CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202192Orig1s014

Trade Name:	JAKAFI
Generic or Proper Name:	(ruxolitinib)
Sponsor:	INCYTE Corp.
Approval Date:	October 10, 2017
Indication:	Jakafi is a kinase inhibitor indicated for treatment of patients with: • intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. • polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

CENTER FOR DRUG EVALUATION AND RESEARCH

202192Orig1s014

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	**X**
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202192/S-014

SUPPLEMENT APPROVAL

Incyte Corporation
Attention: Greg Taylor, PharmD
Executive Director, Regulatory Affairs
1801 Augustine Cut-Off
Wilmington, DE 19803

Dear Dr. Taylor:

Please refer to your Supplemental New Drug Application (sNDA) dated December 15, 2016, received December 15, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jakafi® (ruxolitinib) tablets 5 mg, 10 mg, 15 mg, 20 mg, 25 mg.

This Prior Approval supplemental new drug application provides for the following changes for ruxolitinib:

- Updates to United States Prescribing Information (USPI) based on clinical data from study INCB 18424-351 (COMFORT-I) describing the impact of Jakafi on fatigue in patients with MF
- Updates to the USPI Warnings and Precautions section 5.0
- Revisions to the USPI Use in Specific Populations section 8.0 to comply with Pregnancy and Lactation Labeling Rule (PLLR) content and format regulations

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Rosa Lee-Alonzo, Regulatory Project Manager, at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

ANN T FARRELL
10/10/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use JAKAFI safely and effectively. See full prescribing information for JAKAFI.

JAKAFI® (ruxolitinib) tablets, for oral use
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

Warnings and Precautions (5.2) 10/2017

INDICATIONS AND USAGE

Jakafi is a kinase inhibitor indicated for treatment of patients with:

- intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. (1.1)
- polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea. (1.2)

DOSAGE AND ADMINISTRATION

Doses should be individualized based on safety and efficacy. Starting doses per indication are noted below.

Myelofibrosis (2.1)

- The starting dose of Jakafi is based on patient's baseline platelet count:
  - Greater than 200 X 10^9/L: 20 mg given orally twice daily
  - 100 X 10^9/L to 200 X 10^9/L: 15 mg given orally twice daily
  - 50 X 10^9/L to less than 100 X 10^9/L: 5 mg given orally twice daily
- Monitor complete blood counts every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. Modify or interrupt dosing for thrombocytopenia.

Polycythemia Vera (2.2)

- The starting dose of Jakafi is 10 mg given orally twice daily.

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 10 mg, 15 mg, 20 mg and 25 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Thrombocytopenia, Anemia and Neutropenia: Manage by dose reduction, or interruption, or transfusion. (5.1)
- Risk of Infection: Assess patients for signs and symptoms of infection and initiate appropriate treatment promptly. Serious infections should have resolved before starting therapy with Jakafi. (5.2)
- Symptom Exacerbation Following Interruption or Discontinuation: Manage with supportive care and consider resuming treatment with Jakafi. (5.3)
- Risk of Non-Melanoma Skin Cancer: Perform periodic skin examinations. (5.4)
- Lipid Elevations: Assess lipid levels 8-12 weeks from start of therapy and treat as needed. (5.5)

ADVERSE REACTIONS

The most common hematologic adverse reactions (incidence > 20%) are thrombocytopenia and anemia. The most common non-hematologic adverse reactions (incidence >10%) are bruising, dizziness and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Incyte Corporation at 1-855-463-3463 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Strong CYP3A4 Inhibitors or Fluconazole: Reduce, interrupt, or discontinue Jakafi doses as recommended. Avoid use of Jakafi with fluconazole doses greater than 200 mg. (2.3) (7.1)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: Reduce Jakafi starting dose or avoid treatment as recommended. (2.4) (8.6)
- Hepatic Impairment: Reduce Jakafi starting dose or avoid treatment as recommended. (2.4) (8.7)
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Myelofibrosis

Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF.

1.2 Polycythemia Vera

Jakafi is indicated for treatment of patients with polycythemia vera (PV) who have had an inadequate response to or are intolerant of hydroxyurea.

2 DOSAGE AND ADMINISTRATION

2.1 Myelofibrosis

The recommended starting dose of Jakafi is based on platelet count (Table 1). A complete blood count (CBC) and platelet count must be performed before initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [*see Warnings and Precautions (5.1)*]. Doses may be titrated based on safety and efficacy.

Table 1: Jakafi Starting Doses for Myelofibrosis

Platelet Count	Starting Dose
Greater than 200 X 10^9/L	20 mg orally twice daily
100 X 10^9/L to 200 X 10^9/L	15 mg orally twice daily
50 X 10^9/L to less than 100 X 10^9/L	5 mg orally twice daily

2.1.1 Dose Modification Guidelines for Hematologic Toxicity for Patients with Myelofibrosis Starting Treatment with a Platelet Count of 100 X 10^9/L or Greater

Treatment Interruption and Restarting Dosing

Interrupt treatment for platelet counts less than 50 X 10^9/L or absolute neutrophil count (ANC) less than 0.5 X 10^9/L.

After recovery of platelet counts above 50 X 10^9/L and ANC above 0.75 X 10^9/L, dosing may be restarted. Table 2 illustrates the maximum allowable dose that may be used in restarting Jakafi after a previous interruption.

Table 2: Myelofibrosis: Maximum Restarting Doses for Jakafi after Safety Interruption for Thrombocytopenia for Patients Starting Treatment with a Platelet Count of 100 X 10^9/L or Greater

Current Platelet Count	Maximum Dose When Restarting Jakafi Treatment*
Greater than or equal to 125 X 10^9/L	20 mg twice daily
100 to less than 125 X 10^9/L	15 mg twice daily
75 to less than 100 X 10^9/L	10 mg twice daily for at least 2 weeks; if stable, may increase to 15 mg twice daily
50 to less than 75 X 10^9/L	5 mg twice daily for at least 2 weeks; if stable, may increase to 10 mg twice daily
Less than 50 X 10^9/L	Continue hold

*Maximum doses are displayed. When restarting, begin with a dose at least 5 mg twice daily below the dose at interruption.

Following treatment interruption for ANC below 0.5 X 10^9/L, after ANC recovers to 0.75 X 10^9/L or greater, restart dosing at the higher of 5 mg once daily or 5 mg twice daily below the largest dose in the week prior to the treatment interruption.

Dose Reductions

Dose reductions should be considered if the platelet counts decrease as outlined in Table 3 with the goal of avoiding dose interruptions for thrombocytopenia.

Table 3: Myelofibrosis: Dosing Recommendations for Thrombocytopenia for Patients Starting Treatment with a Platelet Count of 100 X 10^9/L or Greater

	Dose at Time of Platelet Decline				
Platelet Count	**25 mg twice daily**	**20 mg twice daily**	**15 mg twice daily**	**10 mg twice daily**	**5 mg twice daily**
	New Dose	**New Dose**	**New Dose**	**New Dose**	**New Dose**
100 to less than 125 X 10^9/L	20 mg twice daily	15 mg twice daily	No Change	No Change	No Change
75 to less than 100 X 10^9/L	10 mg twice daily	10 mg twice daily	10 mg twice daily	No Change	No Change
50 to less than 75 X 10^9/L	5 mg twice daily	5 mg twice daily	5 mg twice daily	5 mg twice daily	No Change
Less than 50 X 10^9/L	Hold	Hold	Hold	Hold	Hold

2.1.2 Dose Modification Based on Insufficient Response for Patients with Myelofibrosis Starting Treatment with a Platelet Count of 100 X 10^9/L or Greater

If the response is insufficient and platelet and neutrophil counts are adequate, doses may be increased in 5 mg twice daily increments to a maximum of 25 mg twice daily. Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks.

Consider dose increases in patients who meet all of the following conditions:

a. Failure to achieve a reduction from pretreatment baseline in either palpable spleen length of 50% or a 35% reduction in spleen volume as measured by computed tomography (CT) or magnetic resonance imaging (MRI);
b. Platelet count greater than 125 X 10^9/L at 4 weeks and platelet count never below 100 X 10^9/L;
c. ANC Levels greater than 0.75 X 10^9/L.

Based on limited clinical data, long-term maintenance at a 5 mg twice daily dose has not shown responses and continued use at this dose should be limited to patients in whom the benefits outweigh the potential risks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy.

2.1.3 Dose Modifications for Hematologic Toxicity for Patients with Myelofibrosis Starting Treatment with Platelet Counts of 50 X 10^9/L to Less Than 100 X 10^9/L

This section applies only to patients with platelet counts of 50 X 10^9/L to less than 100 X 10^9/L prior to any treatment with Jakafi. See Section 2.1.1 for dose modifications for hematological toxicity in patients whose platelet counts were 100 X 10^9/L or more prior to starting treatment with Jakafi.

Treatment Interruption and Restarting Dosing

Interrupt treatment for platelet counts less than 25 X 10^9/L or ANC less than 0.5 X 10^9/L.

After recovery of platelet counts above 35 X 10^9/L and ANC above 0.75 X 10^9/L, dosing may be restarted. Restart dosing at the higher of 5 mg once daily or 5 mg twice daily below the largest dose in the week prior to the decrease in platelet count below 25 X 10^9/L or ANC below 0.5 X 10^9/L that led to dose interruption.

Dose Reductions

Reduce the dose of Jakafi for platelet counts less than 35 X 10^9/L as described in Table 4.

Table 4: Myelofibrosis: Dosing Modifications for Thrombocytopenia for Patients with Starting Platelet Count of 50 X 10^9/L to Less Than 100 X 10^9/L

Platelet Count	Dosing Recommendations
Less than 25 X 10^9/L	• Interrupt dosing.
25 X 10^9/L to less than 35 X 10^9/L AND the platelet count decline is less than 20% during the prior four weeks	• Decrease dose by 5 mg once daily. • For patients on 5 mg once daily, maintain dose at 5 mg once daily.
25 X 10^9/L to less than 35 X 10^9/L AND the platelet count decline is 20% or greater during the prior four weeks	• Decrease dose by 5 mg twice daily. • For patients on 5 mg twice daily, decrease the dose to 5 mg once daily. • For patients on 5 mg once daily, maintain dose at 5 mg once daily.

2.1.4 Dose Modifications Based on Insufficient Response for Patients with Myelofibrosis and Starting Platelet Count of 50 X 10^9/L to Less Than 100 X 10^9/L

Do not increase doses during the first 4 weeks of therapy, and do not increase the dose more frequently than every 2 weeks.

If the response is insufficient as defined in Section 2.1.2, doses may be increased by increments of 5 mg daily to a maximum of 10 mg twice daily if:

a) the platelet count has remained at least 40 X 10^9/L, and
b) the platelet count has not fallen by more than 20% in the prior 4 weeks, and
c) the ANC is more than 1 X 10^9/L, and
d) the dose has not been reduced or interrupted for an adverse event or hematological toxicity in the prior 4 weeks.

Continuation of treatment for more than 6 months should be limited to patients in whom the benefits outweigh the potential risks. Discontinue Jakafi if there is no spleen size reduction or symptom improvement after 6 months of therapy.

2.1.5 Dose Modification for Bleeding

Interrupt treatment for bleeding requiring intervention regardless of current platelet count. Once the bleeding event has resolved, consider resuming treatment at the prior dose if the underlying cause of bleeding has been controlled. If the bleeding event has resolved but the underlying cause persists, consider resuming treatment with Jakafi at a lower dose.

2.2 Polycythemia Vera

The recommended starting dose of Jakafi is 10 mg twice daily. Doses may be titrated based on safety and efficacy.

2.2.1 Dose Modification Guidelines for Patients with Polycythemia Vera

A complete blood count (CBC) and platelet count must be performed before initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [*see Warnings and Precautions (5.1)*].

Dose Reductions

Dose reductions should be considered for hemoglobin and platelet count decreases as described in Table 5.

Table 5: Polycythemia Vera: Dose Reductions

Hemoglobin and/or Platelet Count	Dosing Recommendations
Hemoglobin greater than or equal to 12 g/dL AND platelet count greater than or equal to 100 X 10^9/L	• No change required.
Hemoglobin 10 to less than 12 g/dL AND platelet count 75 to less than 100 X 10^9/L	• Dose reductions should be considered with the goal of avoiding dose interruptions for anemia and thrombocytopenia.
Hemoglobin 8 to less than 10 g/dL OR platelet count 50 to less than 75 X 10^9/L	• Reduce dose by 5 mg twice daily. • For patients on 5 mg twice daily, decrease the dose to 5 mg once daily.
Hemoglobin less than 8 g/dL OR platelet count less than 50 X 10^9/L	• Interrupt dosing.

Treatment Interruption and Restarting Dosing

Interrupt treatment for hemoglobin less than 8 g/dL, platelet counts less than 50 X 10^9/L or ANC less than 1.0 X 10^9/L.

After recovery of the hematologic parameter(s) to acceptable levels, dosing may be restarted.

Table 6 illustrates the dose that may be used in restarting Jakafi after a previous interruption.

Table 6: Polycythemia Vera: Restarting Doses for Jakafi after Safety Interruption for Hematologic Parameter(s)

Use the **most severe category** of a patient's hemoglobin, platelet count, or ANC abnormality to determine the corresponding maximum restarting dose.

