*-86%*	*-75%*		*-82%*	*-79%*	*-85%*	*-79%*
SVR without ↓TSS	*-19%*	*+14%*	*+12.2*		*-15%*	*+14%*	*+14%*	*-26%*

Contrary to the expectation outlined above in the hypothesis in the discussion following Table 27, the percent change by week 24 for each of the individual symptoms were not different from each other within each responder group category (as defined in Table 26). It appears as if the symptoms in each of the categories are acting in a coordinate fashion (all of them are changing in the same way). This suggests that patients perceive improvement in all symptom categories or they do not perceive improvement in any of the symptom categories. This refutes the hypothesis that individual symptom categories within the TSS inventory might be driving the outcome in terms of achieving a TSS reduction response.

As expected, the magnitude of percentage change among the patients who achieved SVR of ≥35% without a decrease in the TSS of ≥50% was far less than in the other two groups in which the patients exhibited a decrease in TSS of ≥50% and SVR of ≥35% double positives, or the group with a reduction of the TSS of ≥50% without a SVR of ≥35%. The group that developed a SVR of ≥35% without a decrease of TSS of ≥50% had the smallest percent change in individual symptoms by Week 24. Interestingly, in this group of patients who met the spleen volume reduction criterion but not the TSS criterion, 4 out of the 7 symptom categories were perceived as increasing in intensity rather than diminishing.

The next question analyzed was whether the risk category (high risk vs intermediate-2) would be different in the three responder groups shown in Table 26. As shown below in Table 29, the patients were evenly split between high risk and intermediate-2 risk in the two groups of patients which met the criterion of a SVR of ≥35% (the group with a SVR of ≥35% without a decrease of TSS of ≥50%, and the group exhibiting both a decrease in TSS of ≥50% and SVR of ≥35%). As shown in Table 29A, the high risk patients were twice as common as the intermediate-2 group in the patients who exhibited a reduction of the TSS of ≥50% with a SVR of <35%.

Table 29A-Prognostic Risk Category in the Responder Groups

	↓TSS without SVR	*↓TSS and SVR both*	*SVR without ↓TSS*
High risk	*67%*	*46%*	*48%*
Intermdiate-2 risk	*33%*	*54%*	*51%*

The distribution among the three responder groups (see Table 26) of patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPVMF) and post-essential thrombocythemia (PETMF) was also examined since there is some evidence that PMF may have a different prognosis and genetic profile than is the case with PPVMF, and PETMF.

As shown below in Table 29B, there were no differences in the distribution of these three subtypes of MF in the three types of responders: the group with a SVR of ≥35% without a decrease of TSS of ≥50%, those who exhibited both a decrease in TSS of ≥50% and SVR of ≥35%, or the those with a reduction of the TSS of ≥50% without a SVR of ≥35%. The most common MF subtype was PMF, and the least common was PETMF.

Table 29B: Type of MF in Each of Responder Group Categories

	↓TSS without SVR	↓TSS and SVR both	SVR without ↓TSS
Primary MF	39%	40%	44%
Post PV MF	36%	40%	33%
Post ET MF	24%	20%	22%

As shown in Table 27 below, there were no differences of the distribution of the degree of positivity of the test for V617F in the three types of responders: the group with a SVR of ≥35% without a decrease of TSS of ≥50%, those who exhibited both a decrease in TSS of ≥50% and SVR of ≥35%, or the those with a reduction of the TSS of ≥50% without a SVR of ≥35%.

Table 30-Percent of Cells Positive for V617F Mutation

	↓TSS without SVR	↓TSS and SVR both	SVR without ↓TSS
V617F mean %	57%	78%	53%
V617F median %	70%	90%	76%

As shown in Table 31 below, the percent change of the TSS at 24 weeks was less in those with a reduction of the TSS of ≥50% without a SVR of ≥35% than the percent change of the TSS at 24 weeks in those patients who exhibited both a decrease in TSS of ≥50% and SVR of ≥35%. As expected, the percent change of the TSS was lowest in the group with a SVR of ≥35% without a decrease of TSS of ≥50%.

Table 31-Percent Change in TSS at 24 Weeks in Different Responder Groups

	↓TSS without SVR	↓TSS and SVR both	SVR without ↓TSS
Mean % change	-68.7%	-85.6%	-16.5%
Median % change	-64.6%	-91.0%	-20.6%

Finally, as shown in Table 32 below, the percent change of the spleen volume at 24 weeks was least in those with a reduction of the TSS of ≥50% without a SVR of ≥35%, and was less than the percent change of the TSS at 24 weeks in the other two responder groups: those patients who exhibited both a decrease in TSS of ≥50% and SVR of ≥35%, or the group with a SVR of ≥35% without a decrease of TSS of ≥50%.

Table 32-Percent in SVR for Different Responder Groups in INCB-351

	↓TSS without SVR	*↓TSS and SVR both*	*SVR without ↓TSS*
Mean % change	*-19.4%*	*-51.0%*	*-44.7%*
Median % change	*-21.5%*	*-50.0%*	*-20.6%*

Conclusions:

1. *Exploratory analysis of the efficacy results in INCB-351 have not led to an explanation as to why only 35/98 (35.7%) of the patients who achieved the pre-specified criteria for a response on the basis of SVR or decreased TSS, did so in both categories (see Table 22 above). The expectation had been that all of the responders would have fulfilled the criteria for response for both SVR and decreased TSS.*
2. *Having said that, it is clear however from inspection of Figures 2A and 2B above, which present the waterfall plots for SVR and decreased TSS, that the vast majority of the patients entered on the INCB-351 trial exhibited some degree of response to ruxolitinib. Thus, the apparent paradox presented by the data in Table 22 may just be a result of trying to convert a continuous variable of response into a dichotomous variable.*
3. *There is no difference in the distribution of patients with different types of MF, or of risk categories of MF, or of degree of positivity for the V617F mutation in the 3 responder groups in INCB-351: those patients who exhibited both a decrease in TSS of ≥50% and SVR of ≥35%, the group with a SVR of ≥35% without a decrease of TSS of ≥50%, and those with a reduction of the TSS of ≥50% without a SVR of ≥35%.*
4. *There do not appear to be individual symptoms that are driving the changes in the TSS more than the other symptoms. Rather, the changes that are occurring appear to be happening concurrently across individual symptoms.*

6.1.5 Analysis of Additional Secondary Endpoints(s) for INCB-351

6.1.5.a. Durability of SVR by ≥35%

The Kaplan-Meier method could not be used to assess the durability of the response to ruxolitinib as defined by the SVR ≥35% criteria because of the short follow-up time following the conclusion of the 24 week treatment period (please see the very low number of patients in the listing of the number of responding patients who are at risk of losing their response beyond 24 weeks in the Kaplan-Meier analysis provided by the Sponsor in Figure 3 below).

The definition of loss of response was: "the first day in patients who had reached a ≥35% SVR on ruxolitinib that there was a ≥25% increase from the nadir in spleen volume". If a patient was discontinued from the study after achieving ≥35% reduction of spleen volume on ruxolitinib, then the response was censored at that time. If the patient was still in remission at the time of data lock after achieving ≥35% reduction of spleen volume on ruxolitinib, then the response was censored at that time.
[CSR INCB-351, Section 11.2.1.1.3 on p. 64]

The Kaplan-Meier analysis of the duration of the responses defined as ≥35% SVR from baseline among patients who achieved ≥35% SVR at any time during the study and had an additional spleen volume measurement is presented below in Figure 3. A compilation prepared by the Sponsor of patients who lost their response or who were lost from the study is presented below in Table 33. Seventy-one patients were included in the analysis. The median duration of response was not reached as the majority of subjects was still responding at the time of the November 2, 2010 data-lock. At the time of the data lock prior to the NDA submission, 26.8% (19/71 patients) had lost the response of reduction of the splenic volume ≥35%. Using the Kaplan-Meier method, the median duration of the response was estimated to be 44.7 weeks (see Figure 3 below).

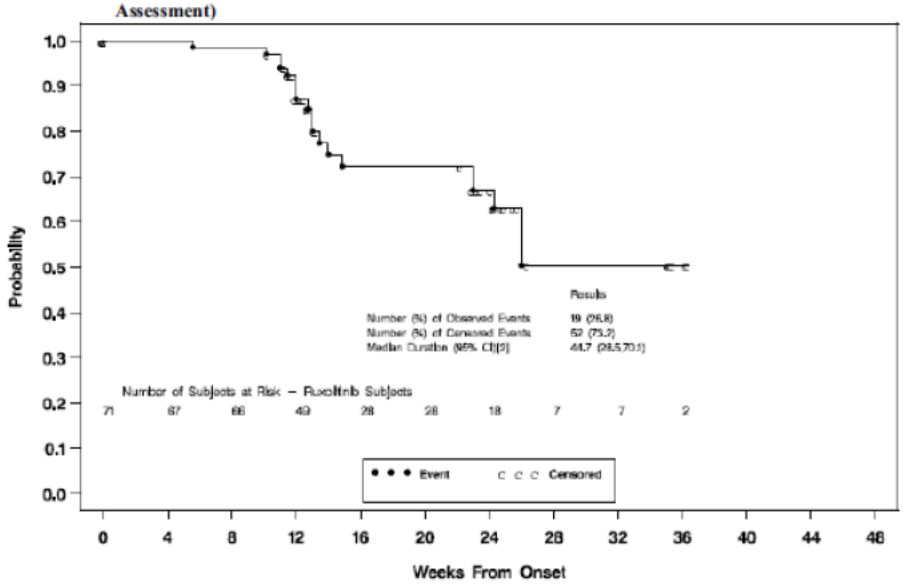
Table 33-Summary of Patients Who Lost SVR Response or Who Left INCB-351

	Week 12	Week 24	Week 36	Week 48
New SVR ≥35%	61	16	3	0
Had SVR ≥35% at Prior Visit	NA	61	65	28
SVR ≥35% Continues	NA	49	25	9
No Longer Has SVR ≥35%	NA	8	9	1
Withdrew from Protocol	NA	3	1	0
Missing	NA	1	1	1
% Evaluable Lost SVR≥35%		12/61=20%	11/65=17%	2/28=7%
Visit Not Reached	NA	0	29	17

[CSR INCB-351, p. 93]

Figure 3-Kaplan-Meier Analysis of Duration of SVR ≥35% on INCB-351

Figure 7: Kaplan-Meier Curve of Duration of ≥35% Reduction of Spleen Volume From Baseline (Subjects Who Achieved a ≥35% Reduction of Spleen Volume at any Time During the Study and had an Additional Spleen Volume Assessment)



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Note: The duration of response was defined for those subjects who had at least 1 measurement of ≥ 35% reduction from Baseline in spleen volume at any time during the study and had at least 1 subsequent measurement or withdrew prior to another assessment. A loss of response was the first date with a less than 35% reduction from Baseline.
Note: The horizontal axis represents the time from onset of response. Subjects could begin responding at Weeks 12, 24, or 36; therefore, weeks from onset does not correspond to weeks in the study.
Note: The median duration was estimated using the exponential model.
Source: Figure 14.4.3.1

[CSR INCB-351, p. 96]

Reviewer Comment: *Because of the short term nature of the follow-up, this Kaplan-Meier estimate is highly unreliable. What is clear from Table 33, is that the follow-up is too short for firm conclusions to be made, and that there are some patients who lost their response after first having achieved it.*

What is not clear from Table 33, is the time interval between the first date of establishing the pre-specified response threshold and the time at which the response was lost before the data lock of November 2, 2010 (for patients who lost their response within the period of observation), or the time interval for each responding patient between the first data of establishing the pre-specified response threshold and the time of censoring at the data lock of November 2, 2010, for those patients who were not observed to have lost their response by the time of the November 2, 2010 data lock. This reviewer analyzed an update of data on the duration of the SVR≥35% as of August 1, 2011. At the time of that analysis, 83 patients had achieved SVR≥35% at the end of 24 weeks of treatment. Progression of disease has been observed in 19 of these 80 patients (23%) and the median time to progression was 25.3 weeks (range 11.6-48.3 weeks). Since 77% of the patients achieving SVR≥35% have not progressed as of August 2, 2011, it is not possible yet to estimate the median duration of these responses.