Hemoglobin, Platelet Count, or ANC	Maximum Restarting Dose
Hemoglobin less than 8 g/dL OR platelet count less than 50 X 10^9/L OR ANC less than 1 X 10^9/L	Continue hold
Hemoglobin 8 to less than 10 g/dL OR platelet count 50 to less than 75 X 10^9/L OR ANC 1 to less than 1.5 X 10^9/L	5 mg twice daily[a] or no more than 5 mg twice daily less than the dose which resulted in dose interruption
Hemoglobin 10 to less than 12 g/dL OR platelet count 75 to less than 100 X 10^9/L OR ANC 1.5 to less than 2 X 10^9/L	10 mg twice daily[a] or no more than 5 mg twice daily less than the dose which resulted in dose interruption
Hemoglobin greater than or equal to 12 g/dL OR platelet count greater than or equal to 100 X 10^9/L OR ANC greater than or equal to 2 X 10^9/L	15 mg twice daily[a] or no more than 5 mg twice daily less than the dose which resulted in dose interruption

[a] Continue treatment for at least 2 weeks; if stable, may increase dose by 5 mg twice daily.

Patients who had required dose interruption while receiving a dose of 5 mg twice daily, may restart at a dose of 5 mg twice daily or 5 mg once daily, but not higher, once hemoglobin is greater than or equal to 10 g/dL, platelet count is greater than or equal to 75 X 10^9/L, and ANC is greater than or equal to 1.5 X 10^9/L.

Dose Management after Restarting Treatment

After restarting Jakafi following treatment interruption, doses may be titrated, but the maximum total daily dose should not exceed 5 mg less than the dose that resulted in the dose interruption. An exception to this is dose interruption following phlebotomy-associated anemia, in which case the maximal total daily dose allowed after restarting Jakafi would not be limited.

2.2.2 Dose Modifications Based on Insufficient Response for Patients with Polycythemia Vera

If the response is insufficient and platelet, hemoglobin, and neutrophil counts are adequate, doses may be increased in 5 mg twice daily increments to a maximum of 25 mg twice daily. Doses should not be increased during the first 4 weeks of therapy and not more frequently than every two weeks.

Consider dose increases in patients who meet all of the following conditions:

1. Inadequate efficacy as demonstrated by one or more of the following:
   a. Continued need for phlebotomy
   b. WBC greater than the upper limit of normal range
   c. Platelet count greater than the upper limit of normal range
   d. Palpable spleen that is reduced by less than 25% from Baseline
2. Platelet count greater than or equal to 140 X 10^9/L
3. Hemoglobin greater than or equal to 12 g/dL
4. ANC greater than or equal to 1.5 X 10^9/L

2.3 Dose Modifications for Concomitant Use with Strong CYP3A4 Inhibitors or Fluconazole

Modify the Jakafi dosage when coadministered with strong CYP3A4 inhibitors and fluconazole doses of less than or equal to 200 mg [*see Drug Interactions (7.1)*], according to Table 7.

Additional dose modifications should be made with frequent monitoring of safety and efficacy.

Avoid the use of fluconazole doses of greater than 200 mg daily with Jakafi.

Table 7: Dose Modifications for Concomitant Use of Strong CYP3A4 Inhibitors or Fluconazole

For patients coadministered strong CYP3A4 inhibitors or fluconazole doses of less than or equal to 200 mg	**Recommended Dose Modification**
Starting dose for patients with MF with a platelet count:	
• Greater than or equal to 100 X 10^9/L	10 mg twice daily
• 50 X 10^9/L to less than 100 X 10^9/L	5 mg once daily
Starting dose for patients with PV:	5 mg twice daily
If on stable dose for patients with PV:	
• Greater than or equal to 10 mg twice daily	Decrease dose by 50% (round up to the closest available tablet strength)
• 5 mg twice daily	5 mg once daily
• 5 mg once daily	Avoid strong CYP3A4 inhibitor or fluconazole treatment or interrupt Jakafi treatment for the duration of strong CYP3A4 inhibitor or fluconazole use

2.4 Dose Modifications for Organ Impairment

Renal Impairment

Patients with Moderate or Severe Renal Impairment

Modify the Jakafi dosage for patients with moderate or severe renal impairment according to Table 8.

Table 8: Dose Modifications for Renal Impairment

Renal Impairment Status	Platelet Count	Recommended Starting Dosage
Patients with MF Moderate (CLcr 30 to 59 mL/min) or Severe (CLcr 15 to 29 mL/min)	Greater than 150 X 10^9/L	No dose modification needed
	100 X 10^9/L to 150 X 10^9/L	10 mg twice daily
	50 to less than 100 X 10^9/L	5 mg daily
	Less than 50 X 10^9/L	Avoid use [*see Use in Specific Populations (8.6)*]
Patients with PV Moderate (CLcr 30 to 59 mL/min) or Severe (CLcr 15 to 29 mL/min)	Any	5 mg twice daily

Patients with End Stage Renal Disease on Dialysis

The recommended starting dose for patients with MF with end stage renal disease (ESRD) on dialysis is 15 mg once after a dialysis session for patients with a platelet count between 100 X 10^9/L and 200 X 10^9/L or 20 mg once after a dialysis session for patients with a platelet count of greater than 200 X 10^9/L.

The recommended starting dose for patients with PV with ESRD on dialysis is 10 mg.

Make additional dose modifications with frequent monitoring of safety and efficacy. Avoid use of Jakafi in patients with ESRD (CLcr less than 15 mL/min) not requiring dialysis [*see Use in Specific Populations (8.6)*].

Hepatic Impairment

Modify the Jakafi dosage for patients with hepatic impairment according to Table 9.

Table 9: Dose Modifications for Hepatic Impairment

Hepatic Impairment Status	Platelet Count	Recommended Starting Dosage
Patients with MF Mild, Moderate, or Severe (Child-Pugh Class A, B, C)	Greater than 150 X 10^9/L	No dose modification needed
	100 X 10^9/L to 150 X 10^9/L	10 mg twice daily
	50 to less than 100 X 10^9/L	5 mg daily
	Less than 50 X 10^9/L	Avoid use [*see Use in Specific Populations (8.7)*]

Patients with PV Mild, Moderate, or Severe (Child-Pugh Class A, B, C)	Any	5 mg twice daily

2.5 Method of Administration

Jakafi is dosed orally and can be administered with or without food.

If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose.

When discontinuing Jakafi therapy for reasons other than thrombocytopenia, gradual tapering of the dose of Jakafi may be considered, for example by 5 mg twice daily each week.

For patients unable to ingest tablets, Jakafi can be administered through a nasogastric tube (8 French or greater) as follows:

- Suspend one tablet in approximately 40 mL of water with stirring for approximately 10 minutes.
- Within 6 hours after the tablet has dispersed, the suspension can be administered through a nasogastric tube using an appropriate syringe.

The tube should be rinsed with approximately 75 mL of water. The effect of tube feeding preparations on Jakafi exposure during administration through a nasogastric tube has not been evaluated.

3 DOSAGE FORMS AND STRENGTHS

5 mg tablets - round and white with “INCY” on one side and “5” on the other.

10 mg tablets - round and white with “INCY” on one side and “10” on the other.

15 mg tablets - oval and white with “INCY” on one side and “15” on the other.

20 mg tablets - capsule-shaped and white with “INCY” on one side and “20” on the other.

25 mg tablets - oval and white with “INCY” on one side and “25” on the other.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia, Anemia and Neutropenia

Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [*see Dosage and Administration (2.1)*].

Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [*see Dosage and Administration (2.1.1), and Adverse Reactions (6.1)*].

Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi.

Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible by withholding Jakafi until recovery [*see Adverse Reactions (6.1)*].

Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. [*see Dosage and Administration (2.1.1), and Adverse Reactions (6.1)*].

5.2 Risk of Infection

Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly.

Tuberculosis

Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly.

Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a

person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed.

For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate.

Herpes Zoster

Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [*see Adverse Reactions (6.1*)].

Hepatitis B

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

5.3 Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi

Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [*see Dosage and Administration (2.5)*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly.

5.4 Non-Melanoma Skin Cancer

Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations.

5.5 Lipid Elevations

Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following

initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Thrombocytopenia, Anemia and Neutropenia [*see Warnings and Precautions (5.1)*]
- Risk of Infection [*see Warnings and Precautions (5.2)*]
- Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [*see Warnings and Precautions (5.3)*]
- Non-Melanoma Skin Cancer [*see Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience in Myelofibrosis

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies.

In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 X 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 X 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy.

In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were thrombocytopenia and anemia [*see Table 11*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [*see Table 10*].

Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo.

Table 10 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 10: Myelofibrosis: Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

	Jakafi (N=155)			Placebo (N=151)		
Adverse Reactions	**All Grades[a] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Bruising[b]	23	<1	0	15	0	0
Dizziness[c]	18	<1	0	7	0	0
Headache	15	0	0	5	0	0
Urinary Tract Infections[d]	9	0	0	5	<1	<1
Weight Gain[e]	7	<1	0	1	<1	0
Flatulence	5	0	0	<1	0	0
Herpes Zoster[f]	2	0	0	<1	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura
[c] includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis
[d] includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
[e] includes weight increased, abnormal weight gain
[f] includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Drug Reactions

Anemia

In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (<1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy.

In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients.

Thrombocytopenia

In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 X 10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in <1% of patients receiving Jakafi and <1% of patients

receiving control regimens. Patients with a platelet count of 100 X 10^9/L to 200 X 10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 X 10^9/L (17% versus 7%).

Neutropenia

In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia.

Table 11 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 11: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study[a]

	Jakafi (N=155)			Placebo (N=151)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Thrombocytopenia	70	9	4	31	1	0
Anemia	96	34	11	87	16	3
Neutropenia	19	5	2	4	<1	1

[a] Presented values are worst Grade values regardless of baseline

[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-controlled Study

25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations.

17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations.

17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations.

6.2 Clinical Trial Experience in Polycythemia Vera

In a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy *[see Clinical Studies (14.2)]*. The most frequent adverse drug reaction was anemia. Table 12 presents the most frequent non-hematologic treatment emergent adverse events occurring up to Week 32.

Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi.

Table 12: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in ≥ 6% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

	Jakafi (N=110)		Best Available Therapy (N=111)	
Adverse Events	**All Grades[a] (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Headache	16	<1	19	<1
Abdominal Pain[b]	15	<1	15	<1
Diarrhea	15	0	7	<1
Dizziness[c]	15	0	13	0
Fatigue	15	0	15	3
Pruritus	14	<1	23	4
Dyspnea[d]	13	3	4	0
Muscle Spasms	12	<1	5	0
Nasopharyngitis	9	0	8	0
Constipation	8	0	3	0
Cough	8	0	5	0
Edema[e]	8	0	7	0
Arthralgia	7	0	6	<1
Asthenia	7	0	11	2
Epistaxis	6	0	3	0
Herpes Zoster[f]	6	<1	0	0
Nausea	6	0	4	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes abdominal pain, abdominal pain lower, and abdominal pain upper
[c] includes dizziness and vertigo
[d] includes dyspnea and dyspnea exertional
[e] includes edema and peripheral edema
[f] includes herpes zoster and post-herpetic neuralgia

Other clinically important treatment emergent adverse events observed in less than 6% of patients treated with Jakafi were:

Weight gain, hypertension, and urinary tract infections

Clinically relevant laboratory abnormalities are shown in Table 13.

Table 13: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment[a]

	Jakafi (N=110)			Best Available Therapy (N=111)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Hematology						
Anemia	72	<1	<1	58	0	0
Thrombocytopenia	27	5	<1	24	3	<1
Neutropenia	3	0	<1	10	<1	0
Chemistry						
Hypercholesterolemia	35	0	0	8	0	0
Elevated ALT	25	<1	0	16	0	0
Elevated AST	23	0	0	23	<1	0
Hypertriglyceridemia	15	0	0	13	0	0

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

7 DRUG INTERACTIONS

Fluconazole

Concomitant administration of Jakafi with fluconazole doses greater than 200 mg daily may increase ruxolitinib exposure due to inhibition of both the CYP3A4 and CYP2C9 metabolic pathways [*see Clinical Pharmacology (12.3)*]. Increased exposure may increase the risk of exposure-related adverse reactions. Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily [*see Dosage and Administration (2.3)*].

Strong CYP3A4 inhibitors

Concomitant administration of Jakafi with strong CYP3A4 inhibitors increases ruxolitinib exposure [*see Clinical Pharmacology (12.3)*]. Increased exposure may increase the risk of exposure-related adverse reactions. Consider dose reduction when administering Jakafi with strong CYP3A4 inhibitors [*see Dosage and Administration (2.3)*].

Strong CYP3A4 inducers

Concomitant administration of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure [*see Clinical Pharmacology (12.3)*]. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

When pregnant rats and rabbits were administered ruxolitinib during the period of organogenesis adverse developmental outcomes occurred at doses associated with maternal toxicity (*see Data*). There are no studies with the use of Jakafi in pregnant women to inform drug-associated risks.

The background risk of major birth defects and miscarriage for the indicated populations is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk in the U.S. general population of major birth defects is 2% to 4% and miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations. Adverse developmental outcomes, such as decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose.

In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily).