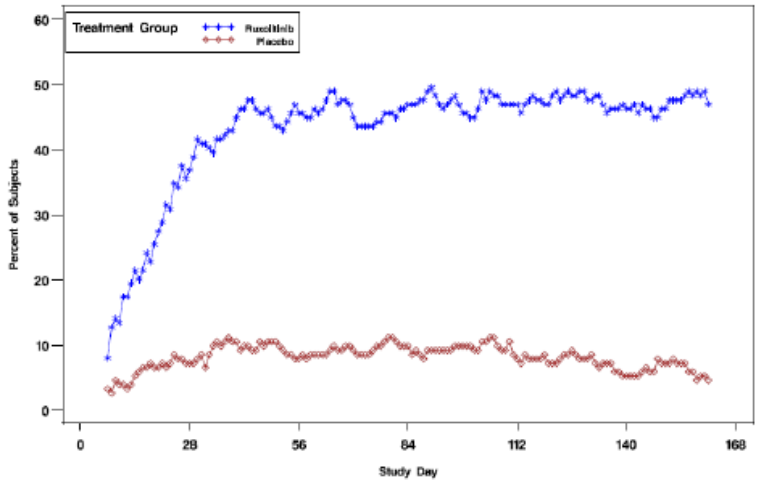
This conclusion suggests that a post marketing commitment on the part of the Sponsor must be part of the approval process to ensure that the question of durability of the SVR response can be resolved in the post marketing period.

6.1.5.b. Time to ≥50% Reduction of TSS

As shown in Figure 4 below, the time to achieve a ≥50% reduction in the TSS from baseline for most patients was 4.4 weeks in the ruxolitinib arm.

Figure 4-Time to *Decrease ≥50% TSS on INCB-351*

Figure 12: Daily Response Rate for Subjects Who Achieved ≥50% Reduction From Baseline in Daily Total Symptom Score Over Time (ITT Subjects)



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[CSR INCB-351, page 109]

6.1.5.c Durability of ≥50% Reduction of TSS responses

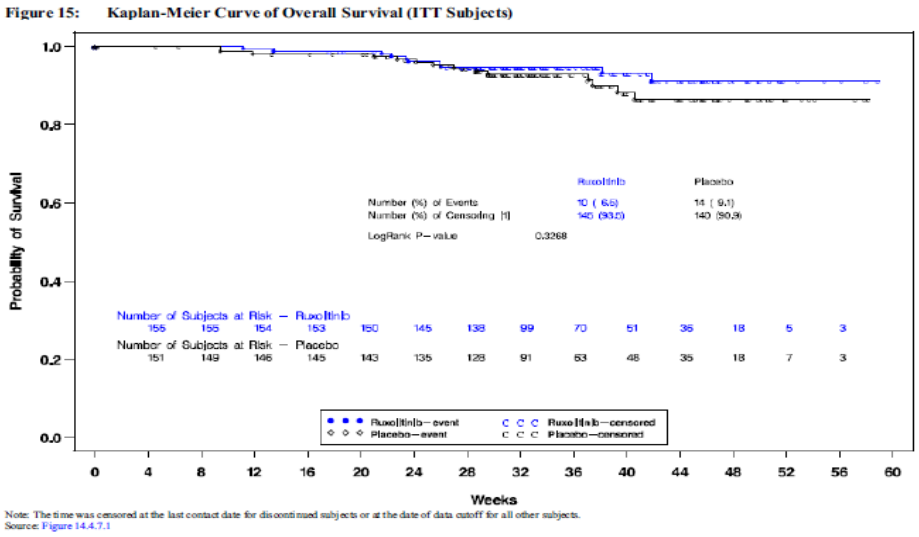
Although measurements of the TSS were made at the following time points: 4, 8, 12, 16, 20, and 24 weeks of treatment, no measurements of the TSS were made beyond 24 weeks on INCB-351.

***Reviewer Comment**: Therefore, it will be impossible to estimate the duration of the ≥50% reduction in the TSS (as defined as the mean and median time intervals between establishment of the TSS response of ≥50% reduction in the TSS and the time of progression), since the measurement of TSS stopped at 24 weeks of treatment.*

6.1.5.d Analysis of Overall Survival on INCB-351

As shown below in Figure 5, the median survival was not reached on either arm. Ten deaths occurred on ruxolitinib and 14 on placebo. The study was not powered for robust analysis of OS.

Figure 5: Analysis of OS in INCB-351



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[CSR INCB-351, p. 121]

Reviewer Comment: It is too early to definitively evaluate the duration of the responses. In addition, INCB-351 is not powered for a robust analysis of OS.

6.1.5.e Bone Marrow Fibrosis

The protocol for INCB-351 provided for evaluation of the extent of fibrosis in the bone marrow before and after ruxolitinib therapy. The protocol provided plans for grading bone marrow fibrosis by analysis of bone marrow biopsies at baseline and at week 49. Bone marrow fibrosis was graded using the European consensus grading system. Baseline bone marrow fibrosis data was available from 144 subjects in the ruxolitinib arm and 141 from the placebo arm. As shown below in Table 34, only 13 subjects in the ruxolitinib group and 11 subjects in the placebo group had fibrosis measurement data collected (or collectable) at Week 48.

Table 34-Number of Patients in INCB-351 Exhibiting Change in Marrow Fibrosis

		Ruxolitinib	Placebo
Baseline		N=155	N=154
	Number of patients with data	144	141
	Percent of patients with data		
Week 48			
	Number of patients with data	13*	11
	Percent of patients with data		
	Number evaluable patients showing increase	4	3

	Number evaluable patients showing decrease	3	0
	Number evaluable patients with no change	5	8
	Percent evaluable patients showing increase	33%	27%
	Percent evaluable patients showing decrease	25%	0%
	Percent evaluable patients with no change	42%	73%

*one patient with Week 48 data had no Baseline data.
[CSR INCB-351, pp. 136-137]

***Reviewer Comment**: Some studies have reported clonality among the stromal (mesenchymal cells) cells in primary myelofibrosis (PMF) as opposed to PPV-MF and PET-MF in which the stromal cells are polyclonal. The secondary endpoint of marrow fibrosis before and after ruxolitinib therapy pre-specified in INCB-351 was of potential interest. However, the time required for resolution of fibrosis (if it ever will resolve) is unknown. It may be too early to measure resolution of fibrosis both from the point of view of the low number of evaluable patients and the time that may be required for resolution of fibrosis, once cytokine release has been diminished by ruxolitinib. Finally, it is clear that there is an enormous amount of missing data since bone marrow biopsies were obtained only in a very small percentage of the treated patients. No clear trend is apparent and nothing can be concluded about this endpoint on the basis of the data provided by the Sponsor.*

6.1.5.f. Reduction of Level of V617F Activating JAK2 Mutation

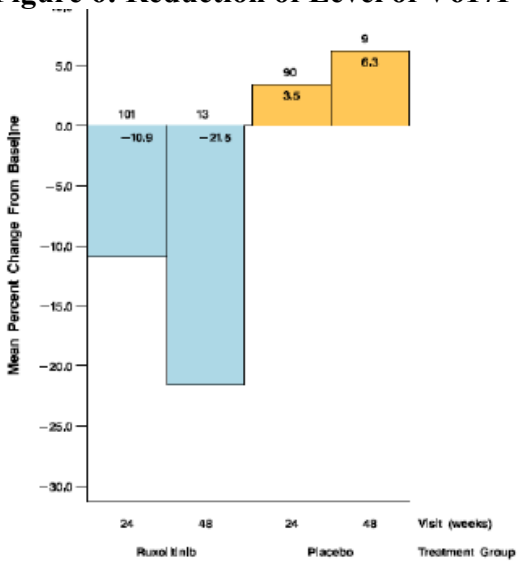
The change in the level of the V617F JAK2 mutation (percent of cells positive for the V617F JAKS activating mutation) on the ruxolitinib arm as compared to the placebo arm at 24 weeks in INCBV-351 is shown below in Figure 6 and in Table 35. In Figure 6 below, the percent reduction of the level of V617F on the ruxolitinib arm of INCB-351 is presented in two histograms to the extreme left in Figure 6 (which project below the line), whereas the percent increase in V617F level on the placebo arm of INCB-351 is presented in the two histograms on the extreme right of Figure 6 (which project above the line). On the ruxolitinib arm, there was a mean percent decrease from V617F baseline values of -11% at week 24. Among patients on the placebo arm, there was an increase of 3.5% at week 24.

Table 35-Reduction of Level of V617F Mutation in INCB-351

Arm of Trial	% Δ Week 24	P value*
Ruxolitinib	-10.9% (n=101)	P<0.0001
Placebo	+3.5% (n=90)	P=0.0179

*Rank sum test
[CSR INCB-351, pp. 136-137]

Figure 6: Reduction of Level of V617F Mutation in INCB-351



Source: Figure 14.4.23.1.1

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[CSR INCB-351 pp 135-136]

Reviewer Comment*: There appears to be statistically significant decreases in the levels of the V617F mutation positive cells as compared to the sum of the mutant and wild type cells on the ruxolitinib arm of INCB-351. However, it may be too soon to analyze the long term outcome. In addition, there is data for only 65% of the ruxolitinib arm and 58% of the placebo arm. Notwithstanding the large amount of missing data, there is a trend for an increased percentage of patients who can achieve a response to ruxolitinib as measured by* ≥35% reduction in spleen volume at 24 weeks *in the group of patients that was positive for V617F as compared to the group that was negative, but the results in these two groups are overlapping (see Figure 9 in Section 6.1.7 below). The conclusion of this Reviewer is that both the V617F positive and V617F negative groups respond well to ruxolitinib. These data and those showing that all of the patients have elevated STAT 3 levels (as compared to normal controls), which is presented in Section 6.1.8 below, suggest that the "wild type" patients who are scored negative for the V617F mutation may have other activating mutations of JAK2 not detected by the assay for V617F, which are overridden by the inhibitory effect of ruxolitinib on the binding of ATP to the ATP binding site near the JAK2 catalytic site.*

6.1.5.g Transfusion Independency

Two different criteria were used to define transfusion dependency and independency (neither of these criteria were pre-specified in the protocol or statistical aqnalysis plan (SAP). The first was adapted by Incyte from the clinical trials in the Revlimid label for MDS. This criterion states that transfusion dependent subjects have received at least 2 units of RBC products over an 8-week period prior to the date of first dose (see Table 36 for the complete criteria).

Table 36: Definition of RBC Transfusion Dependency from SAP of INCB-351

8 wks before therapy	8 wks before therapy	Final 8 wks of therapy	Final 8 weeks of therapy
0 units of RBC	Independent	0 units of RBC	Independent
1 unit of RBC	Indeterminate	1 unit of RBC	Indeterminate
≥2 units of RBC	Dependent	≥2 units of RBC	Dependent

[CSR INCB-351, pp. 63-64]

The second system of criteria for defining transfusion dependency is taken from the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) and is summarized in Table 37 below.

Table 37: Definition of RBC Transfusion Dependency from IWG-MRT

Dependence	≥2 units RBC in the 4 weeks prior to randomization
Independence	Absence of transfusions for any ≥8 week period

[CSR INCB-351, pp. 63-64]
The mean number of transfusions administered on the ruxolitinib arm of INCB-351 was 0.96 units per subject per month, and 0.77 units per subject per month in the placebo group. The frequency of transfusion dependency and independency as defined by the lenalidomide label (see Table 36 above) or the IWB-MRT (see Table 37 above) is presented below in Tables 38 and 39 respectively. These results suggest that the administration of ruxolitinib increased the likelihood of transfusion requirement in subjects initially independent.
[CSR INCB-351, p. 191]

Table 38-Summary of RBC Transfusion Dependency on SAP-Defined Criteria INCB-351

Therapy	Ruxolitinib	Placebo
Number of Patients	n/N (%)	n/N(%)
Dependent to Independent		
8 wks Before Screen to Final 8 wks	6/32 (19%)	10/32 (31%)
Independent to Dependent		
8 wks Before Screen to Final 8 wks	33/123 (27%)	17/118 (14%)

[CSR INCB-351, p. 191]

Table 39-Summary of RBC Transfusion Dependency Based on IWG MRT Criteria

Transfusion Dependent at Baseline	Independent s/p Therapy	Dependent s/p Therapy
Ruxolitinib	17 (41.2%)	20 (58.8%)
Placebo	15 (46.9%)	17 (53.1%)

[CSR INCB-351, p. 191]

Reviewer Analysis and Comment: *The reviewer analyzed the mean of the RBC transfusions during the 8 weeks prior to ruxolitinib treatment and in the final 8 weeks of treatment on INCB-*

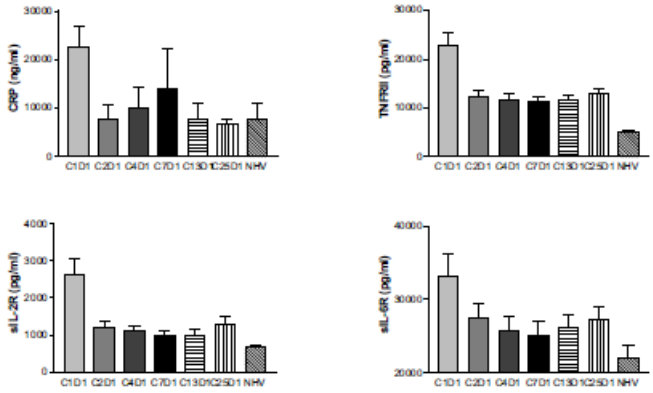
351. On ruxolitinib, the mean number of transfusions increased from 4.44 (baseline) to 5.12 (final 8 weeks of treatment). On the placebo arm, the number of transfusions increased from 4.48 to 6.63. Thus, ruxolitinib did not increase transfusion dependency compared to placebo on INCB-351. Again, the follow-up is very short. The long term effect of ruxolitinib therapy on transfusion dependency cannot be reliably assessed at this time and will require longer follow-up.

6.1.5.h. Reduction of Cytokine Release with Ruxolitinib

The results of the analysis of cytokine levels in the plasma of patients with MF before and after treatment with ruxolitinib appears on page 81 of CSR INCB-351, and in the report INCYTE-IN-VITRO-10.06.1. The most striking observation was that in the baseline values, markers associated with inflammation: CD40, C-reactive protein, ICAM-1, and TNF-alpha, were elevated in patients with MF as compared with normal volunteers. The levels of C-reactive protein showed an 86% decrease within 4 weeks of treatment with ruxolitinib.
[CSR INCB-351, p. 81]

In Figure 7A is presented data on the plasma levels of four plasma protein markers of inflammation at various times in subjects with MF following dosing with ruxolitinib for 24 months in comparison to levels in normal volunteers. This is data from INCB-251 (the phase I/II trial) of ruxolitinib in patients with MF. This data is from a report labeled Incyte-In Vitro-10.06.1 from the CSF for INCB 251 provided in the NDA. It is clear that the administration of ruxolitinib induces a decrease of the levels of markers of inflammation.

Figure 7A: Plasma Levels of Markers of Inflammation Following Ruxolitinib



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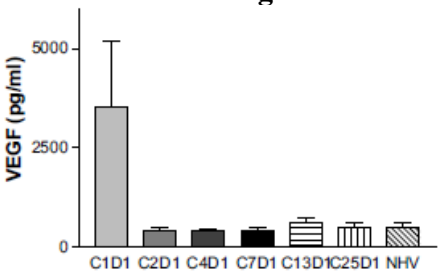
[CSF INCB-251, page 312]

In Figure 7B is presented measurements of the plasma levels of VEGF before and after ruxolitinib therapy. Again, dramatic reductions of the plasma levels of VEGF within a month following the initiation of ruxolitinib therapy to levels present in normal volunteers is documented in this figure.

Figure 7B VEGF Levels Before and After Ruxolitinib



[CSR INCB-251, page 312]

Comment of the Reviewer*: At 24 weeks of ruxolitinib on INCB-351, the level of C-reactive protein decreased 4.7 fold, the level of beta 2-microglobulin and IL-6 decreased 1.4 fold (CSR INCB-351, pages 1931-1980].*

This data lends support to the widely held assumption that the JAK2 activating mutation and consequent activation of STAT3 leads to increased levels of inflammatory cytokines in the plasma of patients with MF and that treatment with ruxolitinib reverses this.

6.1.6 Other Exploratory Endpoints for INCB-351

STAT3 Assays: The data for this analysis and discussion is presented on pages 83-84 of the Clinical Study Report for INCB-351. The analysis was performed using samples from study centers who agreed to provide samples via overnight shipping to the analysis laboratory on the levels of unstimulated (basal) and interleukin-6 (IL-6)-stimulated phosphorylated STAT3 (pSTAT3), a transcription factor that is directly phosphorylated activated but JAKs in response to cytokine stimulation.

This endpoint can serve as an indirect read-out of JAK enzyme inhibition. On Day 1 of Cycle 1 and Week 4 of Cycle 1, venous whole blood samples were collected pre-dose and 2 hours after treatment with ruxolitinib. The levels of pSTAT3 were determined by ELISA assay. Results from individual subjects were averaged based on treatment group (ruxolitinib vs placebo). Maximal inhibition of IL6-stimulated pSTAT3 levels on Day 1 and Week 4 was determined at the 2-hour time point and was expressed as percent inhibition relative to pre-dose values on Day 1 and Week 4, respectively.

A total of 144 subjects from INCB-351 were included in the analysis of pSTAT3 (72 subjects from the ruxolitinib arm and 72 from the placebo arm). The results of these assays are presented below in Table 40 (which is derived from the narrative on pages 83-84 and Table 17.2.27 on page 2021 of the CSR for INCB-351).

As can be seen from these data, the levels of inhibition of activation of JAK2 and STAT3 in cells exposed in vitro following collection from patients on the ruxolitinib arm of INCB-351 2 hours

post ruxolitinib on the first day of treatment is 55% as compared to -7.5% on the placebo arm. In cells collected from patients following 4 weeks of therapy, the levels of inhibition of in vitro activation by IL6 of STAT3 (as measured by pSTAT3) is 33% on the ruxolitinib arm and 06.6% on the placebo arm.

Table 40: Percent Inhibition of STAT3 Activation by In Vitro Exposure to IL6 in Cells Collected from Patients on the Ruxolitinib and Placebo Arms of INCB-351

Study Day	Ruxolitinib Arm	Placebo Arm	P-value*
Day 1, 2 hours post treatment (mean)	55.1%	-7.5%	<0.0001
Week 4, 2 hours post treatment (mean)	33.2%	-6.6%	<0.0001
Day 1, 2 hours post treatment (median)	59.1%	-5.9%	<0.0001
Week 4, 2 hours post treatment (median)	35.3%	-0.2%	<0.0001

*The treatment effect was tested for statistical significance using a 2-sample T-test.

***Reviewer Comment**:*
Among patients entered onto the treatment arm of INCB-351, there was a 55% reduction of the level of pSTAT3 on Day 1, and a 33% reduction of theh pSTAT3 level at 4 weeks.
[CSR INCB-351, p. 84]

Since measurement of pSTAT3 activation is a surrogate for JAK2 activation, this data shows that ruxolitinib is inhibiting the ability of IL6 to activate JAK 2 in vitro in cells collected from patients exposed to ruxolitinib. This is a demonstration that ruxolitinib is inhibiting the enzymatic activity of JAK2 in vivo in patients on the ruxolitinib arm of INCB-351.

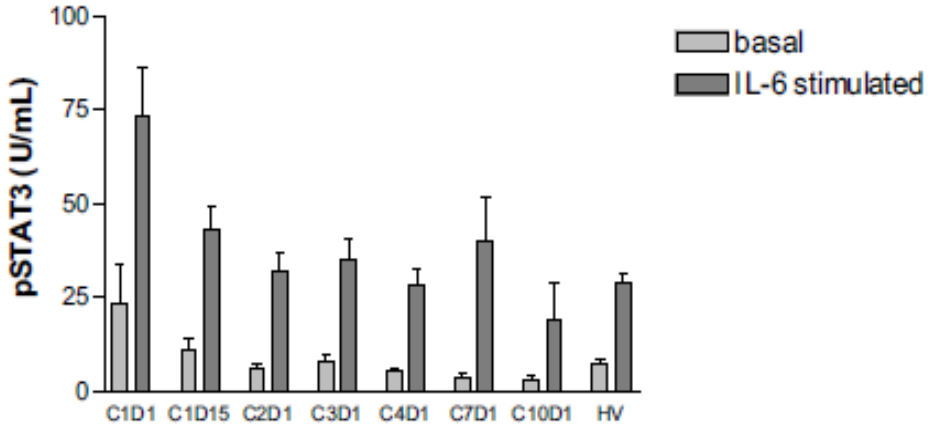
The Sponsor also provided data from INCB-251 that suggested that the inhibition of STAT3 activation by ruxolitinib in vivo is dependent on the dose of ruxolitinib, and that cells from patients exposed to ruxolitinib in vivo who are positive and negative for the V617F mutation in JAK2 are subject to inhibition of in vitro activation of STAT3 by IL6 to the same degree. This data can be accessed in the application from Section 10.2.2 (pSTAT3 Results) which is on page 83 of the CSR INCB-351. On the 8th line of the first paragraph of this section is a link labeled "INCYTE-IN-VITRO-10.06.1". This connects with a report labeled: Pharmaceutical Development Report INCTE-DMB-08.184.1.

The percent inhibition of phosphorylated STAT3 (pSTAT3) in blood cells with and without IL-6 stimulation at baseline (pre-dose Day1), pre-dose at Week 4, and 2 hours after administration of ruxolitinib on Day 1 and week 4, was analyzed. These data made possible to test if the baseline non-stimulated level of STAT3 was declining during 4 weeks of ruxolitinib treatment.

The first set of experiments is derived from INCB-251 in which the baseline levels of pSTAT3 are measured in patients with MF and in normal volunteers. As shown in Figure 7C below, the baseline pre-treatment levels of the unstimulated STAT3 phosphorylation are much higher in patients with MF as compared to normal volunteers. On page 275 of the report labeled INCYTE-IN-VITRO-10.06.2, it is stated: "The constitutive baseline activation (of STAT3) was observed in subjects regardless of the presence (or absence) of the JAK2617F mutation."

Figure 7C-Baseline Levels of pSTAT3 in MF and Normal Volunteers

Figure 1 **Basal and IL-6 Stimulated Levels of pSTAT3 in MF Patients in Predose Samples Taken at Successive Study Visits in Study INCB 18424-251**



HV = healthy volunteers

Whole blood samples from MF patients were taken on Days 1 and 15 of Cycle 1 and Day 1 of Cycles 2, 3, 4, 7 and 10 prior to INCB018424 treatment. All samples were either left unstimulated or stimulated with IL-6 for 15 minutes prior to making cell extracts. The extracts were then analyzed for pSTAT3 levels by ELISA. Values shown represent the mean ± SEM. Data from healthy volunteers were based on historical data obtained from Study INCB 18424-131 and Study INCB 18424-132.

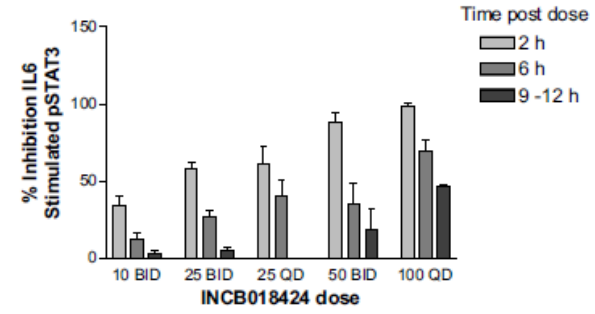
[INCYTE-IN-VITRO-10.06.2, page 275-see link on p. 83 of CSR INCB-351]

The level of inhibition of IL-6 stimulation of STAT3 was shown to be dependent on the dose of ruxolitinib administered. This data is provided below in Figure 8.

Reviewer Comment: *The presence of elevated levels of phosphorylated STAT3 (pSTAT3) in patients who are negative as well as those who are positive for the V617F activating mutation of JAK2 strongly suggests that the patients who are scored "negative" by the assay for the V617F JAK2 activating mutation, may have mutations which are different in terms of their locations on the JAK 2 molecule or have upstream mutations that activate JAK2 to phosphorylate STAT3. Thus, the patients who are designated "wild type" and negative for the V617F mutation by the current assay may actually have JAK2 activating mutations in parts of the JAK2 molecule which are not detected by the current assay for the V617F mutation. In addition, the inhibition of JAK2 dependent signal transduction pathways appears to be dependent on the dose of ruxolitinib (see data in Section 6.1.6 of this report in Figure 8)*

Figure 8-Dependency of Level of pSTAT3 on Ruxolitinib Dose

Figure 2 **Inhibition of IL-6 Stimulated pSTAT3 Levels in MF Patients After Treatment with Different Doses of INCB018424 in Study INCB 18424-251**



Whole blood samples from MF patients were taken at Cycle 1 Day15 at 2, 6 and 9-12 hours post treatment. All samples were stimulated with IL-6 for 15 minutes prior to making cell extracts. The extracts were then analyzed for pSTAT3 levels by ELISA. pSTAT3 levels were compared to predose values on Day 15 of Cycle 1 to derive the % inhibition. Values shown represent the mean ± SEM.

[INCYTE-IN-VITRO-10.06.2, page 275-see link on p. 83 of CSR INCB-351]

.

Finally, in this report of studies on pSTAT3, the following statement was made: "Further, when the effects of ruxolitinib treatment were examined independent of dose, this increased activation of the JAK/STAT pathway was reduced following 24 weeks of treatment with ruxoltinib, returning to the levels observed in healthy volunteers. This reduction in pSTAT3 levels was maintained at all time points examined".