8.2 Lactation

Risk Summary

No data are available regarding the presence of ruxolitinib in human milk, the effects on the breast fed infant, or the effects on milk production. Ruxolitinib and/or its metabolites were present in the milk of lactating rats (*see Data*). Because many drugs are present in human milk and because of the potential for thrombocytopenia and anemia shown for Jakafi in human studies, discontinue breastfeeding during treatment with Jakafi and for two weeks after the final dose.

Data

Animal Data

Lactating rats were administered a single dose of [^{14}C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13-fold the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma.

8.4 Pediatric Use

The safety and effectiveness of Jakafi in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients with MF in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients.

8.6 Renal Impairment

Reduce the Jakafi dosage when administering Jakafi to patients with MF and moderate (CLcr 30 mL/min to 59 mL/min as estimated using Cockcroft-Gault) or severe renal impairment (CLcr 15 mL/min to 29 mL/min) with a platelet count between 50 X 10^9/L and 150 X 10^9/L [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

Reduce the Jakafi dosage for patients with PV and moderate (CLcr 30 to 59 mL/min) or severe renal impairment (CLcr 15 to 29 mL/min) [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

Reduce the Jakafi dosage for all patients with ESRD on dialysis [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Reduce the Jakafi dosage when administering Jakafi to patients with MF and any degree of hepatic impairment (Child-Pugh Class A, B and C) and with a platelet count between 50 X 10^9/L and 150 X 10^9/L [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

Reduce the Jakafi dosage for patients with PV and hepatic impairment (Child-Pugh Class A, B and C) [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

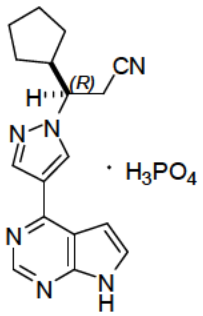
10 OVERDOSAGE

There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given.

Hemodialysis is not expected to enhance the elimination of Jakafi.

11 DESCRIPTION

Ruxolitinib phosphate is a kinase inhibitor with the chemical name (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate and a molecular weight of 404.36. Ruxolitinib phosphate has the following structural formula:



Ruxolitinib phosphate is a white to off-white to light pink powder and is soluble in aqueous buffers across a pH range of 1 to 8.

Jakafi (ruxolitinib) Tablets are for oral administration. Each tablet contains ruxolitinib phosphate equivalent to 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base together with microcrystalline cellulose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxypropyl cellulose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ruxolitinib, a kinase inhibitor, inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

MF and PV are myeloproliferative neoplasms (MPN) known to be associated with dysregulated JAK1 and JAK2 signaling. In a mouse model of JAK2V617F-positive MPN, oral administration of ruxolitinib prevented splenomegaly, preferentially decreased JAK2V617F mutant cells in the spleen and decreased circulating inflammatory cytokines (e.g., TNF-α, IL-6).

12.2 Pharmacodynamics

Jakafi inhibits cytokine induced STAT3 phosphorylation in whole blood from patients with MF and PV. Jakafi administration resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 10 hours in patients with MF and PV.

Cardiac Electrophysiology

At a dose of 1.25 to 10 times the highest recommended starting dosage, Jakafi does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Mean ruxolitinib C_{max} and AUC increased proportionally over a single dose range of 5 mg to 200 mg. Mean ruxolitinib C_{max} ranged from 205 nM to 7100 nM and AUC ranged from 862 nM*hr to 30700 nM*hr over a single dose range of 5 mg to 200 mg.

Absorption

Ruxolitinib achieves maximal plasma concentration (C_{max}) within 1 hour to 2 hours post-dose. Oral absorption of ruxolitinib is estimated to be at least 95%.

Food Effect

No clinically relevant changes in the pharmacokinetics of ruxolitinib were observed upon administration of Jakafi with a high-fat, high-calorie meal (approximately 800 to 1000 calories of which 50% were derived from fat).

Distribution

The mean volume of distribution at steady-state is 72 L (coefficient of variation [CV] 29%) in patients with MF and 75 L (23%) in patients with PV.

Binding to plasma proteins is approximately 97%, mostly to albumin.

Elimination

The mean elimination half-life of ruxolitinib is approximately 3 hours and the mean half-life of ruxolitinib + metabolites is approximately 5.8 hours.

Ruxolitinib clearance was 17.7 L/h in women and 22.1 L/h in men with MF (39% inter-subject variability).

Ruxolitinib clearance was 12.7 L/h in patients with PV (42% inter-subject variability).

Metabolism

Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9.

Excretion

Following a single oral dose of radiolabeled ruxolitinib, elimination was predominately through metabolism with 74% of radioactivity excreted in urine and 22% excretion via feces. Unchanged drug accounted for less than 1% of the excreted total radioactivity.

Specific Populations

No clinically relevant differences in ruxolitinib pharmacokinetics were observed with regard to age, race, sex, or weight.

Patients with Renal Impairment

The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects [CLcr 72 mL/min to 164 mL/min as estimated using Cockcroft-Gault] and in subjects with mild [CLcr 53 mL/min to 83 mL/min], moderate [CLcr 38 mL/min to 57 mL/min], or severe renal impairment [CLcr 15 mL/min to 51 mL/min]. Additional subjects with ESRD requiring hemodialysis were also enrolled.

The pharmacokinetics of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function, but the plasma AUC values of ruxolitinib metabolites increased with increasing severity of renal impairment. This was most marked in the subjects with ESRD requiring hemodialysis. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out.

Patients with Hepatic Impairment

The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects and in subjects with mild [Child-Pugh A], moderate [Child-Pugh B], or severe hepatic impairment [Child-Pugh C]. The mean AUC for ruxolitinib was increased by 87% in patients with mild impairment, 28% in patients with moderate impairment and 65% in patients with severe hepatic impairment compared to patients with normal hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy subjects (4.1 hours to 5 hours versus 2.8 hours). The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in ruxolitinib exposure except in the severe hepatic impairment cohort where the pharmacodynamic activity was more prolonged in some subjects than expected based on plasma concentrations of ruxolitinib.

Drug Interactions

Fluconazole

Simulations suggest that fluconazole (a dual CYP3A4 and CYP2C9 inhibitor) increases steady state ruxolitinib AUC by approximately 100% to 300% following concomitant administration of 10 mg of Jakafi twice daily with 100 mg to 400 mg of fluconazole once daily [*see Dosage and Administration (2.3) and Drug Interactions (7)*].

Strong CYP3A4 inhibitors

Ketoconazole (a strong CYP3A4 inhibitor) increased ruxolitinib C_{max} by 33% and AUC by 91%. Ketoconazole also prolonged ruxolitinib half-life from 3.7 hours to 6 hours [*see Dosage and Administration (2.3) and Drug Interactions (7)*].

Moderate CYP3A4 inhibitors

Erythromycin (a moderate CYP3A4 inhibitor) increased ruxolitinib C_{max} by 8% and AUC by 27% *[see Drug Interactions (7)*].

Strong CYP3A4 inducers

Rifampin (a strong CYP3A4 inducer) decreased ruxolitinib C_{max} by 32% and AUC by 61%. The relative exposure to ruxolitinib's active metabolites increased approximately 100% *[see Drug Interactions (7.1)*].

In vitro studies

Ruxolitinib and its M18 metabolite did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Ruxolitinib did not induce CYP1A2, CYP2B6 or CYP3A4 at clinically relevant concentrations.

Ruxolitinib and its M18 metabolite did not inhibit the P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1 or OAT3 transport systems at clinically relevant concentrations. Ruxolitinib is not a substrate for the P-gp transporter.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ruxolitinib was not carcinogenic in the 6-month Tg.rasH2 transgenic mouse model or in a 2-year carcinogenicity study in the rat.

Ruxolitinib was not mutagenic in a bacterial mutagenicity assay (Ames test) or clastogenic in *in vitro* chromosomal aberration assay (cultured human peripheral blood lymphocytes) or *in vivo* in a rat bone marrow micronucleus assay.

In a fertility study, ruxolitinib was administered to male rats prior to and throughout mating and to female rats prior to mating and up to the implantation day (gestation day 7). Ruxolitinib had no effect on fertility or reproductive function in male or female rats at doses of 10, 30 or 60 mg/kg/day. However, in female rats doses of greater than or equal to 30 mg/kg/day resulted in increased post-implantation loss. The exposure (AUC) at the dose of 30 mg/kg/day is approximately 34% the clinical exposure at the maximum recommended dose of 25 mg twice daily.

14 CLINICAL STUDIES

14.1 Myelofibrosis

Two randomized Phase 3 studies (Studies 1 and 2) were conducted in patients with MF (either primary MF, post-polycythemia vera MF or post-essential thrombocythemia-MF). In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate 2 (2 prognostic factors) or high risk (3 or more prognostic factors) based on the International Working Group Consensus Criteria (IWG).

The starting dose of Jakafi was based on platelet count. Patients with a platelet count between 100 and 200 X 10^9/L were started on Jakafi 15 mg twice daily and patients with a platelet count greater than 200 X 10^9/L were started on Jakafi 20 mg twice daily. Doses were then individualized based upon tolerability and efficacy with maximum doses of 20 mg twice daily

for patients with platelet counts between 100 to less than or equal to 125 X 10^9/L, of 10 mg twice daily for patients with platelet counts between 75 to less than or equal to 100 X 10^9/L, and of 5 mg twice daily for patients with platelet counts between 50 to less than or equal to 75 X 10^9/L.

Study 1

Study 1 was a double-blind, randomized, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. The median age was 68 years (range 40 to 91 years) with 61% of patients older than 65 years and 54% were male. Fifty percent (50%) of patients had primary MF, 31% had post-polycythemia vera MF and 18% had post-essential thrombocythemia MF. Twenty-one percent (21%) of patients had red blood cell transfusions within 8 weeks of enrollment in the study. The median hemoglobin count was 10.5 g/dL and the median platelet count was 251 X 10^9/L. Patients had a median palpable spleen length of 16 cm below the costal margin, with 81% having a spleen length 10 cm or greater below the costal margin. Patients had a median spleen volume as measured by magnetic resonance imaging (MRI) or computed tomography (CT) of 2595 cm^3 (range 478 cm^3 to 8881 cm^3). (The upper limit of normal is approximately 300 cm^3).

Patients were dosed with Jakafi or matching placebo. The primary efficacy endpoint was the proportion of patients achieving greater than or equal to a 35% reduction from baseline in spleen volume at Week 24 as measured by MRI or CT.

Secondary endpoints included duration of a 35% or greater reduction in spleen volume and proportion of patients with a 50% or greater reduction in Total Symptom Score from baseline to Week 24 as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary.

Study 2

Study 2 was an open-label, randomized study in 219 patients. Patients were randomized 2:1 to Jakafi versus best available therapy. Best available therapy was selected by the investigator on a patient-by-patient basis. In the best available therapy arm, the medications received by more than 10% of patients were hydroxyurea (47%) and glucocorticoids (16%). The median age was 66 years (range 35 to 85 years) with 52% of patients older than 65 years and 57% were male. Fifty-three percent (53%) of patients had primary MF, 31% had post-polycythemia vera MF and 16% had post-essential thrombocythemia MF. Twenty-one percent (21%) of patients had red blood cell transfusions within 8 weeks of enrollment in the study. The median hemoglobin count was 10.4 g/dL and the median platelet count was 236 X 10^9/L. Patients had a median palpable spleen length of 15 cm below the costal margin, with 70% having a spleen length 10 cm or greater below the costal margin. Patients had a median spleen volume as measured by MRI or CT of 2381 cm^3 (range 451 cm^3 to 7765 cm^3).

The primary efficacy endpoint was the proportion of patients achieving 35% or greater reduction from baseline in spleen volume at Week 48 as measured by MRI or CT.

A secondary endpoint in Study 2 was the proportion of patients achieving a 35% or greater reduction of spleen volume as measured by MRI or CT from baseline to Week 24.