Reviewer Comment*: This data further supports that observation that ruxolitinib inhibits STAT3 phosphorylation (activation) independent of whether the cells of the patient are positive for the V617F mutation. This data thereby suggests that the V617F negative patients may have JAK2 mutations or upstream mutations that activate JAK2 to phosphorylate STAT3, or that these "wild type" patients with MF actually have JAK2 activating mutations in parts of the JAK2 molecule which are not detected by the current assay for the V617F mutation.*

6.1.7 Subpopulations for INCB-351

The primary analysis method was applied to each subgroup. Additionally, a Logistic-Regression model with sex, age group, MF type, previous hydroxyurea use, baseline spleen volume, baseline palpable spleen length, and treatment as the model effects was performed to estimate treatment differences in the odds ratio (active versus control) with 95% confidence intervals after controlling for all the subgroup factors. The result of this analysis is presented below in Figure 9. The proportion of subjects in the ruxolitinib group who achieved a ≥35% SVR in INCB-351 was 25.3% in men and 59.2% in women. A gender difference was also

seen in the INCB-352 trial (although of a smaller magnitude). Among patients who had the V617F mutations, 47.8% of patients achieved ≥35% SVR, whereas 27.5% of the patients without the V617F mutation achieved ≥35% SVR.

Figure 9: Subgroup Analysis of Responders in INCB-351

Figure 23: Proportions of Subjects in Each Subgroup Who Achieved a ≥ 35% Reduction From Baseline in Spleen Volume at Week 24 (Ruxolitinib-Treated ITT Subjects)

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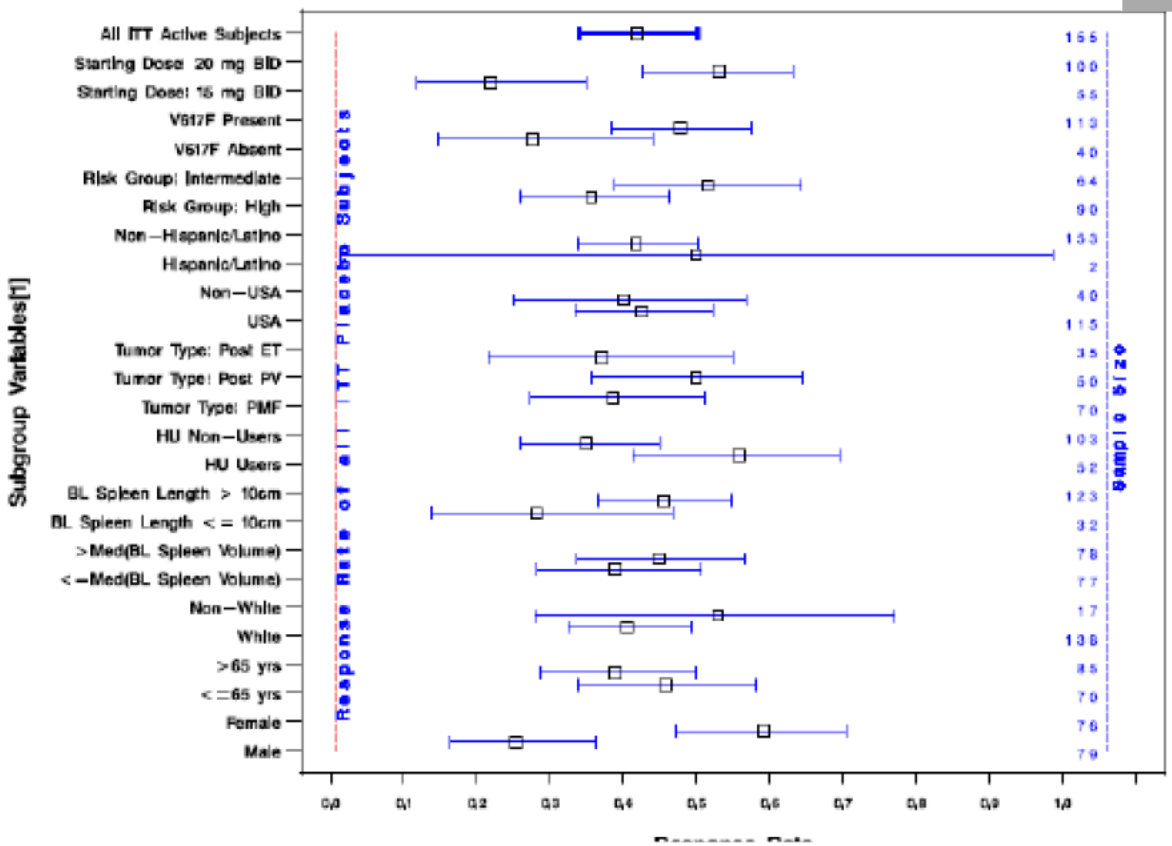


[CSR INCB-351, p. 139]

***Reviewer Comment**: There are dramatic non-overlapping differences for the percentage of patients who show a ≥35% SVR at 24 weeks in the following sub-groups: gender and initial dose. Starting at a dose of 20 mg po bid produces an increased probability of achieving a ≥35% SVR at 24 weeks. Female gender also produces an advantage but the origin of this difference is not apparent at the present time. It is possible to speculate that this difference could reflect the fact that the dose of ruxolitinib is a flat dose and is not weight adjusted. There are differences in the percentage of patients who show spleen volume reduction between patients who were positive (higher=48.7%) vs negative (lower=27.5%) for the V617F, but the confidence intervals are overlapping for the two groups.*

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The 20 mg vs 15 mg bid beginning dose selection system along with the dose adjustment system during therapy based on the platelet count used in INCB-351 appears to be successful in terms of avoiding an increase in the rate of clinically significant bleeding episodes when one compared the ruxolitinib arms with the placebo arm. In addition, based on the half-life of the unmodified parental form of ruxolitinib of 3.1 hours and the half-life for all of the known active metabolites of ruxolitinib 5.8 hours, the BID schedule of administration is optimal.

6.1.9 Discussion of Persistence of Efficacy for INCB-351

Although it appears to be too early in the evolution of the clinical data set from INCB-351 to make final conclusions about the durability of the SVR responses to ruxolitinib, the data that appears in Section 6.1.5.a of this report suggests that the responses of SVR ≥35% persist for at least 36 weeks in over 80% of patients. Additional follow-up will be required to definitively answer the question of durability of responses. The data in Section 6.1.5.d of this report suggests that the percentage of patients who are scored as positive for the response defined by ≥50% reduction of the TSS is stable from 8-24 weeks.

6.1.10 Additional Efficacy Issues/Analyses for INCB-351

There are no issues for discussion.

***Reviewer Comment-Summary Statement on Efficacy in INCB-351**:*

All pre-specified primary and key secondary efficacy endpoints (a statistically significant difference between the ruxolitinib and placebo arms in terms of the percentage of patients who achieve a ≥35% SVR and a ≥50% reduction in TSS by week 24) have been met in INCB-351. The magnitude of the effect appears to define a benefit for patients treated with ruxolitinib.

Efficacy Summary for INCB-352

Indication: The proposed indication is "for the treatment of patients with MF, including patients with PMF, PPV-MF, and PET-MF."

***Reviewer Comment**: Because the follow-up of the patients on the two phase III trials (INCB-351) is insufficient to establish the durability of responses, the Sponsor should carry out additional follow-up for the patients on these or other clinical trials to establish the durability of the ≥35% SVR response.*

6.1.11 Methods for INCB-352

This section will describe design issues for INCB-352. For additional details, see Section 5.3 above.

Design: The study was performed in 56 sites in 9 European countries. This was an open-label phase III trial which prospectively randomized patients with MF 2:1 to ruxolitinib (N=146) or Best Available Therapy (N=73). The randomization was stratified for IWG risk category (high-risk vs intermediate-2). There were 5 phases to the trial:

1. Screening (28 days maximum)
2. Baseline (7 days)
3. Randomized Treatment Phase (48 weeks)
4. Extension (a maximum of 144 weeks of therapy)
5. Follow-up (28-37 days)

Eligibility: The inclusion criteria are summarized below in Table 41:

Table 41-Eligibility for INCB-352

1. PMF, PPV-MF or PET-MF ≥18 years
2. Resistant, refractory, or intolerant of available therapy, or previously untreated but ineligible for SCT
3. In need of treatment (see Table 15 above for definition)
4. ECOG PS= 0-3
4. Life expectancy ≥6 months
5. Spleen length ≥5cm below left costal margin
6. Peripheral blood blast count <10%
6. Intermediate-2 risk or high risk by IWG criteria
7. Hb <10 g/dL or dependency on red blood cell transfusions

[Clin Protocol, July 21, 2009]

The definition or criteria for patients who are in need of therapy is given above in Table 15.

Dose Adjustment: The patients were started on treatment with a ruxolitinib starting dose of 20 mg po bid if the pre-treatment platelet count was >200,000/microL, and the dose of 20 mg po bid was reduced to 15 mg po bid if the pre-treatment platelet count was >100,000/microL, and <200,000/microL. The dose could be increased by 5 mg incremental intervals by the fourth week of therapy if the following 3 conditions obtained:

a. The spleen length below the left costal margin had been reduced by ≤40% by 4 weeks as compared to baseline;

b. The platelet count at Week 4 was ≥150,000/microL and the platelet count had never been <150,000/microL from the time of baseline;

c. The absolute neutrophil counts (ANC) remained ≥1,000/microL since baseline.

[CSR INCB-351, page 39]

Endpoints: This study has a single primary endpoint: the proportion of subjects achieving ≥35% SVR from baseline at Week 48 as measured by MRI or CT. The key secondary endpoint was the proportion of subjects achieving a ≥35% SVR from baseline at Week 24 as measured by MRI or

CT. Other secondary endpoints included the duration of maintenance of SVR (DoMRS) ≥35%, PFS, LFS, OS, transfusion dependency/independency, and a change in bone marrow histomorphology.

Statistical Analysis and Missing Data: The study will have achieved the efficacy objective if the primary endpoint showed a significant result at 2-sided alpha of 0.05 at final analysis (48 weeks). The proportions at 48 and 24 weeks were compared using the Cochran-Mantel-Haenszel (CMH) test stratified by prognostic category (intermediate-2 or high risk). There was no specified order of analysis of the secondary endpoints.

Missing Data Handling: Subjects without a baseline SV measurement will be excluded from the analysis. Subjects who drop out of the trial or subjects missing a splenic volume determination at Weeks 24, 36 and 48 will be considered as not having achieved the ≥35% SVR. Missing values will not be imputed.

6.1.12 Demographics for INCB-352

The demographic features of patients entered onto each arm of INCB-352 at baseline are presented below in Table 42.

Table 42-Demographic Features at Baseline for INCB-352

Feature	Ruxolitinib	Best Available Therapy (BAT)
	N=146	N=73
Age (median)	67 years	66 years
Female	67%	66%
PMF	53%	53%
PPV-MF	33%	27%
PET-MF	14%	19%
Baseline spleen volume	2662 cm^3	2631 cm^3
IWG High-risk	60%	59%
Circulating blasts ≥1%	90%	86%
Hb < 10g/dL	45%	52%
Constitutional symptoms	72%	67%
Prior hydroxyurea therapy	75%	69%

[CSR INCB-352, p. 113-114]

Reviewer Comment: The arms appear to be well balanced with respect to baseline demographic features.

6.1.13 Subject Disposition for INCB-352

The disposition of human subjects entered onto INCB-352 is summarized in Table 43.

Table 43-Disposition of Patients in INCB-352

	Ruxolitinib	BAT
	N=146	N=73
Median duration of treatment	51.4 weeks	45.1 weeks
Weeks of treatment: ≤36 weeks	20.6%	41.1%
Weeks of treatment: >36-≤48 weeks	10.3%	9.6%
Weeks of treatment: >48 weeks	69.1%	49.3%
% on study at data lock (01/20/11)	62.3%	42.5%
% discontinued	37.7%	57.5%
a. % ruxolitinib entered on extension study	19.9%	25%
b. adverse events	8.2%	5.5%
c. progression of disease	0.7%	4.1%
d. consent withdrawn	1.4%	12.3%
e. protocol deviation	1.4%	0.0%
f. non-compliance with study medication	1.4%	0.0%
g. non-compliance with study procedures	0.0%	1.4%
h. other	4.8%	9.6%

[CSR INCB-352, p.111]

***Reviewer Comment**: There is a greater percentage of patients remaining on the trial at the time of data lock in the ruxolitinib arm as compared to the BAT arm. Entry into the extension phase of therapy was the most common reason for discontinuation in the BAT arm. All 18 of the patients from the BAT arm who entered into the extension phase had crossed over from the BAT arm to the ruxolitinib arm. These data suggest activity of ruxolitinib that exceeds that of BAT.*

6.1.14 Analysis of Primary Endpoint and Key Secondary Endpoint for INCB-352

The efficacy results for the primary endpoint and the key secondary endpoint for INCB-352 are presented in Table 44.