Study 1 and 2 Efficacy Results

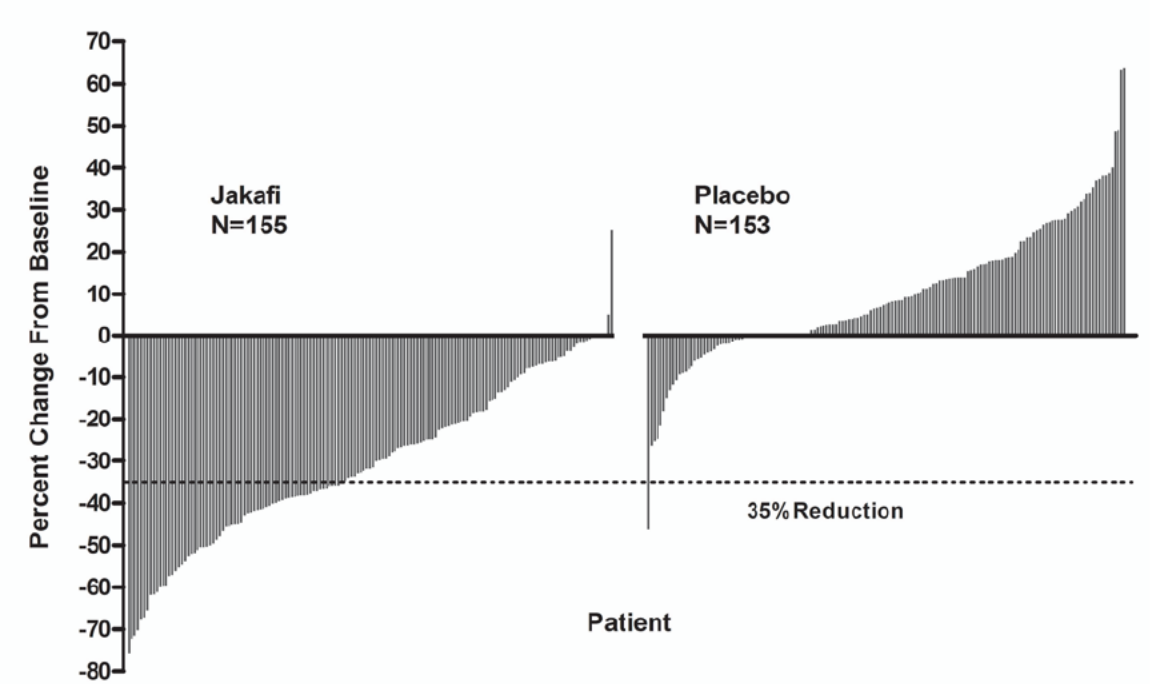
Efficacy analyses of the primary endpoint in Studies 1 and 2 are presented in Table 14 below. A significantly larger proportion of patients in the Jakafi group achieved a 35% or greater reduction in spleen volume from baseline in both studies compared to placebo in Study 1 and best available therapy in Study 2. A similar proportion of patients in the Jakafi group achieved a 50% or greater reduction in palpable spleen length.

Table 14: Percent of Patients with Myelofibrosis Achieving 35% or Greater Reduction from Baseline in Spleen Volume at Week 24 in Study 1 and at Week 48 in Study 2 (Intent to Treat)

	Study 1		Study 2	
	Jakafi (N=155)	**Placebo (N=154)**	**Jakafi (N=146)**	**Best Available Therapy (N=73)**
Time Points	Week 24		Week 48	
Number (%) of Patients with Spleen Volume Reduction by 35% or More	65 (42)	1 (<1)	41 (29)	0
P-value	< 0.0001		< 0.0001	

Figure 1 shows the percent change from baseline in spleen volume for each patient at Week 24 (Jakafi N=139, placebo N=106) or the last evaluation prior to Week 24 for patients who did not complete 24 weeks of randomized treatment (Jakafi N=16, placebo N=47). One (1) patient (placebo) with a missing baseline spleen volume is not included.

Figure 1: Percent Change from Baseline in Spleen Volume at Week 24 or Last Observation for Each Patient (Study 1)



In Study 1, MF symptoms were a secondary endpoint and were measured using the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary. The modified MFSAF is a daily diary capturing the core symptoms of MF (abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain and early satiety). Symptom scores ranged from 0 to 10 with 0 representing symptoms "absent" and 10 representing "worst imaginable" symptoms. These scores were added to create the daily total score, which has a maximum of 60.

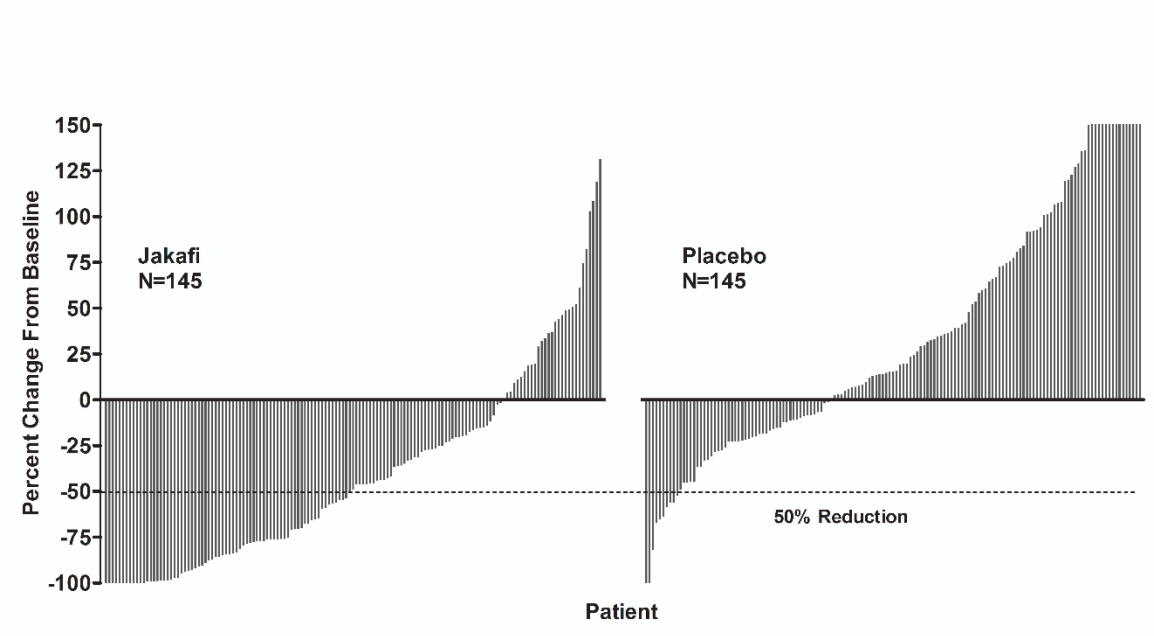
Table 15 presents assessments of Total Symptom Score from baseline to Week 24 in Study 1 including the proportion of patients with at least a 50% reduction (ie, improvement in symptoms). At baseline, the mean Total Symptom Score was 18.0 in the Jakafi group and 16.5 in the placebo group. A higher proportion of patients in the Jakafi group had a 50% or greater reduction in Total Symptom Score than in the placebo group, with a median time to response of less than 4 weeks.

Table 15: Improvement in Total Symptom Score in Patients with Myelofibrosis

	Jakafi (N=148)	Placebo (N=152)
Number (%) of Patients with 50% or Greater Reduction in Total Symptom Score by Week 24	68 (46)	8 (5)
P-value	< 0.0001	

Figure 2 shows the percent change from baseline in Total Symptom Score for each patient at Week 24 (Jakafi N=129, placebo N=103) or the last evaluation on randomized therapy prior to Week 24 for patients who did not complete 24 weeks of randomized treatment (Jakafi N=16, placebo N=42). Results are excluded for 5 patients with a baseline Total Symptom Score of zero, 8 patients with missing baseline and 6 patients with insufficient post-baseline data.

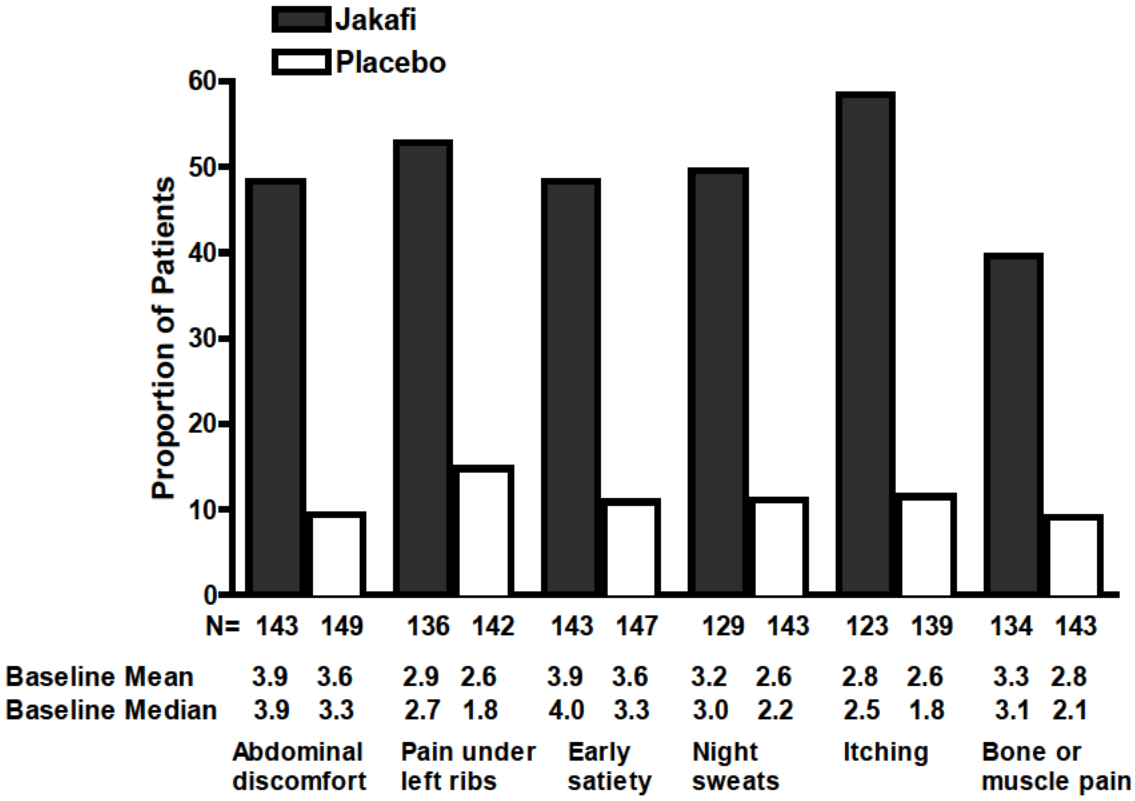
Figure 2: Percent Change from Baseline in Total Symptom Score at Week 24 or Last Observation for Each Patient (Study 1)



Worsening of Total Symptom Score is truncated at 150%.

Figure 3 displays the proportion of patients with at least a 50% improvement in each of the individual symptoms that comprise the Total Symptom Score indicating that all 6 of the symptoms contributed to the higher Total Symptom Score response rate in the group treated with Jakafi.

Figure 3: Proportion of Patients With Myelofibrosis Achieving 50% or Greater Reduction in Individual Symptom Scores at Week 24



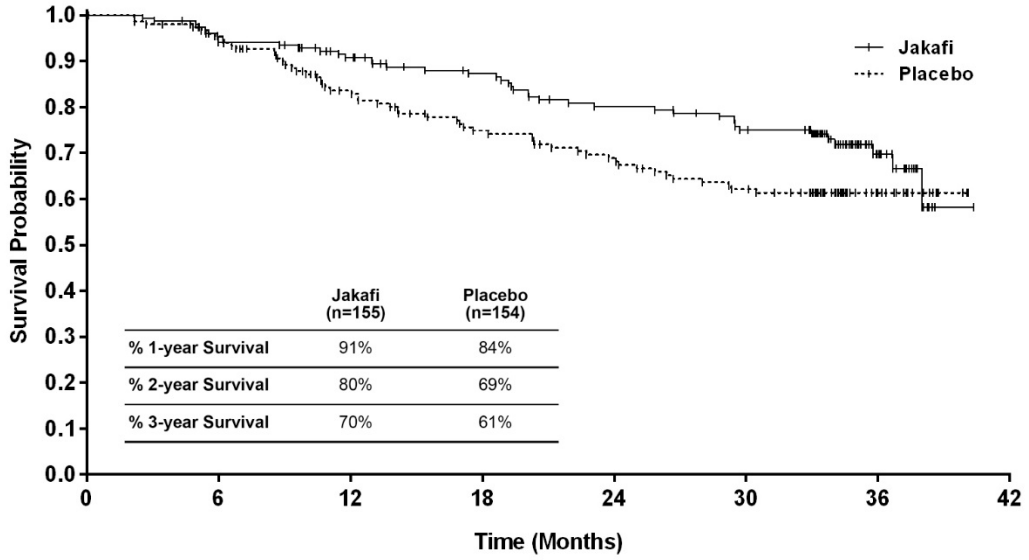
Individual score range = 0 to 10

An exploratory analysis of patients receiving Jakafi also showed improvement in fatigue-related symptoms (i.e., tiredness, exhaustion, mental tiredness, and lack of energy) and associated impacts on daily activities (i.e., activity limitations related to work, self-care, and exercise) as measured by the PROMIS® Fatigue 7-item short form total score at Week 24. Patients who achieved a reduction of 4.5 points or more from baseline to Week 24 in the PROMIS® Fatigue total score were considered to have achieved a fatigue response. Fatigue response was reported in 35% of patients in the Jakafi group versus 14% of the patients in the placebo group.

Overall survival was a secondary endpoint in both Study 1 and Study 2. Patients in the control groups were eligible for crossover in both studies, and the median times to crossover were 9 months in Study 1 and 17 months in Study 2.

Figure 4 and Figure 5 show Kaplan-Meier curves of overall survival at prospectively planned analyses after all patients remaining on study had completed 144 weeks on study.