Table 44-Outcome of Primary and Key Secondary Endpoint for INCB-352

	Ruxolitinib	BAT	P value*
Number randomized	N=146	N=73	
Primary Endpoint: % SVR ≥35% at 48 weeks	29%	0%	<0.0001
Key Secondary Endpoint: % SVR ≥35% at 24 weeks	32%	0%	<0.0001

[CSR INCB-352, p. 116]

***Reviewer Comment**: The trial results met its pre-specified primary endpoint and key secondary endpoint: a statistically significant difference between the two arms in terms of the proportion of patients achieving a SVR ≥35% at 48 and 24 weeks respectively. In addition, the results of INCB-352 confirmed the results of INCB-351 in terms of the statistical significance of the differences between the ruxolitinib and comparison arms (placebo in INCB-351 and BAT in INCB-352) in terms of the proportion of patients who achieved a inducing a SVR ≥35% at 24 weeks of therapy.*

6.1.15 Analysis of Other Secondary Endpoints(s) for INCB-352

6.1.15.a. Duration of SVR ≥35%

Kaplan-Meier analysis was utilized to estimate the median duration of the responses. The duration of the response (*SVR* ≥35%) was defined as the longest duration of consecutive measurements of ≥35% reduction prior to the time of data base lock for subjects who had at least one measured 35% reduction in SV. This analysis involves only the ruxolitinib arm and only those patients on that arm who had at least one measured 35% SVR. As shown in Figure 10 by the listing of the patients at risk at various time points during the 48 weeks of the treatment period on this protocol, there are very few patients who have been followed beyond 36 weeks.

Reviewer Comment*: Therefore, there are insufficient numbers of patients who have been followed long enough to make the Kaplan-Meier estimate provided in Figure 10 reliable. In addition, it is not possible from this data presentation to ascertain the interval between the first date on which ≥35% SVR occurred and either progression occurred or the patients were censored due to the data lock of February, 2011. An update provided by the Sponsor on August 1, 2011 shows that 23 (33%) of the patients who had achieved ≥35% SVR on INCB-352 during 48 weeks of ruxolitinib treatment had progressed by the time of the August 1, 2011 update. The median time to progression among the 23 patients who had progressed was 24.1 weeks. At the time of the August 1, 2011 update, 67% of the patients who had achieved ≥35% SVR were still in a response status. This data shows that there must be a Post-marketing commitment to follow the patients on this or other trials to characterize the durability of the ≥35% SVR.*

6.1.15.b. PFS, LFS, and OS

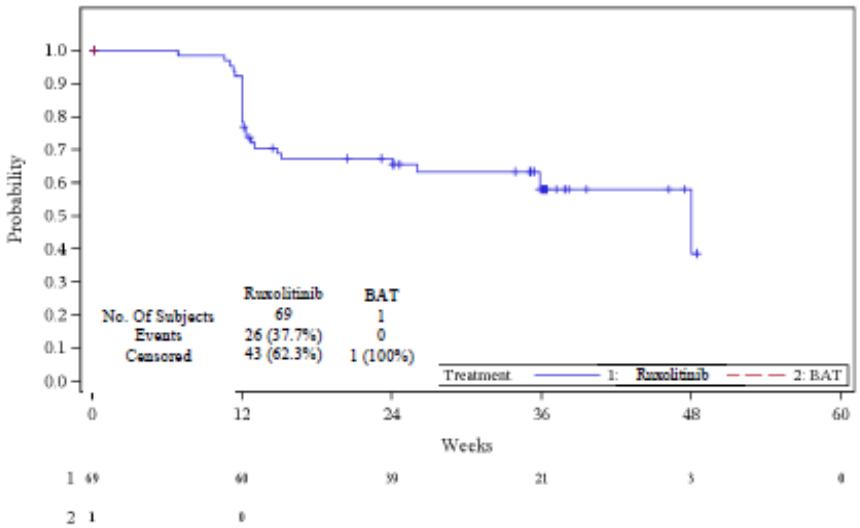
In Table 45 (see below) are presented the Kaplan-Meier estimates of the progression free survival (PFS), the leukemia free survival (LFS) and overall survival (OS). As shown by this analysis, there were no statistically significant differences in the secondary time to event endpoints analyzed in this study between the treatment arms.

Table 45-PFS, LFS, and OS Results on INCB-352

	Ruxolitinib	BAT	Log-rank P value	HR (95% CI)
	N=146	N=73		
PFS				
No. of events	44 (30.1%)	19 (26.0%)	P=0.46	0.81 (0.47, 1.39)
No. censored	102 (69.9%)	54 (74.0%)		
LFS				
No. of events	6 (4.1%)	4 (5.5%)	P=0.51	0.65 (0.18, 2.31)
No. censored	140 (95.9%)	69 (94.5%)		
OS				
No. of events	6 (4.1%)	4 (5.5%)	P=0.58	0.70 (0.20, 2.49)

[CSR INCB-352, pp. 120-121]

Figure 10: Median Duration of SVR ≥35% in INCB-352



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Subjects at risk: 1=ruxolitinib, 2=BAT

6.1.15.c Fibrosis Grade on INCB-352

No conclusion can be reached since 47% of the patient samples were missing on the ruxolitinib arm and 65% were missing on the BAT arm, and the follow-up was of insufficient time.

6.1.15.d RBC Transfusion Dependency on INCB-352

Among patients who were RBC transfusion dependent at baseline, 11% of these became transfusion independent at week 48 of ruxolitinib treatment, whereas only 1.9% of patients receiving BAT became transfusion independent. However, 17.8% of patients who were RBC transfusion independent at baseline became dependent by week 48 on the ruxolitinib arm, whereas only 5.3% of the transfusion independent at baseline became dependent by week 48 on the BAT arm. As shown in Table 46 (see below), the percentage of patients receiving RBC transfusions increased during the first 8 weeks on therapy on both arms, and then gradually decreased to baseline by week 48. Platelet transfusions were very infrequent on both arms.

Table 46-Percent of Patients Receiving RBC Transfusions on INCB-352

	Ruxolitinib	Ruxolitinib	BAT	BAT
	N=146	N=146	N=73	N=73
Units/time period	Any Units	≥2 Units	Any Units	≥2 Units
	n (%)	n (%)	n (%)	n (%)
0-4 weeks	20 (13.7%)	17 (11.6%)	20 (27.4%)	19 (26.0%)
4-8 weeks	49 (33.6%)	47 (32.2%)	21 (28.8%)	21 (28.8%)
8-12 weeks	40 (27.4%)	36 (24.7%)	16 (21.9%)	16 (21.9%)
12-16 weeks	50 (34.2%)	47 (32.2%)	20 (27.4%)	20 (27.4%)

16-24 weeks	51 (34.9%)	47 (32.2%)	19 (26.0%)	19 (26%)
24-36 weeks	46 (31.5%)	42 (28.8%)	17 (23.3%)	15 (20.5%)
36-48 weeks	32 (21.9%)	32 (21.9%)	10 (13.7%)	9 (12.3%)
48-60 weeks	21 (14.4%)	20 (13.7%)	8 (11.0%)	7 (9.5%)

***Reviewer Comment**: The continued need for RBC transfusions on the ruxolitinib arm despite diminution of spleen volume and symptoms remains a problem. Generally, a greater percentage of patients in the ruxolitinib arm received transfusions through the 60 weeks of observation than on the placebo arm.*

6.1.16 Other Endpoints INCB-352: Level of JAK2 V617F Allele on INCB-352

The change in the level of V617F during therapy on the ruxolitinib and BAT arms is shown in Table 47 below.

Table 47-Change in Level of V617F Mutation During INCB-352

	Ruxolitinib (N=146) n (%)	BAT (N=73) n (%)
Week 24 of Therapy Compared to Baseline	76 (-6.0%)	22 (+0.5%)
Week 48 of Therapy Compared to Baseline	60 (-7.0%)	22 (0.0%)

***Reviewer Comment**: This result confirms the observation in INCB-351 that ruxolitinib treatment is associated with a gradual but measurable decline of the V617F allele burden.*

6.1.17 Subpopulations for INCB-352

No comparisons.

6.1.18 Analysis of Information Relevant to Dosing Recommendations for INCB-352

No analysis.

6.1.19 Discussion of Persistence of Efficacy and/or Tolerance Effects for INCB-352

See Section 6.1.15.a above.

6.1.20 Additional Efficacy Issues/Analyses for INCB-352

***Reviewer Comment**: The results of INCB-352 confirm that ruxolitinib therapy can induce ≥35% SVR in patients with MF and can induce gradual reductions in the mutant allele burden. This data confirms the primary efficacy endpoint results on INCB-351. This data also confirms that a continued dependency on RBC transfusions (0.9/subject/month) remains despite the other effects of ruxolitinib therapy. The follow-up is insufficient to make estimates of the duration of the response as defined by ≥35% SVR. There will need to be a post-marketing commitment on the*

part of the Sponsor to characterize more fully the durability of the responses of patients with intermediate-2 and high risk MF to ruxolitinib.

7 Review of Safety

Safety Summary

Based on the review of the ISS of NDA 202192, the following conclusions have been reached:

1. There was no increase in early deaths or SAEs on the ruxolitinib arms vs the comparator arms in the two phase III randomized trials involving more than 301 patients with MF treated on the ruxolitinib arms and 224 patients with MF treated on the comparator arms (151 on placebo in INCB-351 and 73 on BAT in INCB-352).
2. There was no significant increase in the incidence of Grade 3-4 AEs on the ruxolitinib arm vs the placebo arm (47% vs 44%) on INCB-351, whereas the incidence of Grade 3-4 AEs were increased on the ruxolitinib arm vs the BAT arm in INCB-352 (42% vs 25%).
3. There was no increase of the number of patients who discontinue therapy due to adverse events on the ruxolitinib vs the comparator arms of INCB-351 (11% on both arms) or of INCB-352 (8% on both arms).
4. There was an increase of the frequency with which dose adjustments of the therapy occurred on the ruxolitinib vs the comparator arms of INCB-351 (51% for ruxolitinib vs 26% for placebo) and of INCB-352 (64% for ruxolitinib vs 15% for BAT). The major generator of this increase in dose adjustments was ruxolitinib induced thrombocytopenia of all grades which occurs at an increased frequency on the ruxolitinib arm vs the comparator in both INCB-351 (35% for ruxolitinib vs 9% for placebo) and INCB-352 (45% for ruxolitinib vs 10% for BAT). One result of the pre-specified provisions in both protocols for adjustments of the dose of ruxolitinib for thrombocytopenia (both pre and post initiation of therapy), may be that there was no significant increase in the incidence of bleeding on the ruxolitinib arms when compared to the comparator arms in both INCB-351 (10% for ruxolitinib vs 8% for the placebo) as well as in INCB-352 (13% for ruxolitinib vs 10% for BAT).
5. The most common adverse events occurring in >1% of the patients in descending order of frequency on the ruxolitinib arm of INCB-351 (see Table 56) were: thrombocytopenia, anemia, fatigue, diarrhea, dyspnea, headache, dizziness, nausea, confusion, pneumonia and urinary tract infections. Neutropenia was less frequent than any of these other adverse events). The only one of these adverse events (in addition to thrombocytopenia) for which there were measurable increases of Grade 3 and Grade 4 adverse events was anemia.
6. The significant complication arising from an adverse event other than thrombocytopenia that increased in the phase III trials with ruxolitinib vs the comparator arms was an increase of the incidence of RBC transfusions/subject/month from 0.7 on the comparator arm (in INCB-351) to 0.9 on the ruxolitinib. Importantly, this requirement for RBC transfusions does not yet appear to be diminishing with the short term follow-up that is available.

Summary of Analysis of the ISS: The adverse events were manageable compared to the very impressive reduction in splenomegaly and MF symptoms on the ruxolitinib arms of the two phase III trials. A 4 month update on the adverse events beyond the initial data lock of November

2, 2010 for INCB-351 and after the data lock of February, 2011 for INCB-352 was submitted on August 25, 2011. No major safety signals were seen. However, the data lock data for this 4-month safety update was March, 2011. Although this barely qualifies for a 4 month update for INCB-351, this update will only add 1-2 months of additional follow-up for INCB-352. A post-marketing commitment will be requested of the Sponsor for additional follow-up of the toxicity of long-term administration of daily ruxolitinib.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The patient population for the analysis of safety is provided below in Table 48.