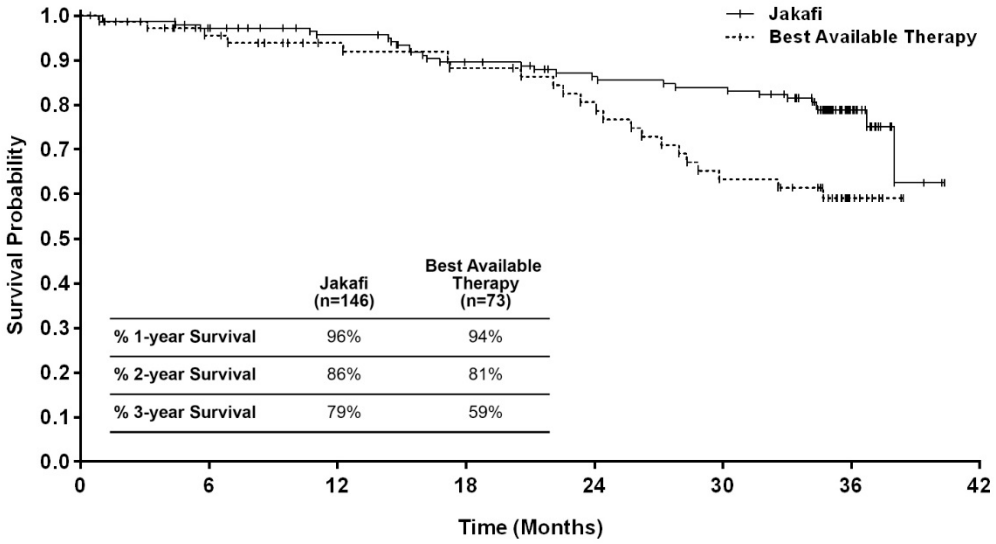
Figure 4: Overall Survival - Kaplan-Meier Curves by Treatment Group in Study 1



	Jakafi (n=155)	Placebo (n=154)
% 1-year Survival	91%	84%
% 2-year Survival	80%	69%
% 3-year Survival	70%	61%

Number at Risk:								
Jakafi	155	145	134	122	111	102	29	0
Placebo	154	142	117	101	92	82	32	0

Figure 5: Overall Survival - Kaplan-Meier Curves by Treatment Group in Study 2



	Jakafi (n=146)	Best Available Therapy (n=73)
% 1-year Survival	96%	94%
% 2-year Survival	86%	81%
% 3-year Survival	79%	59%

Number at Risk:								
Jakafi	146	135	126	115	107	104	33	0
Best Available Therapy	73	58	50	47	42	33	9	0

14.2 Polycythemia Vera

Study 3 was a randomized, open-label, active-controlled Phase 3 study conducted in 222 patients with PV. Patients had been diagnosed with PV for at least 24 weeks, had an inadequate response to or were intolerant of hydroxyurea, required phlebotomy and exhibited splenomegaly. All patients were required to demonstrate hematocrit control between 40-45% prior to randomization. The age ranged from 33 to 90 years with 30% of patients over 65 years of age and 66% were male. Patients had a median spleen volume as measured by MRI or CT of 1272 cm^3 (range 254 cm^3 to 5147 cm^3) and median palpable spleen length below the costal margin was 7 cm.

Patients were randomized to Jakafi or best available therapy. The starting dose of Jakafi was 10 mg twice daily. Doses were then individualized based upon tolerability and efficacy with a maximum dose of 25 mg twice daily. At Week 32, 98 patients were still on Jakafi with 8% receiving greater than 20 mg twice daily, 15% receiving 20 mg twice daily, 33% receiving 15 mg twice daily, 34% receiving 10 mg twice daily, and 10% receiving less than 10 mg twice daily. Best available therapy (BAT) was selected by the investigator on a patient-by-patient basis and included hydroxyurea (60%), interferon/pegylated interferon (12%), anagrelide (7%), pipobroman (2%), lenalidomide/thalidomide (5%), and observation (15%).

The primary endpoint was the proportion of subjects achieving a response at Week 32, with response defined as having achieved both hematocrit control (the absence of phlebotomy eligibility beginning at the Week 8 visit and continuing through Week 32) and spleen volume reduction (a greater than or equal to 35% reduction from baseline in spleen volume at Week 32). Phlebotomy eligibility was defined as a confirmed hematocrit greater than 45% that is at least 3 percentage points higher than the hematocrit obtained at baseline or a confirmed hematocrit greater than 48%, whichever was lower. Secondary endpoints included the proportion of all randomized subjects who achieved the primary endpoint and who maintained their response 48 weeks after randomization, and the proportion of subjects achieving complete hematological remission at Week 32 with complete hematological remission defined as achieving hematocrit control, platelet count less than or equal to 400 X 10^9/L, and white blood cell count less than or equal to 10 X 10^9/L.

Results of the primary and secondary endpoints are presented in Table 16. A significantly larger proportion of patients on the Jakafi arm achieved a response for the primary endpoint compared to best available therapy at Week 32 and maintained their response 48 weeks after randomization. A significantly larger proportion of patients on the Jakafi arm compared to best available therapy also achieved complete hematological remission at Week 32.

Table 16: Percent of Patients with Polycythemia Vera Achieving the Primary and Key Secondary Endpoints in Study 3 (Intent to Treat)

	Jakafi (N=110)	Best Available Therapy (N=112)
Number (%) of Patients Achieving a Primary Response at Week 32	25 (23%)	1 (<1%)
95% CI of the response rate (%)	(15%, 32%)	(0%, 5%)
P-value	< 0.0001	
Number (%) of Patients Achieving a Durable Primary Response at Week 48	22 (20%)	1 (<1%)
95% CI of the response rate (%)	(13%, 29%)	(0%, 5%)
P-value	< 0.0001	
Number (%) of Patients Achieving Complete Hematological Remission at Week 32	26 (24%)	9 (8%)
95% CI of the response rate (%)	(16%, 33%)	(4%, 15%)
P-value	0.0016	

Primary Response defined as having achieved both the absence of phlebotomy eligibility beginning at the Week 8 visit and continuing through Week 32 and a greater than or equal to 35% reduction from baseline in spleen volume at Week 32.

Additional analyses for Study 3 to assess durability of response were conducted at Week 80 only in the Jakafi arm. On this arm, 91 (83%) patients were still on treatment at the time of the Week 80 data cut-off. Of the 25 patients who achieved a primary response at Week 32, 19 (76% of the responders) maintained their response through Week 80, and of the 26 patients who achieved complete hematological remission at Week 32, 15 (58% of the responders) maintained their response through Week 80.

In an assessment of the individual components that make up the primary endpoint, there were 66 (60%) patients with hematocrit control on the Jakafi arm vs. 21 (19%) patients on best available therapy at Week 32; 51 (77% of hematocrit responders) patients on the Jakafi arm maintained hematocrit control through Week 80. There were 44 (40%) patients with spleen volume reduction from baseline greater than or equal to 35% on the Jakafi arm vs. 1 (<1%) patient on best available therapy at Week 32; 43 (98% of spleen volume reduction responders) patients on the Jakafi arm maintained spleen volume reduction through Week 80.

16 HOW SUPPLIED/STORAGE AND HANDLING

Jakafi (ruxolitinib) Tablets are available as follows:

Jakafi Trade Presentations

NDC Number	Strength	Description	Tablets per Bottle
50881-005-60	5 mg	Round tablet with "INCY" on one side and "5" on the other	60
50881-010-60	10 mg	Round tablet with "INCY" on one side and "10" on the other	60
50881-015-60	15 mg	Oval tablet with "INCY" on one side and "15" on the other	60
50881-020-60	20 mg	Capsule shaped tablet with "INCY" on one side and "20" on the other	60
50881-025-60	25 mg	Oval tablet with "INCY" on one side and "25" on the other	60

Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Discuss the following with patients prior to and during treatment with Jakafi:

Thrombocytopenia, Anemia and Neutropenia

Inform patients that Jakafi is associated with thrombocytopenia, anemia and neutropenia, and of the need to monitor complete blood counts before and during treatment. Advise patients to observe for and report bleeding.

Infections

Inform patients of the signs and symptoms of infection and to report any such signs and symptoms promptly.

Inform patients regarding the early signs and symptoms of herpes zoster and of progressive multifocal leukoencephalopathy, and advise patients to seek advice of a clinician if such symptoms are observed.

Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi

Inform patients that after discontinuation of treatment, signs and symptoms from myeloproliferative neoplasms are expected to return. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician.

Non-Melanoma Skin Cancer

Inform patients that Jakafi may increase their risk of certain non-melanoma skin cancers. Advise patients to inform their healthcare provider if they have ever had any type of skin cancer or if they observe any new or changing skin lesions.

Lipid Elevations

Inform patients that Jakafi may increase blood cholesterol, and of the need to monitor blood cholesterol levels.

Drug-drug Interactions

Advise patients to inform their healthcare providers of all medications they are taking, including over-the-counter medications, herbal products and dietary supplements.

Dialysis

Inform patients on dialysis that their dose should not be taken before dialysis but only following dialysis.

Lactation

Inform women not to breastfeed during treatment with Jakafi and for two weeks after the final dose.

Compliance

Advise patients to continue taking Jakafi every day for as long as their physician tells them and that this is a long-term treatment. Patients should not change dose or stop taking Jakafi without first consulting their physician. Patients should be aware that after discontinuation of treatment, signs and symptoms from myeloproliferative neoplasms are expected to return.

Manufactured for:
Incyte Corporation
Wilmington, DE 19803

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202192Orig1s014

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	202192, S-014
Priority or Standard	Standard
Submit Date(s)	12/15/16
Received Date(s)	12/15/16
PDUFA Goal Date	10/15/17
Division / Office	DHP/OHOP
Reviewer Name(s)	Virginia Kwitkowski Rosanna Setse
Review Completion Date	09/11/17
Established Name	Ruxolitinib phosphate
Trade Name	Jakafi®
Therapeutic Class	Kinase inhibitor
Applicant	Incyte Corp.
Formulation(s)	Oral Tablet
Dosing Regimen	5-20 mg twice daily
Indication(s)	1. Intermediate or high-risk myelofibrosis, including primary MF, post-polycythemia MF, and post-essential thrombocythemia MF 2. Polycythemia vera
Intended Population(s)	Adults

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical review team recommends approval of Supplement-14 with revised labeling to describe the exploratory analysis of the effect of ruxolitinib on “fatigue”.

1.2 Risk Benefit Assessment

A benefit:risk analysis was not conducted for this supplement.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No new REMS are indicated for this supplement.

1.4 Recommendations for Postmarket Requirements and Commitments

No new PMRs or PMCs are recommended for this supplement.

2 Introduction and Regulatory Background

2.1 Product Information

Drug Established Name:	Ruxolitinib
Trade Name:	Jakafi
Dosage Forms:	Tablets (5, 10 15, 20, and 25 mg)
Chemical Class:	Heterocyclic pyrazolyl-substituted pyrrolopyrimidine
Therapeutic Class:	Kinase Inhibitor
Mechanism of Action:	Inhibits JAK1 and JAK2, thereby blocking the action of cytokine signaling through the JAK-STAT pathway in hematopoiesis and immune function

2.2 Tables of Currently Available Treatments for Proposed Indications

This supplement does not propose a new indication.

2.3 Availability of Proposed Active Ingredient in the United States

Ruxolitinib phosphate is currently marketed in the U.S. as Jakafi oral tablets.

2.4 Important Safety Issues With Consideration to Related Drugs

There are two approved JAK inhibitors in the US; ruxolitinib and tofacitinib. Toxicities specific to the class of JAK inhibitors include infections, anemia, neutropenia, and elevated cholesterol. Tofacitinib use was also associated with the development of lymphomas and other cancers, gastrointestinal perforation, lymphopenia, drug induced liver injury, and after long-term use, renal insufficiency.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

The hallmarks of myelofibrosis 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.

During the development of COMFORT-I trial, Incyte met with DHP (under IND 77456) to discuss the development of the Myelofibrosis Symptom Assessment Form (MFSAF) to measure myelofibrosis symptoms. (b) (4) The final MFSAF (Version 2.0) contained the following items: abdominal discomfort, pain under left ribs, itching, bone/muscle pain, and early satiety. (b) (4)

On 07/11/16, FDA issued written responses to Type C meeting request. Listed below each response (in italics) is Incyte's responses to each response (provided in the Clinical Overview of this sNDA).

Sponsor Question: Does the Division agree that available data supports the submission of a Labeling Supplement to describe the results related to fatigue (b) (4) in the Clinical Studies section of the prescribing information?

FDA Response to Question 1:
Results from the analysis of "fatigue" (b) (4) based on data collected in the COMFORT-I trial using the PROMIS Fatigue scale (b) (4) (b) (4) nominally showed a statistically significant difference between patients in the ruxolitinib group compared to the placebo group from baseline to Week

24. These findings are consistent with other assessments of treatment benefit in the COMFORT-1 trial. While we acknowledge that fatigue [redacted] are important and relevant concepts to measure in this patient population, these data may not be adequate to support new labeling text in the Clinical Studies Section of the prescribing information for the following reasons:

- [redacted] your analyses are lacking the statistical rigor required to support a claim.