Table 48-Population of Ruxolitinib Treated Patients for the ISS

Number of Patients	Trial Type	Trial ID Number	Type of Patients
155	Phase III	INCB-351	MF randomized to ruxolitinib
146	Phase III	INCB-352 (CINC424)	MF randomized to ruxolitinib
54	Phase III	INCB-351 and 352	MF crossed over from comparator
154	Phase II	INCB-251	MF
22	Phase II	INCB-254	Prostate cancer
13	Phase II	INCB-255	Myeloma
73	Phase II	INCB-256	Polycythemia Vera (PV) and Essential Thrombocythemia (ET)
301	Phase III	INCB-351, 352	MF on Phase III
509	Phase II, III	INCB-351, 352, 251	MF on all trials (Phase II and III)
617	Phase II, III	All Trials	MF, PV, ET, Cancer, Myeloma

[ISS, p. 26]

Reviewer Comment*: The bulk of the data presentation and analysis of the ISS patients will be restricted to patients with intermediate-2 and high risk MF and will exclude the patients with prostate cancer, myeloma, PV and ET.*

The demographics for the patients in the ISS (focusing on the phase III trials INCB-351 and INCB-352) are summarized below in Table 49.

Table 49-Demographics in Phase III Trials of the ISS

Trial	INCB-351	INCB-351	INCB-352	INCB-352
Arm	Ruxolitinib	Placebo	Ruxolitinib	BAT
Median age (yrs)	66	70	67	66
Female gender	49%	43%	43%	46%
High-risk*	58%	65%	60%	59%

Int-2 risk*	41%	35%	40%	40%
Prior HU therapy	67%	56%	75%	69%
Plat Ct (median)	262 x 10^9/L	235 x 10^9/L	432 x 10^9/L	228 x 10^9/L
PMN Ct (median)	11.9 x 10^9/L	15.1 x 10^9/L	9.4 x 10^9/L	11.5 x 10^9/L
Hb (g/dL)	10.5	10.5	10.6	10.3

[ISS, pp. 48 and 52]

The median duration of continuous therapy for patients initially started on ruxolitinib in the phase III trials and all phase II trials was 14.8 months. The median duration of continuous therapy for patients initially randomized to the comparator arms on the phase III trials and who then crossed over to the ruxolitinib arms was 3.8 months (see Table 11, page 39 of the ISS). The disposition of patients from the ISS who have MF (intermediate-2 or high risk) who were treated with ruxolitinib is presented in Table 50, and the disposition of patients on INCB-351 and INCB-352, including the reasons for discontinuation in phase III trials are summarized below in Table 51.

Table 50: Disposition of Patients with MF Treated with Ruxolitinib in ISS

	MF Subjects
Subject disposition, n (%)	N = 509
Ongoing[a]	377 (74.1)
Discontinued treatment	132 (25.9)
Death[c]	11 (2.2)
Adverse event	31 (6.1)[d]
Consent withdrawn	20 (3.9)
Protocol deviation	7 (1.4)
Disease progression	20 (3.9)
Intercurrent illness	3 (0.6)
Unacceptable toxicity	3 (0.6)
Non-compliance with study medication	3 (0.6)
Non-compliance with study procedures	0 (0.0)
Physician decision to withdraw subject	15 (2.9)
Other	19 (3.7)

[a] Receiving treatment with ruxolitinib.
[b] Notes the primary reason for withdrawal as noted on the eCRF. Because of differing CRF designs with regard to reasons for discontinuation across the studies, pooling of these data lead to difficulties in interpretation.
[c] Includes only those subjects for whom death was reported as the primary reason for discontinuation of therapy and may exclude subjects who discontinued for a fatal AE.
[d] This number is artificially low because there was no AE category on the INCB 18424-251 termination CRF.
[ISS, p. 46]

Table 51- Disposition of Patients with MF in Phase III Trials

Study	INCB-351	INCB-351	INCB-352	INCB-352
Arm	Ruxolitinib	Placebo	Ruxolitinib	BAT
Number Patients	N=155	N=151	N=146	N=73
	n (%)	n (%)	n (%)	n (%)
Continue on Treatment[a]	135 (87.1%)	78 (51.7%)	91 (62.3%)	31 (42.5%)
Discontinued Treatment	20 (12.9%)	73 (48.3%)	55 (37.7%)	42 (57.5%)
Reasons for Withdrawal[b]				
Adverse Event (all)[c]	16 (10.3%)	14 (9.3%)	12 (8.2%)	4 (5.5%)
Consent Withdrawn[d]	1 (0.6%)	7 (4.6%)	2 (1.4%)	9 (12.3%)
Protocol Deviation	0 (0.0%)	0 (0.0%)	2 (1.4%)	0 (0.0%)
Disease Progression[e]	3 (1.9%)	13 (8.6%)	1 (0.7%)	3 (4.1%)
Non-compliance Meds	0 (0.0%)	0 (0.0%)	2 (1.4%)	0 (0.0%)
Non-compliance with Study Procedures	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Other	0 (0.0%)	3 (2.0%)	7 (4.8%)	7 (9.6%)
Cross-over ruxolitinib	NA	36 (23.8%)	NA	18 (24.7%)
Continued in Extension	NA	NA	29 (19.9)	NA

[a]The number of ongoing subjects does not match the number in the CSR for INCB-351 because one patient died 1 day after the data cutoff.

[b]Patients whose date of death and withdrawal were the same were categorized as death.

[c] 8 subjects on each arm of INCB-351 were characterized as death in the CSR and as AEs in this table.

[d]Two patients who died in CSR for INCB-351 were captured as consent withdrawn in this table.

[e]One subject in the placebo group of INCB-351 was characterized as death in CSR and as disease progression in this table.

[f]Subjects met criteria for progression remained on ruxolitinib in the extension.

[ISS, pp. 44 and 56]

7.1.2 Categorization of Adverse Events

Adverse events were categorized as treatment related or not treatment related adverse events (Grades 3-5), or as treatment related or not treatment related SAEs, according to NCI Common Toxicity Criteria (CTCAE) version 4.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Based on Tables 48-51, it appears as if the data is adequate for analysis of the safety of ruxolitinib in MF at the schedule and doses given.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses in Target Populations

The analysis of exposure of patients on the ruxolitinib arms of the phase III trials which are associated with the two starting doses (based on Baseline platelet count) is presented below in Table 52.

Table 52-Exposure to Ruxolitinib In Different Starting Dose Categories

Study	Dose BID	INCB-351	INCB-351	INCB-352	INCB-352
Arm		Ruxolitinib	Ruxolitinib	Ruxolitinib	Ruxolitinib
		Subjects	Patient Months	Subjects	Patient Months
$<200 \times 10^9$/L	15 mg	54	423.6	55	578.1
$\geq 200 \times 10^9$/L	20 mg	101	856.0	91	1007.0

[ISS, p. 37]

7.2.2 Explorations for Dose Response

The dose dependency for ruxolitinib in MF (intermediate-2 and high risk) was characterized in INCB-251.

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal and/or in vitro testing. For an analysis of the pre-clinical testing please see the Pharmacology/Toxicology review.

7.2.4 Routine Clinical Testing

The adverse events of ruxolitinib are followed by the collection of blood samples for CBC with the ANC, the hemoglobin, and the platelet count and chemistries weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 for the first 6 months.

7.2.5 Metabolic, Clearance, and Interaction Workup

An analysis of these issues will be found in the Clinical Pharmacology review. The parent unchanged compound, ruxolitinib, has a serum half life of 3.1 hours. The active metabolites have a serum half-life of 5.8 hours. Only 1% of the parent compound is excreted unchanged. This drug is metabolized by CYPC3A4. One of the issues discovered was that the response rate range was higher in women than in men in INCB-351 (non-overlapping ranges in the forest plot analysis which is presented in Figure 9 on page 49 of the report and Figure 23 on page 139 of the CSR for INCB-351). The possibilities identified by Clinical Pharmacology analysis include: greater exposure of the tissues in women due to a higher dose in mg/kg or mg/body surface area,

greater dose/lean body mass in women, and antagonism of metabolism in women due to effects of estrogens.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This is the first of its class. Therefore, there is no opportunity for analysis of potential adverse events in similar drugs.

7.3 Major Safety Results

7.3.1 Deaths

The summary of the total number of deaths and the deaths on study (within 28 days of the last dose of study medication) reported by Sponsor is presented below in Table 53. The specific causes of deaths on the ruxolitinib and comparator arms of the phase III trials are provided in Table 54.

Reviewer Analysis and Comment*: In the randomized trials for MF (INCB-351 and INCB-352), there was no significant increase in "on study deaths" on the ruxolitinib arm vs the comparator arms. In fact, the number of deaths when expressed as percentages were lower on the ruxolitinib arms as compared to the comparator arms in INCB-351 and INCB-352 (see below Tables 53 and 54). There was no increase of deaths among the MF patients who crossed over from the comparator arm to the ruxolitinib arm in INCB-351 or INCB-352.*

In INCB-256 (ruxolitinib for PV and ET), there were no deaths among the 63 patients on that trial who received ruxolitinib for more than 12 months. Causes of death among the MF patients included hemorrhages, infections, and leukemic transformations. None of these deaths were attributed to ruxolitinib by the investigators. Among the patients treated with ruxolitinib, disease progression was the most frequently reported adverse event leading to death in the control groups (3), and that number was higher than in the ruxolitinib group (1). A review of narratives of all deaths from INCB-351 and INCB-352 confirmed the reports of Incyte summarized below in Tables 54 and 55.

Table 53-Deaths on Study

Study	Treatment	Total # deaths	On-study Deaths n(%)	Death after cross-over during extension[b]	Death during follow-up[c]
INCB-251-MF	Ruxolitinib	12[d]	12[d]		0
INCB-351-MF	Ruxolitinib	10	9(6%)	0	1
INCB-351-MF	Placebo	14	10(7%)	1	2
INCB-352-MF	Ruxolitinib	6	4(3%)	0	2
INCB-352-MF	BAT	4	3(5%)	1	0

[a] Death occurred during treatment or within 28 days after last dose of study medication.
[b] Death occurred during treatment with ruxolitinib or within 28 days after last dose of ruxolitinib.
[c] Death occurred more than 28 days after last dose of study medication.
[d] In the INCB018424-251 CSR, only 11 deaths are reported. The cut-off date for the CSR and ISS analysis is 31 December 2009. Subject 001-092 died in February 2010, but death date appears in the database as 10 February 2009. Therefore, 12 deaths are reported for this study in the ISS. PC=prostate cancer; MM=myeloma; MF=myelofibrosis; PV=polycythemia vera; ET=essential thrombocythemia.

[ISS, p. 73]

Table 54-Deaths, and Non-fatal SAEs and AEs as Percentage of Total

Study	INCB-351	INCB-351	INCB-352	INCB-352
Treatment	Ruxolitinib	Placebo	Ruxolitinib	BAT
Grade 3-4 AEs	47%	44%	42%	25%
Grade 5 <28days	6%	7%	3%	4%
SAEs	28%	35%	30%	29%
AEs → discontinuation	11%	11%	8%	8%
AEs→ dose reduction	51%	26%	64%	15%

[ISS, p. 56]

Table 55: Specific Causes of Death on Phase III Trials

Treatment group Subject No.	Age/ Sex/ Race	Day of last dose	Day of death	Principal cause reported
INCB 18424-351				
Ruxolitinib				
305-001	77/M/WH	156	156	Muscular weakness
012-001	76/M/WH	182	182	Subdural hematoma
015-005	71/M/WH	164	164	Septic shock
046-010	84/M/WH	94	94	Pneumonia
052-004	78/M/BL	165	165	Renal failure
059-002	73/M/WH	151	151	Non-small cell lung cancer metastatic
059-004	81/F/WH	78	78	Sepsis
062-004	86/F/WH	Missing data	293	Pneumonia
315-001	66/F/WH	182	182	Acute myeloid leukemia
Placebo[a]				
201-002	62/M/WH	207	207	Disease progression
004-009	71/M/WH	176	178	Staphylococcal infection
010-001	52/M/WH	66	66	Gastrointestinal hemorrhage
027-003	78/F/WH	83	83	Intestinal perforation
046-003	75/M/WH	260	260	Pneumonia
046-009	64/F/WH	159	159	Sepsis
074-001	62/M/WH	147	147	Myelofibrosis
101-002	51/M/WH	201	201	Disease progression
101-004	78/F/WH	66	66	Multi-organ failure
105-002	70/M/WH	189	189	Disease progression

Placebo crossed over to Ruxolitinib				
022-003	79/M/BL	275 (D207 crossover)	275	Septic shock
CINC424A2352				
Ruxolitinib				
306-004	68/M/WH	134	135	Retroperitoneal hemorrhage
603-001	63/M/WH	33	33	Intestinal perforation
701-015	65/M/ WH	322	326	Hepatic failure, portal vein thrombosis, cerebral hemorrhage
802-002	71/M/ WH	22	31	Disease progression
BAT				
006-004	46/M/ WH	95	95	Respiratory failure
502-001	68/M/ WH	26	26	Renal impairment
401-012	67/F/WH	176	176	Respiratory failure
BAT crossed over to Ruxolitinib				
603-003	50/M/WH	191 (D178 crossover)	209	Klebsiella sepsis