Incyte Response: *We acknowledge and recognize the concern regarding Type I error control for these additional analyses. For this reason, the proposed labeling language does not make any specific claims about significance, but instead presents the data related to the outcomes measures in a descriptive manner, without p-values. There are also several points that should be considered while reviewing the data. 1) The COMFORT-I study applied a sequential gatekeeping strategy for 3 alpha-controlled endpoints: ≥ 35% reduction from baseline in spleen volume by MRI, ≥ 50% reduction from baseline in TSS for the MFSAF v2.0, and overall survival as compared by log-rank test. At the Week 24 analysis, both the spleen volume and TSS endpoints were highly statistically significant. Analysis of data with longer-term follow-up at Week 144, accepted by the Agency, also led to overall survival results (Kaplan-Meier curves with 1, 2, and 3 year estimates) being included in labeling. This may be interpreted as meeting each of these 3 endpoints in the alpha control plan. Although subsequent alpha allocation was not defined in the Statistical Analysis Plan, the results do suggest a robust efficacy result that might allow the Agency to consider additional data displays that are highly significant and are based on strong evidence.* [redacted] *The results have been analyzed and tested using a variety of different psychometric measures, correlations with other clinical endpoints and PRO analyses, and sensitivity analyses, and the outcomes of those analyses have consistently supported differences favoring ruxolitinib to placebo. These points are discussed in further detail in the Evidence Dossier.*

- It is unclear if the differences observed using the PROMIS Fatigue scale [redacted] are of sufficient magnitude to be clinically meaningful for this patient population.

Incyte Response: *Clinically meaningful change was assessed using an anchor-based method for the PROMIS Fatigue scales. A conservative approach was taken to set thresholds for meaningful change in order to evaluate responders among the ruxolitinib and placebo groups.* [redacted]

[redacted] (b) (4)

- The patients on the ruxolitinib arm received more transfusions than those on the control arm, and it is not clear whether the difference in fatigue [redacted] (b) (4) reflect the difference in transfusions rather than an effect of ruxolitinib.

Incyte Response: *The difference in fatigue* [redacted] (b) (4) *do not reflect a difference in transfusions rather than an effect of ruxolitinib, as detailed in Section 4 of the INCB 18424-351 CSR Addendum. In summary, a "tipping" analysis, which defined ruxolitinib responders with transfusions as nonresponders while keeping placebo subjects with their original response status, showed the treatment effect was still significantly different favoring ruxolitinib. In addition, when the Breslow-Day test was utilized for responder analyses, it indicated no significant difference in the odds ratios between blood transfusion positive and negative groups.*

- We have concerns regarding the content validity [redacted] (b) (4) proposed to evaluate fatigue [redacted] (b) (4)

- Fatigue: Items 1, 2, and 3 are considered “symptom” items, whereas items 4, 5, 6, and 7 are considered “impact” items which focus on the impact of fatigue on patients’ functioning (i.e., work functioning, ability to think clearly, ability to bathe or shower, ability to exercise strenuously, respectively). In general, we recommend collecting and analyzing symptoms and impacts separately. In addition, you have not evaluated whether individual items of the PROMIS Fatigue scale contribute similarly to change in the total score and to understand which item(s) may be driving the result.

Incyte Response: *To address this concern, 2 subscales were formed from the PROMIS-7 Fatigue Scale. The PROMIS Fatigue 3-item Symptom scale comprised items 1 to 3 and reflected only the symptoms of fatigue, while the PROMIS Fatigue 4-Item Impact scale was composed of items 4 to 7 and assessed the impacts of fatigue. Both subscales were analyzed for psychometric quality and used for efficacy evaluation. Analyses detailed in Section 3.2 of the Psychometric Report indicate that the separation of the symptom and impact subscales met or exceeded the standards for reliability, validity, and responsiveness. Additionally, item-item correlations among the 7 items comprising the PROMIS-7 Fatigue Scale were calculated using Pearson correlation coefficients. All 7 items significantly contributed to the instrument total score, and no redundancy of content was indicated among the 7 items (see Section 3.2.2 of the Psychometric Report). Score changes were evaluated at the item level to ensure no single* item(s) *were driving the overall score changes identified on the PROMIS Fatigue Scale. All items move in the positive direction, indicating no 1 item is driving the scale score changes (see INCB 18424-351 CSR Addendum).*

- (b) (4)

(b) (4)

Nonetheless, if these issues can be addressed, we would be willing to consider a labeling supplement with the understanding that the revised text of the prescribing information and approvability would be a review issue dependent on the information you submit to support your proposal. Each of the points above should be addressed in your submission.

A thorough review of a full report of the clinical study results and PRO evidence dossier (b) (4) will be conducted at the time of the sNDA submission. It is important to note that it is not possible to interpret the quantitative findings without first having confidence that the instruments are content valid (i.e., well-defined). That said, we would like to see some additional data and support for the psychometric properties and performance (b) (4) (b) (4) Your submission should therefore also address the following:

1. Provide all data tables for the psychometric analyses (i.e., reliability, validity, and

responsiveness) performed for the PROMIS Fatigue scale [redacted], including item descriptive analyses (frequency distribution of item responses, floor and ceiling effects, and percentage of missing response).

Incyte Response: *All data tables for the psychometric analyses conducted to demonstrate the reliability, validity, and responsiveness of the PROMIS Fatigue scales [redacted] are provided in the Psychometric Report. Specifically, Table 3 to 6 (Section 3.2.1) and Table 15 (Section 3.3.1) present the item descriptive analyses for the PROMIS Fatigue scale and subscales [redacted] respectively. As detailed in the INCB 18424-351 CSR Addendum, the percentage of missing data is less than 5%.*

2. The proposed threshold for meaningful change (i.e. responder definition) for PROMIS Fatigue is based on the minimal important difference (MID) estimate. For regulatory purposes, we are more interested in what constitutes a meaningful within-patient change in the instrument's score than what is an MID. We suggest that you create cumulative distribution function (CDF) plots for the PROMIS Fatigue scale [redacted] using the COMFORT-I trial data Provide cumulative distribution function (CDF) plots for PROMIS Fatigue [redacted] to help inform interpretation of your data.

a. A CDF plot for PROMIS Fatigue change scores from baseline to Week 24 by treatment arms (i.e., one curve for treatment and one curve for placebo). [redacted]

Incyte Response: *Rather than relying on the MID estimates, conservative anchor-based analyses were conducted to identify what is meaningful change on the PROMIS scales from the patient perspective (see Evidence Dossier, Section 7). In addition, cumulative distribution function (CDF) plots for PROMIS Fatigue change scores from baseline to Week 24 are provided by treatment (1 curve for ruxolitinib and 1 curve for placebo) in Figure 17, Figure 18, and Figure 19 for the PROMIS Fatigue 3-item Symptom Score, PROMIS Fatigue 4-item Impact Score, and PROMIS Fatigue 7-Item Score, respectively. [redacted]. These results provide strong evidence that the PROMIS Fatigue scales [redacted] are sensitive enough to differentiate treatment effects from most to least improved.*

b. A CDF plot for PROMIS Fatigue change scores from baseline to Week 24 for all patients (both treatment and placebo arms pooled) by PGIC response options at Week 24 (i.e., separate curves for each PGIC response option). [redacted]

Incyte Response: *The CDF plots for PROMIS Fatigue change scores from baseline to Week 24 are provided by Patient Global Impression of Change (PGIC) response options (1- "very much improved" through 7- "very much worse") in Figure 11, Figure 12, and Figure 13 for the PROMIS Fatigue 3-item Symptom Score, PROMIS Fatigue 4-item Impact Score, and*

PROMIS Fatigue 7-Item Score, respectively. [redacted] *. The CDF plots for the 3 PROMIS scales* [redacted] *show that all four are very sensitive to incremental changes in PGIC response score.*

c. A CDF plot for the PROMIS Fatigue change scores from baseline to Week 24 for all patients (both treatment and placebo arms pooled) by score point changes for improvement in the PGIC (i.e., with separate curves for +3 point change, +2 point change, +1 point change, 0 point change, -1 point change, -2 point change, -3 point change). [redacted]

Incyte Response: *The PGIC was used to evaluate a subject's overall sense of treatment effect since the start of treatment in the study. As this scale is itself a measure of change from baseline, we believe this request is addressed by the CDF plots noted in the response to 2.b above.*

3. Your tertile approach to assessing known-groups validity does not clearly define groups with known meaningful differences. There is concern regarding the interpretation of results from this approach as the results may be misleading (i.e., more likely to find significant score differences among the groups).

Incyte Response: *A median approach was applied to 2 established indicators of MF disease, spleen volume and MFSAF TSS, defining 2 distinct groups for each variable (above and below median value at baseline) and compared with the 3 PROMIS Fatigue scores (total and symptom and impact subscales) to determine known-groups validity. These analyses and results, which revealed significant differences among the clinically different groups, are described in Section 3.2.4 of the Psychometric Report.* [redacted] *Again, the results revealed significant differences among the clinically different groups, as described in Section 3.3.3 of the Psychometric Report.*

2.6 Other Relevant Background Information

Jakafi (ruxolitinib) was granted regular (full, traditional) approval on November 16, 2011 for "treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

On June 12, 2013, a supplement was approved that provided a new starting dose and dosing strategy for patients who initiate therapy with platelet counts between 50 and 100 x 10^9/L.

On June 4, 2014, Jakafi was granted a new indication for "the treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea".

Since the initial approval of Jakafi in 2011, DHP has reconsidered some of the issues surrounding the use of the concept of fatigue in labeling. (b) (4)

(b) (4)

(b) (4)

(b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of the submission was adequate for review.

3.2 Compliance with Good Clinical Practices

This section is not applicable to this supplement because the Applicant has not submitted new trials or new data; just additional analyses of previously submitted data.

3.3 Financial Disclosures

This section is not applicable to this supplement because the Applicant has not submitted new trials or new data; just additional analyses of previously submitted data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There was no CMC module with this supplement.

4.2 Clinical Microbiology

There was no clinical microbiology module with this supplement.

4.3 Preclinical Pharmacology/Toxicology

There was no Pharmacology/Toxicology module with this supplement.

4.4 Clinical Pharmacology

There was no Clinical Pharmacology module with this supplement.

4.4.1 Mechanism of Action

Not relevant to this supplement; refer to reviews for original approval in 2011.

4.4.2 Pharmacodynamics

Not relevant to this supplement; refer to reviews for original approval in 2011.

4.4.3 Pharmacokinetics

Not relevant to this supplement; refer to reviews for original approval in 2011.

4.5 Clinical Outcomes Assessment Staff

DHP consulted the COA Staff for review of the submitted supplement. The consultation was completed by Michelle Campbell and signed by her Team Leader Selena Daniels and the Associate Director, COA Staff, Elektra Papadopoulos. Her Executive Summary is provided below.

"This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Division of Hematology regarding NDA 202192. The applicant has completed a phase 3 trial of their drug development program. This request for consultation is for a NDA supplement for the inclusion of fatigue (b) (4) *in the label. The indication of ruxolitinib is the treatment of patients with intermediate or high-risk myelofibrosis including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.*

The applicant used the following patient-reported outcome (PRO) assessments in their phase3 clinical trials in adult patients with immediate (sic) "intermediate" or high risk primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia-myelofibrosis.

Instrument name (COA Type)	***Concept(s)***	***Endpoint***	***Copy of Instrument***
PROMIS Fatigue 7-item short form	*Fatigue*	*Exploratory*	*Appendix A*
(b) (4)			

PROMIS®: Patient-Reported Outcomes Measurement Information System

The applicant proposed PRO-related labeling claim:

(b) (4)

The review concludes the following:
PROMIS Fatigue 7-item Short Form

The evidence provided by the applicant supports that the PROMIS Fatigue 7-item short form (PROMIS® Fatigue)is fit for purpose in the context of this particular drug development program to measure fatigue-related symptoms and impacts in adult

patients with immediate(sic) "intermediate" or high risk primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia-myelofibrosis. The applicant established content validity of this measure in the target population through qualitative research (i.e., a review of literature, interviews with key opinion leaders and with patients), as well as other measurement properties (construct validity, reliability, ability to detect change). Further, the applicant supported their responder threshold using anchor-based methods (a score reduction of 4.5 or more from baseline to week 24 in PROMIS Fatigue total score) supplemented with cumulative distribution function (CDF) plots. While the PROMIS® Fatigue total score is a composite that combines both symptoms and impacts, all individual items showed general improvement (i.e. items moved in the correct direction) and there is no item driving the result, which mitigates the concern of the use of a total score.

Best Practices When Developing COA Endpoint Measurement Strategy:
For future medical product development, if a claim of superiority in a particular PRO concept is sought, we recommend that the PRO hypothesis is pre-specified and tested within the statistical hierarchy of hypothesis testing in the clinical trial and controlled for type 1 error. Further, statistical analysis methods, including a threshold for meaningful change, should be prospectively defined, especially procedures for handling missing values. We recommend sponsors to engage FDA early (e.g., Pre-IND) and throughout drug development to discuss COA endpoint strategy to ensure the selected instruments are fit-for-purpose and are well-defined and reliable for the contexts of use prior to initiation of pivotal studies."

4.6 Statistical Review

Dr. Chia-Wen Ko, PhD was the primary statistical reviewer for this application. Her Team Leader was Lei Nie, PhD and Deputy Division Director of DB5, Tom Gwise, PhD, also concurred on the review.