7.3.2 Nonfatal Serious Adverse Events

The non-fatal SAEs and adverse events (AEs) in the phase III trials for patients with MF are summarized above in Table 54. As shown in Table 54, the numbers of SAEs were lower on the ruxolitinib arm as compared to the comparator arms on INCB-351 and INCB-352. In Table 56 (see below) are shown the individual causes of SAEs in INCB-351 and INCB-352. The SAEs due to thrombocytopenia were slightly increased on the ruxolitinib arm of INCB-351 but no SAEs due to thrombocytopenia were seen on INCB-352. The SAEs due to bleeding on INCB-351 were not increased on the ruxolitinib arm (3.7%) as compared to the placebo (4.1%), whereas on INCB-352, the incidence of SAEs due to bleeding was higher on the ruxolitinib arm (4.2%) as compared to the BAT arm (0.0%).
[ISS, pp. 78-81]

Table 56-Individual Causes of Non-fatal SAEs in ≥1 Subject

Study	INCB-351	INCB-351	INCB-352	INCB-352
Therapy	Ruxolitinib	Placebo	Ruxolitinib	BAT
Number of Patients	N=155	N=151	N=146	N=73
	n (%)	n (%)	n (%)	n (%)
Any	43 (27.7%)	53 (35.1%)	44 (30.1%)	21 (28.8%)
Anemia	5 (3.2%)	3 (2.0%)	7 (4.8%)	3 (4.1%)
Pneumonia	10 (6.5%)	5 (3.3%)	1 (0.7%)	4 (5.5%)
Thrombocytopenia	3 (1.9%)	1 (0.7%)	0 (0.0%)	1 (1.4%)
Bleeding	7 (3.7%)	7 (4.1%)	6 (4.2%)	0 (0.0%)
GI Bleed	2 (1.3%)	2 (1.3%)	2 (1.4%)	0 (0.0%)
CNS Bleed	0 (0.0%)	0 (0.0%)	2 (1.4%)	0 (0.0%)

Post Proc Bleed	1 (0.6%)	1 (0.7%)	1 (0.7%)	0 (0.0%)
UGI Bleed	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Epistaxis	1 (0.6%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
Retroperitoneal Bleed	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
Splenic Bleed	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subdural Hematoma	1 (0.6%)	1 (0.7%)	0 (0.0%)	0 (0.0%)

[ISS, pp. 78-81)

7.3.3 Dropouts and/or Discontinuations

As shown above in Table 51, there was no increase of drop outs or discontinuations on the phase III trials for patients with MF due to adverse events on the ruxolitinib arms as compared to the comparator arms of INCB-351 or INCB-352. The individual causes of adverse events leading to discontinuations on the phase III trials for patients with MF are presented below in Table 57. As shown in Table 55, the adverse events leading to dose adjustments on the phase III trials for MF were increased on the ruxolitinib arms of both INCB-351 and INCB-352.
[ISS, pp. 78-81]

Table 57-Individual Causes of Discontinuations due to Hematological AEs on the Phase III Trials (MF Patients)

Study	INCB-351	INCB-351	INCB-352	INCB-352
Treatment	Ruxolitinib	Placebo	Ruxolitinib	BAT
Number of Patients	N=155	N=151	N=146	N=73
Thrombocytopenia	1%	1%	1%	1%
Neutropenia	1%	0%	0%	0%
Anemia	1%	1%	0%	0%
Diarrhea	1%	0%	0%	0%
Septic Shock	1%	0%	0%	0%
Subdural Hematoma	1%	0%	0%	0%
Retroperitonal Hemorrhage	1%	0%	1%	0%

[ISS, pp. 85-86]

***Reviewer Comment**: The low frequency of discontinuations due to thrombocytopenia and bleeding may due to the dose adjustment used to set the starting dose and to adjust the dose of ruxolitinib after initiation of therapy on the basis of the pre-treatment platelet count (see above Section 6.1.1 on pages 26-27).*

7.3.4 Significant Adverse Events

The adverse events in ≥1% on the phase III trials for patients with MF area presented below in Table 56. The top two adverse events were thrombocytopenia and anemia, along with headache, dizziness and confusion, were the adverse events in the top ten categories that were increased on the ruxolitinib arms of both of the phase III trials (these are in bold font in Table 58).

Reviewer Comment: The mechanism of the increased frequency of thrombocytopenia and anemia on the treatment arms is clear, but the mechanism through which ruxolitinib causes increases in headache, dizziness and confusion is not clear.

Table 58-AEs ≥1% of Patients in the Phase III Trial in the ISS

Study	INCB-351	INCB-351	INCB-352	INCB-352
Treatment	Ruxolitinib	Placebo	Ruxolitinib	BAT
Number of Patients	N=155	N=151	N=146	N=73
Thrombocytopenia	**34%**	**9%**	**45%**	**10%**
Anemia	**31%**	**14%**	**40%**	**12%**
Fatigue	25%	34%	12%	8%
Diarrhea	23%	31%	23%	11%
Dyspnea	17%	17%	16%	18%
Headache	**15%**	**5%**	**10%**	**4%**
Dizziness	**15%**	**7%**	**7%**	**5%**
Nausea	15%	19%	13%	7%
Confusion	**14%**	**5%**	**2%**	**1%**
Pneumonia	8%	6%	2%	7%
UTI	7%	5%	7%	3%
Neutropenia	3%	1%	3%	2%

[ISS, pp. 60-66]

7.3.5 Submission Specific Primary Safety Concerns

Reviewer Analysis and Comment: Thrombocytopenia and anemia are the two adverse events associated with ruxolitinib therapy that are safety concerns. Dose adjustments (on the basis of the baseline platelet count for the starting dose and on the basis of further lowering of the platelet count during therapy) were pre-specified in both phase III protocols (INCB-351 and INCB-351). These dose adjustments probably explain why there was no increase of bleeding on the ruxolitinib arm of INCB-351 and only a minor level (4.2%) on ruxolitinib on INCB-351 (see Tables 56-58).

There is no evidence that the thrombocytopenia worsened during the treatment period of exposure on INCB-351 (24 weeks) but the therapy has not been administered long enough to rule out a cumulative effect of ruxolitinib therapy on the platelet count. Since ruxolitinib acts at the thrombopoietin receptor, a cumulative impact is not anticipated. It is possible that given the observed gradual reduction of the mutant clone of cells with ruxolitinib therapy, that the platelet counts could actually eventually increase. However, until patients are followed on therapy for prolonged periods of time (1-2 years), a cumulative negative impact of ruxolitinib on the platelet count cannot be ruled out and remains a long term safety concern.

Hemoglobin <10g/dL was part of the eligibility for entry into the phase III trials. Given that all patients started out being anemic before ruxolitinib therapy and in view of the known mechanisms of action of ruxolitinib, it is not surprising that the incidence of RBC transfusions increased from 0.7/subject/month on the placebo arm to 0.9/subject/month on the ruxolitinib arm of INCB-351 (see Section 6.5.1.g above).

There is evidence that the anemia and RBC transfusion dependency worsened during the treatment period of exposure on INCB-351 (24 weeks). Whether this problem will continue to get worse due to a cumulative negative effect of ruxolitinib therapy on the hemoglobin level will require longer follow-up. It is possible that given the observed gradual reduction of the mutant clone of cells with ruxolitinib therapy, that the sensitivity of patients to the effects of ruxolitinib on the hemoglobin level could actually eventually decrease in the long term.

However, until it is possible to follow patients on therapy for prolonged periods of time (1-2 years), a cumulative negative impact of ruxolitinib therapy on the hemoglobin remains a long term safety concern. The fact that ruxolitinib blocks the action of erythropoietin, suggests that it will be necessary to support severely anemic patients on ruxolitinib with long term RBC transfusion therapy.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events other than thrombocytopenia and anemia which were among the top ten categories (see Table 58 above) to be associated with the administration of ruxolitinib included headache, dizziness and confusion. Fewer patients receiving ruxolitinib on INCB-351 were reported to have infections than the placebo arm (38.1% vs 41.7% on the placebo), whereas in INCB-352, infections occurred more commonly on ruxolitinib (63%) than on BAT (42.5%). This difference was attributed by the Sponsor to the longer treatment period with ruxolitinib on INCB-352 as compared to INCB-351, but there is no evidence for a time dependency of infectious adverse events presented in the ISS.

In Table 59 (see below) are listed the Grade 3 and Grade 4 adverse events on the ruxolitinib and comparator arms of INCB-351 and INCB-352. Data on Grade 3 and Grade 4 adverse events are presented for those adverse events which are listed as increased on the ruxolitinib arm as compared to the placebo or BAT arms on INCB-351 and INCB-352 in Table 58 above. The major finding is that of the adverse events >1% which are increased on the ruxolitinib arms of INCB-351 and INCB-352 in Table 58 above, the only ones that have significant Grade 3 and Grade 4 adverse events are thrombocytopenia and anemia.

Reviewer Comment: *The incidence of Grade 4 thrombocytopenia is low both on the ruxolitinib arms as well as on the comparator arms (placebo and BAT arms) in both the INCB-351 and INCB-352 protocols. This may be due in great part to the pre-specified dose adjustments in both trials based on platelet counts, before and after initiation of therapy. The success of the pre-specified adjustments of the dose of ruxolitinib in limiting or preventing clinically significant bleeding can be seen from inspection of both Tables 56-58.*

The adverse events of confusion, headache and dizziness, which were shown to increase on the ruxolitinib arms in Table 58, are not listed as having clinical significant (Grade 3 or Grade 4) increases of adverse events in Table 59. It is not clear that there are clinically significant increases in Grade 3 or Grade 4 pneumonias on the ruxolitinib arms vs the comparator arms in Table 59. This leaves anemia as the only adverse event for which significant Grade 3 and Grade 4 increases occur on the ruxolitinib arms on INCB-351(from 5 to 10% for Grade 3 and from 0 to 5% for Grade 4) and for which significant Grade 3 but not Grade 4 increases occur on the ruxolitinib arm on INCB-352 (3 to 11% for Grade 3). Anemias were not seen to be a cause of discontinuations on the ruxolitinib arms of either INCB-351 or INCB-352 (see Table 57).

Table 59: Percent Grade 3 and Grade 4 Adverse Events on INCB-351 and INCB-352

Trial	351	351	351	351	352	352	352	352
Therapy	Ruxolitinib	Ruxolitinib	Placebo	Placebo	Ruxolitinib	Ruxolitinib	BAT	BAT
Number	N=155	N=155	N=151	N=151	N=146	N=146	N=73	N=73
Grade AE	G3	G4	G3	G4	G3	G4	G3	G4
Thrombocytopenia	7.1%	1.3%	9.3%	1.3%	6.8%	0.7%	4.1%	0.0%
Anemia	10.3%	5.2%	4.6%	0.0%	11.0%	0.0%	2.7%	1.4%
Neutropenia	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Diarrhea	1.9%	0.0%	0.0%	0.9%	1.4%	0.0%	0.0%	0.0%
Epistaxis	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%
Headache	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.7%	0.0%
Dizziness	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.0%
Confusion	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Pneumonia	3.2%	1.9%	3.3%	0.7%	1.4%	0.0%	2.3%	1.0%

[ISS, pages 70-71]

7.4.1.a. Dizziness, Confusion and Headache

Dizziness and headache were increased on the ruxolitinib arms in both phase III trial (see Table 56 above) but no mechanism was apparent for these adverse events. However, none of these rose to the Grade 3 or Grade 4 levels (see Table 59).
[ISS, pp. 110-111]

7.4.1.b. Pneumonias

There was no significant increase of Grade 3 and Grade 4 pneumonias on the ruxolitinib arm of INCB-351 at the 3.9% and 1.9% respectively as compared to the placebo arm of INCB-351 displayed Grade 3 and 4 pneumonias at the 4% and 0.7% (see Table 59). On INCB-352, Grade 3 pneumonias in patients on the ruxolitinib arm were at the 3.4% level, while pneumonias were seen in 2.7% on the BAT arm, again not significantly increased (see Table 59).
[ISS, pp. 96-104]

7.4.1.c. Urinary Tract Infections

Urinary tract infections (UTI) were higher in the ruxolitinib treated patients (7%) than in the comparators in both phase III trials (5% and 3% in INCB-351 and -352] but the incidence of Grade 3 or 4 UTI was only 1.7% in the ruxolitinib arms.
[ISS, p. 108]