Dr. Ko's review was archived on 09/07/17 and concludes the following:

"This labeling supplement submission is based on exploratory analyses, whose results will not be used to make any efficacy claims. This reviewer agrees with adding information in the label on improvement in fatigue by ruxolitinib, if content validity is considered adequate by the clinical outcome assessment reviewer Dr. Campbell. However, because the exact magnitude of improvement in response may be uncertain due to a potential confounding from a higher transfusion rate in the treatment group (as suggested by subgroup and tipping point analyses presented in section 3.2.3.4 of this review), this reviewer recommends either not presenting the response rates or presenting the response rates with an additional caveat statement regarding the imbalance in transfusions between study arms (b) (4)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 Studies/Clinical Trials

Trial Number	Number of Patients	Type of Trial	Type of Patients
INCB-351	309	Phase 3, RCT	Myelofibrosis

5.2 Review Strategy

The following submissions were reviewed under this supplement:
Module 1: Regional
1.1 Forms FDA 356h, FDA 3397
1.2 Cover Letters:
1.3 Administrative Information: Debarment Certification, Financial Certification and Disclosure
1.6 Meetings: Correspondence Regarding Meetings
1.12 Other Correspondence
1.14 Labeling

Module 2: Common Technical Document Summaries
2.5 Clinical Overview

Module 5: Clinical Study Reports
5.3.5 Reports of Efficacy and Safety Studies [Indication]
Clinical Study Report (INCB 18424-351) US-Specific Addendum for Fatigue (b) (4)
(b) (4)
5.4 Literature References

FDA Documents Consulted:
Initial NDA 202192 Review by Albert Deisseroth (archived 11/04/11)
COA Staff Consult Review by Michelle Campbell (archived 09/08/17)

5.3 Discussion of Individual Studies/Clinical Trials

INCB-351: COMFORT I
[Source: Primary Medical Officer Review of initial NDA by Albert Deisseroth archived 11/04/11]
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% spleen volume reduction (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]

Table 2 COMFORT I Trial Characteristics

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

(b) (4)

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed targeted COA-related labeling claim is:

(b) (4)

6.1.1 Methods

The concepts of fatigue [redacted] (b) (4) were assessed in the previously reviewed COMFORT I trial (Protocol Number INCB 18424-351) [refer to previous Nov 2011 review by Dr. Albert Deisseroth].

6.1.2 Demographics

The demographics of enrolled patients were assessed in the previously reviewed COMFORT I trial (Protocol Number INCB 18424-351) [refer to previous Nov 2011 review by Dr. Albert Deisseroth].

6.1.3 Subject Disposition

Subject disposition was assessed in the previously reviewed COMFORT I trial (Protocol Number INCB 18424-351) [refer to previous Nov 2011 review by Dr Albert Deisseroth].

6.1.4 Analysis of Primary Endpoint(s)

No reanalysis of the primary endpoint of COMFORT I occurred during this review.

6.1.5 Analysis of Secondary Endpoints(s)

No reanalysis of the secondary endpoints of COMFORT I occurred during this review.

6.1.6 Other Endpoints

The following exploratory endpoints were reviewed in this supplement:

- Change in PROMIS 3-item Symptoms and PROMIS 4-item Impacts scores
- [redacted] (b) (4)

PROMIS Fatigue

The PROMIS® (Patient-Reported Outcomes Measurement Information System) Fatigue short form 1 contains 7 frequency items (see Appendix A). Each of the items uses a 5-point response option with scores of 1 (Never) to 5 (Always) with Item 7 (energy) requiring reverse scoring. The PROMIS Fatigue includes a recall period of 7 days and

was administered to patients on paper at baseline and the Week 4, 8, 12, 16 and 24 visits. The raw score is calculated as the sum of the responses and can be converted to a T-score (mean 50, SD 10, 0-100 range) by means of a table provided in the scoring manual. *[Source: COA Review, Michelle Campbell, August 2017]*

Conclusion by Michelle Campbell on Content Validity of PROMIS Fatigue:

The applicant has demonstrated that PROMIS Fatigue 7-item short form has content validity in this patient population. It is felt to be symptom of the disease and is important to both patients and clinicians. The review division has acknowledged that fatigue is an important concept for this patient population.

Conclusion by Michelle Campbell on other measurement properties of PROMIS Fatigue Scale:

The measurement properties for PROMIS fatigue have been well established and can be found in the literature.

Table 3 below (Source: Applicant US-Specific Addendum for Fatigue (b) (4) provides the results of the Summary of PROMIS Fatigue Scores.

Table 3 Summary of PROMIS Fatigue Scores

Summary of PROMIS Fatigue Scores

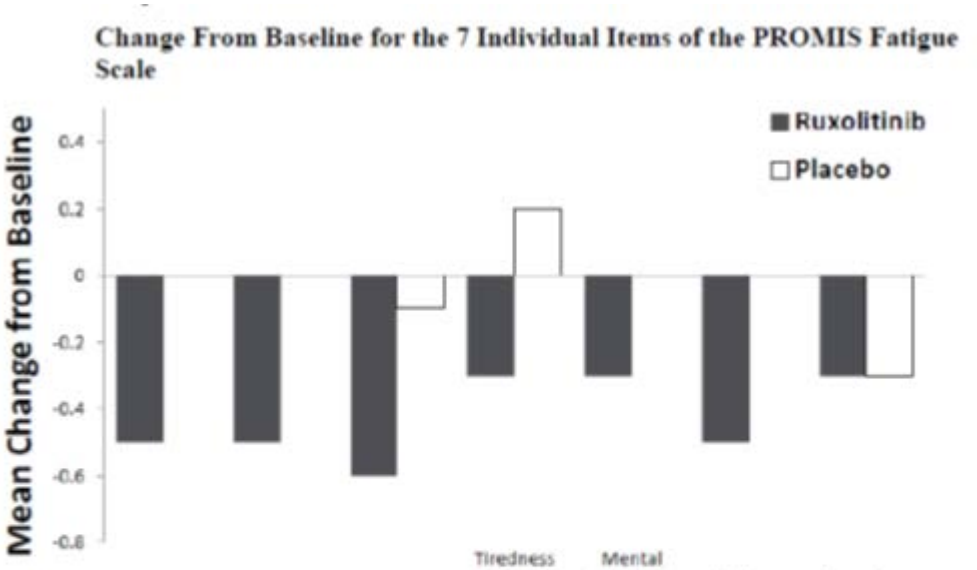
	Ruxolitinib			Placebo		
	7-Item Short Form	3-Item Symptom	4-Item Impact	7-Item Short Form	3-Item Symptom	4-Item Impact
Baseline[a]						
N	153	153	153	151	151	151
Mean (SD)	20.9 (5.11)	9.7 (2.45)	11.2 (2.98)	21.0 (5.06)	9.7 (2.46)	11.2 (3.02)
Median	21	10	12	21	10	11
Min, max	10, 33	4, 15	5, 18	7, 35	3, 15	4, 20
Week 24[b]						
N	143	143	143	111	111	111
Mean (SD)	17.9 (5.26)	8.1 (2.62)	9.8 (2.99)	20.8 (5.81)	9.6 (2.74)	11.2 (3.38)
Median	17	8	9	20	10	11
Min, max	8, 32	3, 15	4, 17	9, 33	3, 15	4, 18
Change from baseline						
N	142	142	142	111	111	111
Mean (SD)	-2.9 (5.06)	-1.6 (2.57)	-1.3 (3.04)	-0.1 (4.37)	-0.1 (2.22)	-0.1 (2.72)
Median	-3	-1	-1	0	0	0
Min, max	-16, 14	-7, 6	-9, 8	-12, 12	-5, 6	-8, 7

Source: Tables 2.2.1.1 and 2.2.1.3.

At baseline, scores for the ruxolitinib and placebo groups were similar for the PROMIS Fatigue 7-Item Short Form score as well as the 3-Item Symptom and 4-Item Impact scores. At Week 24, subjects in the ruxolitinib group showed larger mean improvement from baseline in the PROMIS Fatigue 7-Item Short Form score (-2.9 vs -0.1), 3-Item Symptom score (-1.6 vs -0.1) and 4-Item Impact score (-1.3 vs -0.1) compared with subjects in the placebo group.

There was very little missing data for this analysis. At baseline, ≤ 3% of values were missing across the 7 PROMIS items. The smaller number of subjects included in the analysis of change from baseline for the placebo group is primarily accounted for by the subjects who either discontinued or crossed over to ruxolitinib before Week 24.

Figure 1 Applicant Figure: Change from Baseline PROMIS Fatigue



Source: Table 2.2.1.3.

PROMIS Responder Analysis

The MH test was used to compare response rates of the 2 groups (ruxolitinib and placebo. There were significantly larger proportions of responders in the ruxolitinib group compared with the placebo group for the PROMIS Fatigue 7-Item Short Form score (35.2% vs 14.4%,

OR = 3.23, p = 0.0002), 3-Item Symptom score (38.7% vs 13.5%, OR = 4.05, p < 0.0001), and 4-Item Impact score (38.7% vs 15.3%, OR = 3.50, p < 0.0001).

Table 4 Responder Analysis PROMIS Fatigue

Proportions of Responders on the PROMIS Fatigue 7-Item Short Form Score, 3-Item Symptom Score, and 4-Item Impact Score

	Ruxolitinib			Placebo		
	7-Item Short Form	3-Item Symptom	4-Item Impact	7-Item Short Form	3-Item Symptom	4-Item Impact
Proportions of responders	50/142 (35.2%)	55/142 (38.7%)	55/142 (38.7%)	16/111 (14.4%)	15/111 (13.5%)	17/111 (15.3%)
Odds ratio[a]	3.23	4.05	3.50			
p-value[a]	0.0002	< 0.0001	< 0.0001			

[a] MH test used for OR and p-value.
Source: Table 2.2.1.5.

Evaluation of Confounding Effects of Transfusion:
Receipt of red blood cell transfusions can result in reduced fatigue in patients with myelofibrosis. An imbalance in transfusions between treatment arms could confound the analysis of “fatigue” in the Comfort I study.

During the first 8-12 weeks of therapy, the mean transfusion rate was higher with ruxolitinib versus 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.

Comfort I: Mean # of transfusions
- Ruxolitinib arm 0.96 units/subject/month
- Placebo arm 0.77 units/subject/month
- Of transfusion independent pts, 27% on RUX arm because transfusion dependent vs. 14% on placebo arm.

The difference in fatigue [redacted] (b) (4) do not reflect a difference in transfusions rather than an effect of ruxolitinib, as detailed in Section 4 of the INCB 18424-351 CSR Addendum. In summary, a "tipping" analysis, which defined ruxolitinib responders with transfusions as non-responders while keeping placebo subjects with their original response status, showed the treatment effect was still significantly different favoring ruxolitinib. In addition, when the Breslow-Day test was utilized for responder analyses, it indicated no significant difference in the odds ratios between blood transfusion positive and negative groups.

Reviewer Comment: The analysis for the impact of ruxolitinib on the concept of "fatigue" was conducted by comparing the change from baseline score to the Week 24 score of the PROMIS Fatigue 7-item short form score, 3-item symptom score, and 4-item impact score between patients who received ruxolitinib and those who received placebo. In this exploratory analysis, there was a statistically significant and clinically meaningful improvement in fatigue in patients who received ruxolitinib as measured by the PROMIS Fatigue 7-item short form, 3-Item Symptom, and 4-Item Impact scales. The tippling analysis described above (where ruxolitinib responders who received transfusions were counted as non-responders) demonstrates that the analysis of "fatigue" was not likely confounded by an imbalance in transfusions between treatment arms.
Because this analysis was an exploratory endpoint without control of the Type-I error rate, this concept is suggested for inclusion in labeling in a descriptive fashion, without p-values.

(b) (4)


(b) (4)

Reviewer Comment: the clinical meaningfulness of this improvement is not clear because the Applicant has not established Content Validity for this item [see conclusion above by Michelle Campbell, COA Staff]. The analyses are not recommended for inclusion in the prescribing information.

6.1.7 Subpopulations

n/a

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

n/a

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

n/a

6.1.10 Additional Efficacy Issues/Analyses

n/a

7 Review of Safety

No new safety data were received and no new safety analyses were conducted during the review of this supplement. Refer to Dr. Deisseroth's original NDA review in November of 2011 for review of safety in the pivotal trials.

9 Appendices

9.1 Literature Review/References

References

1. Gwaltney C, Paty J, Kwitkowski VE, Mesa R, Dueck AC, Papadopoulos EJ, Wang L, Feliciano J, Coons, SJ. Development of a harmonized patient-reported outcome questionnaire to assess myelofibrosis symptoms in clinical trials. Leukemia Research 59 (2017) 26-31.