7.4.1.d. Leukemic Transformation

Leukemic transformation to AML was low in frequency among all patients in the phase III trials. Two subjects out of 155 in the ruxolitinib treatment arm of INCB-351 underwent leukemic transformation, and both of these patients had elevated blast counts and a chromosome 8 abnormality prior to the start of ruxolitinib therapy. No patients on the placebo arm of INCB-351 underwent leukemic transformation. In the INCB-352 trial, 2 patients underwent transformation to AML on the BAT arm and no patients on the ruxolitinib arm underwent leukemic transformation.
[ISS, pp. 109-110]

7.4.1.e. Malignant Neoplasms

The overall frequency of confirmed malignant neoplasms was similar in the control groups as compared with the ruxolitinib groups in the phase III studies. These included on the ruxolitinib arm of INCB-351: 2 cases of AML (1.3%), basal cell carcinoma (1 case (0.6%)), colon cancer (1 case (0.6%), 1 case of lung cancer (0.6%), and 1 case of transitional cell cancer of the bladder (0.6%). On the ruxolitinib arm of INCB-352, there was 1 case of AML (0.7%), 2 cases of squamous cell carcinoma of the skin (1.4%), 1 case of carcinoma in situ (0.7%), and 1 case of metastatic squamous cell carcinoma (0.7%).
[ISS, pp. 108-109]

7.4.1.f. Cardiac Murmurs

Grade 1 cardiac flow murmurs were reported more frequently in the ruxolitinib groups of both phase III studies (7.1% vs 3.3% in INCB-351, and 4.1% vs 2.7% in INCB-352 respectively).
[ISS, p.112]

Reviewer Comment*: In Tables 58-59, anemia was increased on the ruxolitinib arms of the phase III arms perhaps suggesting that these murmurs were high output flow murmurs.*

7.4.1.g. Extremity Pain

Pain in the extremities occurred in 12.3% of subjects in the ruxolitinib arm as compared to 9.9% on the placebo arm of INCB-351.
[ISS, p. 113]

7.4.1.h. Chills and Pyrexia

Chills and pyrexia occurred more frequently on ruxolitinib (5.2% and 11.0% respectively) as compared to the placebo arm (2.0% and 7.3% respectively) in the INCB-351 trial. Interestingly, 17 cases of pyrexia were reported in INCB-351 of which 7 occurred during interruptions of ruxolitinib therapy.
[ISS, p. 113]

7.4.2 Laboratory Findings

As outlined above in Tables 58-59, the major laboratory findings for adverse events were thrombocytopenia and anemia. In addition, the efficacy analysis showed a decrement in the levels of inflammatory cytokines (see Section 6.15.h) and cells positive for the V617F mutant allele of JAK2 (see Section 6.1.5.f) during ruxolitinib therapy.

7.4.2.a. Platelet Count

The platelet count declined over the first 4 weeks of therapy and then stabilized between 190 and 200 X 10^9/L. New or worsening thrombocytopenia (Grade 3 and Grade 4) were reported by 12.9% of subjects in the ruxolitinib group and 1.3% of the placebo group in INCB-351. In INCB-352, 7.5% of patients in the ruxolitinib group and 5.8% in the BAT groups reported thrombocytopenia. The time to resolution of Grade 3 or 4 thrombocytopenia to Grade 2 or less was 14 days (median) in both studies. Platelet transfusions were given to 8 subjects in the ruxolitinib group and to 4 subjects in the placebo group in INCB-351, and to 6 subjects in the ruxolitinib group as compared to 4 subjects in the BAT group in INCB-352. One subject in the ruxolitinib group in each phase III study withdrew for thrombocytopenia (see Table 57 above).
[ISS, pp. 120-126]

7.4.2.b. Hemoglobin

The hemoglobin reached a nadir of 9.6 g/dL between 8-12 weeks of ruxolitinib therapy, and then was observed in patients not receiving RBC transfusions to slowly return to the baseline value of 10 g/dL over the ensuing 12 weeks on INCB-351. The majority of subjects being treated with ruxolitinib did not have Grade 3 or 4 anemia, but as outlined above, the average RBC transfusion

requirement on INCB-351 increased during the 24 weeks of ruxolitinib treatment. (see Section 6.1.5.g)
[ISS, pp. 127-131]

7.4.2.c. White Blood Cell Count

The WBC was elevated in all patients prior to the onset of ruxolitinib therapy and tended to approach normal values during the therapy on both of the phase III studies. The baseline WBCs in the placebo and BAT arms on INCB-351 and INCB-352 respectively were 15.1 and 11.5 X 10^9/L, whereas the WBCs on the ruxolitinib arms after the therapy periods were completed (24 and 48 weeks on INCB-351 and INCB-352) were: 11.9 and 9.4 X 10^9/L.
[ISS, p. 141 and 141, and see Table 48 of this report which was taken from ISS pp. 48 and 52]

7.4.2.d. RBC Transfusions

During the first 8-12 weeks of therapy in INCB-351, the mean transfusion rate was higher with ruxolitinib vs placebo, but in the ensuing 12 weeks, the level of transfusions with ruxolitinib approached that of placebo, during which the rate decreased on both arms. In INCB-352, the rates of transfusions/subject/month were similar on both arms. [ISS, pp. 142-144]

Reviewer Analysis and Comment*: The reviewer analyzed the mean of the RBC transfusions during the 8 weeks prior to ruxolitinib treatment and in the final 8 weeks of treatment on INCB-351. On the ruxolitinib arm, the mean number of transfusions increased from 4.44 (baseline) to 5.12 (final 8 weeks of treatment. On the placebo arm, the number of transfusions increased from 4.48 to 6.63. Thus, ruxolitinib did not increase the transfusion dependency overall as compared to placebo on INCB-351.*

7.4.2.e. Serum Transaminases

There was a 5-10 U/L mean increase in ALT and AST in the ruxolitinib arms of the phase III trials as compared to the placebo or BAT arms of INCB-351 and INCB-352 respectively. This was a constant change during the entire treatment period in each protocol, and there was no worsening with time.
[ISS, p. 159]

7.4.2.f. Serum Creatinine

In the phase III studies, there was no difference between the ruxolitinib arms and the placebo or BAT comparator arms in the INCB-351 and INCB-352 randomized phase III studies.
[ISS, p. 164]

7.4.2.g. Serum Cholesterol

Blood cholesterol levels increased by 1 mmole/L during the first month of ruxolitinib therapy and then remained stable during the ensuing months of the treatment period in both phase III trials.
[ISS, p. 166]

7.4.2.h. Iron and Serum Ferritin Levels

The majority of patients in both arms of both phase III trials maintained normal levels of serum iron during the study treatment periods (4-30 micromol/L). On the ruxolitinib arm of INCB-351, the serum iron level increased during the first 4 weeks of therapy by 13 micromol/L, which then decreased by 304 micromol/L by Week 8, after which it remained stable. Patients who received RBC transfusions had higher levels of serum iron than patients not receiving RBC transfusions, but the absolute levels remained with normal limits during the treatment periods.

In INCB-351, median serum ferritin increased within the normal range at Week 4 in the patients treated in the ruxolitinib group who did not receive transfusions, and decreased by Week 24, to remain approximately 50% above baseline, but within the normal range.

In subjects receiving transfusions, serum ferritin increased. There were no differences in the serum ferritin between ruxolitinib and placebo groups among subjects not receiving RBC transfusions. There were no differences between the ruxolitinib and placebo groups in INCB-351 in the percentage of subjects who increased their serum ferritin to a level greater than 500 microgram/L (a level which suggests increased iron stores).
[ISS, p. 169]

7.4.2.i. Serum Calcium, Glucose, Potassium and Sodium Levels

There were no significant differences for calcium, glucose, potassium nor sodium between the ruxolitinib and the comparator groups in INCB-351 and INCB-352.
[ISS, p. 170]

7.4.3 Vital Signs

There were no safety signals for vital signs (see Section 6.1 and Table 4.1-1.3 in the ISS).

7.4.4 Electrocardiograms (ECGs)

The studies of ECGs showed no evidence for QT prolongation according to the definitions outlined in the ICH E14 Guidance (see Section 6.2 of ISS).

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies.

7.4.6 Immunogenicity

There were no studies of immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was a pre-specified adjustment of the starting dose of ruxolitinib on the basis of the pre-treatment platelet count and dose adjustments during therapy for thrombocytopenia. This was the only dose adjustment. No dose adjustments were made for anemia. As outlined above, there was a relationship between the dose of ruxolitinib administered and the extent of inhibition of phosphorylated STAT3 levels, a down stream target of activated JAK2 (see Figure 8 in Section 6.1.6 above).

7.5.2 Time Dependency for Adverse Events

There was no evidence for a time dependency for adverse events except for thrombocytopenia, which reached a nadir during the first four weeks of therapy of ruxolitinib (190 x 10^9/L), then stabilized (see Section 7.2.4.a above), and anemia, which reached a nadir of 9.5 g/dL between 8-12 weeks of therapy, and then slowly returned to baseline levels over the next 12 weeks on INCB-351 (see Section 7.2.4.b above).
[ISS, pp. 120-131]

7.5.3 Drug-Demographic Interactions

There was no evidence for drug-demographic interactions for adverse events (see Tables 29-30). The adverse events were similar for patients >65 years as compared to ≤65 years, and for male and female genders. There were no differences for adverse events among the groups PMF, PPV-MF and PET-MF. There were no differences for incidence of AEs for patients positive or negative for the V617F mutant allele of JAK2.
[ISS, pp. 181, 185]

As mentioned above in Section 6.1.7, females had a greater probability of achieving a ≥35% reduction in volume of the spleen while on ruxolitinib than did males.
[CSR INCB-351, p. 139]

7.5.4 Drug-Disease Interactions

The pharmacokinetics of ruxolitinib in patients with MF appeared to be similar to that seen in healthy subjects (see Module 2.7.2).
[ISS, p. 203]

There was no evidence of an interaction between ruxolitinib and drugs which are hepatotoxic.
[ISS, p. 204]

The PK and PK of ruxolitinib in individuals with varying degrees of renal impairment was similar to that in matching health subjects, except in subjects with end-stage renal disease on hemodialysis. For further details, see CSR INCB-142.
(ISS, p. 204]

7.5.5 Drug-Drug Interactions

Ruxolitinib is metabolized by CYP3A4 (INCB 18424-133). The plasma AUC of ruxolitinib doubled with co-administration of ketoconazole (a potent inhibitor of CYP3A4), while only a modest increase was seen with co-administration of erythromycin (a moderate CYP3A4 inhibitor).
[ISS, p. 203]

Subjects on moderate CYP3A4 inhibitors throughout the studies who were randomized to ruxolitinib were similar to the overall population of ruxolitinib-treated subjects in terms of average doses, changes in platelet counts, and spleen volume reductions. The AE profile in subjects randomized to ruxolitinib who were on potent or moderate CYP3A4 inhibitors (continuously or transiently during the studies) was similar to the overall phase III population.
[ISS, p. 187]

Ruxolitinib can be administered with or without food. For additional data, see CSR INCB-121.
[ISS, p. 206]

7.6 Additional Safety Evaluation

7.6.1 Human Carcinogenicity

No new cases of solid tumors or leukemias.

7.6.2 Human Reproduction and Pregnancy Data

No data.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no abuse potential. The highest daily dose tested in clinical studies was 200 mg in the QTc study. No AEs were associated with this level. Dialysis does not remove ruxolitinib.

7.7 Additional Submissions

There were no additional submissions.

8 Postmarket Experience

There is no postmarket experience. The applicant proposes routine pharmacovigilance including cumulative analysis in the PSUR (Periodic Safety Update Reports) and periodic safety report as required per the US regulations. This routine monitoring is designed to evaluate an characterize any risk and will include an evaluation of risk factors such as co-morbidities, co-medication, dose relation, and duration of associated risks identified through routine pharmacoviligance. [ISS, p. 190-191]

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

This is under development.

9.3 Advisory Committee Meeting

No advisory committee meeting is planned.

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/s/

ALBERT B DEISSEROTH
10/27/2011

EDVARDAS KAMINSKAS
11/04/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202192 **Applicant: Incyte** **Stamp Date:**

Drug Name: ruxolitinib **NDA/BLA Type: NME**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number:INCB18424-251 Study Title: Phase ½ OL study of the JAK2 inhibitor INCB018424 given po to patients with MF, PPVMF and PETMF Sample Size: 153 Arms: Single Location in submission:CSR INCB 18424-251	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 INCB 18424-351 Indication: PMF, PPVMF, PETMF	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 INCB 18424-352 Indication: PMF, PPVMF, PETMF				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___X_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

Albert Deisseroth, MD, PhD	July 1, 2011
Reviewing Medical Officer	Date
Edvardas Kaminskas, MD	July 1, 2011
Clinical Team Leader	Date

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/s/

ALBERT B DEISSEROTH
07/01/2011

EDVARDAS KAMINSKAS
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