Appendix I—PROMIS FATIGUE SCALE QUESTIONNAIRE

PROMIS FATIGUE SCALE QUESTIONNAIRE

PROMIS Item Bank v. 1.0 - Fatigue Short - Form 1

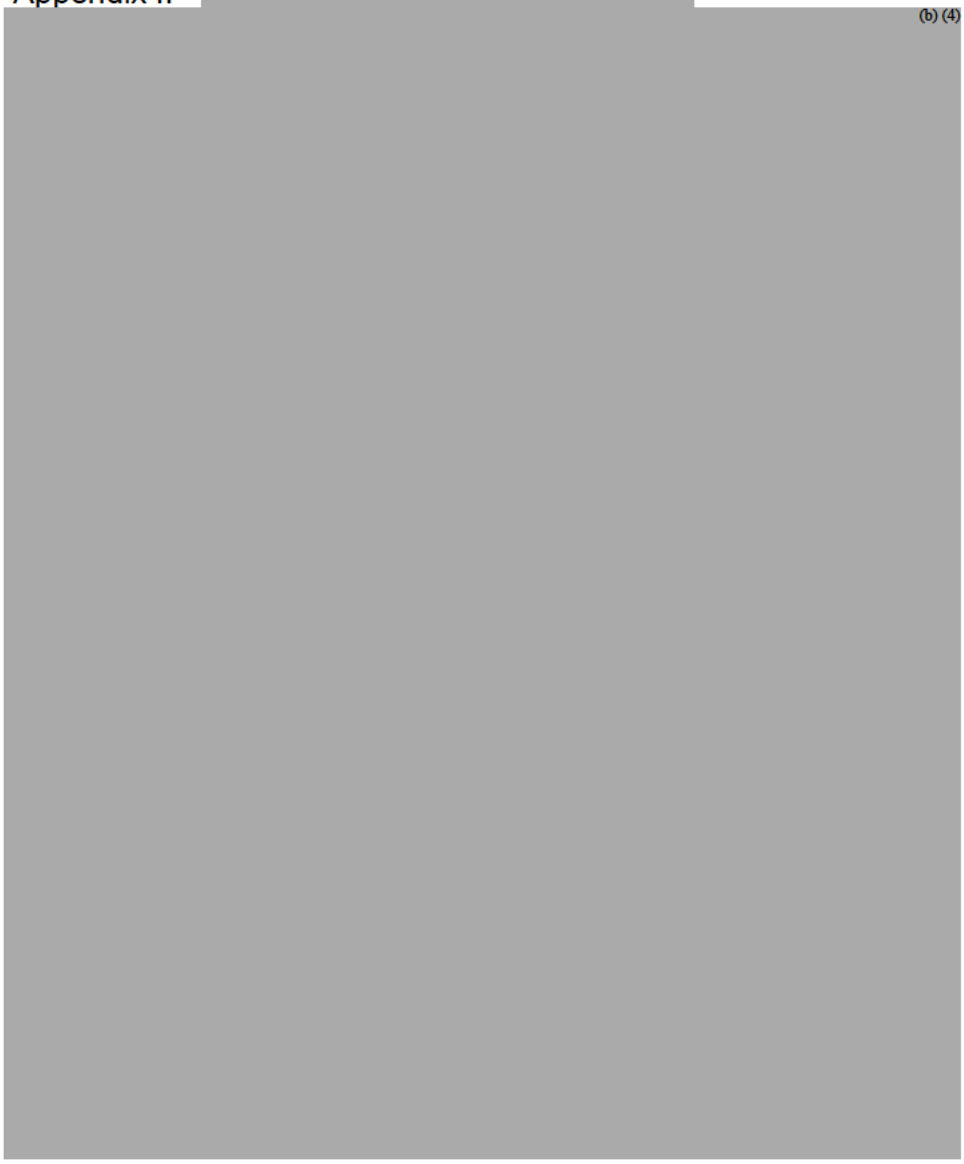
Fatigue - Short Form 1

Please respond to each question by marking one box per row.

In the past 7 days…

	Never	Rarely	Sometimes	Often	Always
How often did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often did you experience extreme exhaustion?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often did you run out of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often did your fatigue limit you at work (include work at home)?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often were you too tired to think clearly?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often were you too tired to take a bath or shower?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How often did you have enough energy to exercise strenuously?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Appendix II—(b) (4)



9.2 Labeling Recommendations

The Applicant proposed the following text for addition to Section 14.1 Myelofibrosis:

The clinical team and COA staff edited the labeling language to read as follows:

"Patients receiving Jakafi also showed improvement in fatigue-related symptoms (i.e., tiredness, exhaustion, mental tiredness, and lack of energy) and associated impacts on daily activities (i.e., activity limitations related to work, self-care, and exercise) as measured by the PROMIS® Fatigue 7-item short form at Week 24."

Some consideration has been given to include the response rates proposed by the Applicant, but the reliability of these estimates was called into question by Dr. Ko (Statistics) because of the possible confounding effects of the higher transfusion rates in the Jakafi treatment arm. Dr. Ko was potentially amenable to including the rates as long as a caveat statement regarding the imbalance in transfusions between study arms was also added.

This will be negotiated with the Sponsor.

Labeling negotiations have not been completed at the time of this review, so decisions on labeling are tentative.

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

/s/

VIRGINIA E KWITKOWSKI
09/11/2017

ROSANNA W SETSE
09/12/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202192Orig1s014

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number #:	NDA 202-192 / 0134
Supplement #:	SUPPL-14 (Efficacy supplement with clinical data)
Drug Name:	JAKAFI® (Ruxolitinib) tablets
Indication(s):	JAKAFI® is currently indicated for treatment of patients with intermediate to high-risk myelofibrosis. This efficacy supplement is not seeking a new indication, but to propose revisions to the labeling based on clinical data from Study INCB 18424-351 (COMFORT-1) (b) (4)
Applicant:	Incyte Corporation
Date(s):	Submission date: 15 December 2016 PDUFA date: 15 October 2017 Review completion date: 07 September 2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Statistical Reviewer:	Chia-Wen Ko, Ph.D.
Concurring Reviewers:	Lei Nie, Ph.D., Team Leader Tom Gwise, Ph.D., Deputy Division Director
Medical Division:	Division of Hematology Products
Clinical Team:	Rosanna Setse, M.D., Primary Reviewer Virginia Kwitkowski, R.N., M.S., ACNP-BC, Team Leader
Project Manager:	Rosa J. Lee-Alonzo

Keywords: patient-reported outcome, anchor-based responder threshold

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

This supplemental New Drug Application (sNDA) proposes no changes to the indications and usage of JAKAFI® (ruxolitinib). The purpose of this supplemental application is to present information, based on additional analyses that utilized patient data through the first 24 weeks of treatment in previously completed registration trial COMFORT-1, to support adding language to the Clinical Studies section of labeling to describe treatment benefit as related to fatigue (b) (4) (b) (4) in patients with myelofibrosis (MF).

Ruxolitinib was approved in November 2011 for the treatment of patients with intermediate or high risk myelofibrosis. The approval was based on clinical data from a double-blind placebo controlled trial COMFORT-1 and an open-label best-alternative-therapy controlled trial COMFORT-2 in adult patients with MF. The Clinical Studies section of the label described treatment benefit of ruxolitinib based on the rate of >=35% reduction in spleen volume from baseline as the primary endpoint in COMFORT-1 and COMFORT-2, and based on the proportion of patients with a 50% or greater reduction in Total Symptom Score from baseline to Week 24 as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary as a secondary endpoint in COMFORT-1.

Data on 'fatigue' as obtained from Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue 7-item Short Form (b) (4) (b) (4) the Agency did not agree to include these patient-reported outcomes (PROs) in the approved label, because there was no correction for multiplicity in the analyses of these outcomes and there was a concern with the content validity (b) (4). However, the Agency did agree that fatigue (b) (4) are relevant concepts to patients with MF.

The applicant agreed with the Agency, that efficacy claims should not be made from analyses on fatigue (b) (4). With this application, the applicant is proposing to add only descriptive language as the following:

(b) (4)

The proposed language is based on exploratory (b) (4) analyses. Responders were defined as patients who had an improvement of greater than or equal to a clinically meaningful threshold from baseline to Week 24. The thresholds for fatigue scores were developed by applicant using an anchor-based approach. (b) (4)

(b) (4)

.

This labeling supplement submission is based on exploratory analyses, whose results will not be used to make any efficacy claims. This reviewer agrees with adding information in the label on improvement in fatigue by ruxolitinib, if content validity is considered adequate by the clinical outcome assessment reviewer Dr. Campbell. However, because the exact magnitude of improvement in response may be uncertain due to a potential confounding from a higher transfusion rate in the treatment group (as suggested by subgroup and tipping point analyses presented in section 3.2.3.4 of this review), this reviewer recommends either not presenting the response rates or presenting the response rates with an additional caveat statement regarding the imbalance in transfusions between study arms. (b) (4)

.

2 INTRODUCTION

2.1 Purpose

This supplemental New Drug Application (sNDA) proposes no changes to the indications and usage of JAKAFI® (ruxolitinib). The purpose of this sNDA is to present information, based on additional analyses that utilized patient data through the first 24 weeks of treatment in previously completed registration trial COMFORT-1, to support adding language to the Clinical Studies section of labeling to describe treatment benefit as related to fatigue (b) (4) in patients with myelofibrosis (MF).

2.2 Proposed Labeling

The proposed additional language is: " (b) (4)

(b) (4)

2.3 Background

Ruxolitinib is a selective inhibitor of Janus kinase (JAK)1 and JAK2 that was approved by the Agency in November of 2011 for the treatment of patients with intermediate- or high-risk myelofibrosis (MF), including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis. The approval was based on clinical data from a double-blind placebo controlled trial COMFORT-1 and an open-label best-alternative-therapy controlled trial COMFORT-2 in adult patients with MF. The Clinical Studies section of the label described treatment benefit of ruxolitinib based on the rate of >=35% reduction in spleen volume from baseline as the primary endpoint in COMFORT-1 and COMFORT-2, and based on the proportion of patients with a 50% or greater reduction in Total Symptom Score from baseline to Week 24 as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary as a secondary endpoint in COMFORT-1.

Data on 'fatigue' as obtained from Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue 7-item Short Form (b) (4)

(b) (4) the Agency did not agree to include these patient-reported outcomes (PROs) in the approved label, because there was no correction for multiplicity in the analyses of these outcomes and there was a concern with the content validity (b) (4)

The applicant initiated discussions with the Agency in April 2016 regarding adding fatigue (b) (4) (b) (4) results from COMFORT-1 to the product labeling. The Agency issued a written response, as the following: "We acknowledge that these concepts are relevant to this patient population, these data may not be adequate to support new labeling text because lack of pre-specification, no alpha-allocation, unclear clinical meaningfulness of differences observed, higher transfusions in treatment arm, and concerns regarding content validity. Nevertheless, if these issues can be addressed, we would consider a labeling supplement."

In this application, the applicant has included an Evidence Dossier documenting qualitative evidence from interviews and literature, as well as quantitative evidence from analyses on the outcome measurement properties and justification of clinically meaningful differences for fatigue (b) (4) in order to support these PRO assessments to be fit for purpose of labeling. In addition, a study report amendment providing additional analyses regarding fatigue (b) (4) data in COMFORT-1 is included in this application.

2.4 Data Sources

This sNDA submission includes only one analysis dataset, containing analysis variables on patient baseline characteristics and efficacy outcomes including fatigue (b) (4) This analysis dataset is located at:
\\cdsesub1\evsprod\NDA202192\0134\m5\datasets\incb-18424\analysis\legacy\datasets

3 STATISTICAL EVALUATION

The statistical evaluation for this sNDA will be based on statistical analyses conducted on fatigue (b) (4) data from COMFORT-1. Evidence presented in applicant's Evidence Dossier for instrument psychometric properties and clinically meaningful difference threshold justification will be reviewed by the clinical outcome assessment reviewer Dr. Michelle Campbell.

3.1 Data and Analysis Quality

COMFORT-1 was one of the two registration trials that supported the original approval of JAKAFI®. Data from the original approval had been previously reviewed. This sNDA submission includes only one analysis dataset, containing analysis variables on patient baseline characteristics and patient-reported outcomes on fatigue (b) (4) The dataset was provided electronically with legacy formats. A dataset define document was included with sufficient details for this reviewer to reproduce the applicant's analyses results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study COMFORT-1 was a double-blind, randomized, placebo-controlled study in 309 patients with myelofibrosis who were refractory to or were not candidates for available therapy. The

primary efficacy endpoint was the proportion of patients achieving greater than or equal to a 35% reduction from baseline in spleen volume at Week 24 as measured by magnetic resonance imaging or computed tomography scans. The key secondary endpoint was proportion of patients with a 50% or greater reduction in Total Symptom Score from baseline to Week 24 as measured by MFSAF v2.0 diary. Treatment benefit was demonstrated by both endpoints (spleen volume reduction: ruxolitinib 41.9% versus placebo 0.7%; total symptom alleviation: ruxolitinib 45.9% versus placebo 5.3%). Other protocol-specified secondary endpoints included change from baseline to Week 24 in total symptom score and overall survival.

(b) (4)

The PROMIS Fatigue 7-item Short Form is a self-reported health-related quality of life instrument. It consists of 7 items, grouped into two subscales by the applicant: a 3-item Symptom scale and a 4-item Impact scale (see Appendix for the individual items). Each item has 5 response options with scores from 1 to 5 (1= 'Never', 2= 'Rarely', 3= 'Sometimes', 4= 'Often', 5= 'Always'), with the exception that scores are reversed for Item 7 "How often did you have enough energy to exercise strenuously?". The recall period for PROMIS Fatigue 7-item Short Form is 7 days. A total score is calculated as the sum of the non-missing scores. If at least half of the items are non-missing, the scale is derived by taking the average of the non-missing scores and multiplying by 7 to rescale the score to a maximum of 35; if more than half of the items are missing, the scale is missing for that visit. The subscale scores for Symptom and Impact are derived in a manner similar to the PROMIS Fatigue 7-Item Short Form total score.

(b) (4)

In Study COMFORT-1, the PROMIS Fatigue 7-item Short Form was administrated to patients on paper at baseline and during the Week 4, 8, 12, 16, and 24 visits. Patient responses were then entered onto corresponding clinical report form by site personnel. (b) (4)

3.2.2 Statistical Methodologies

The PROMIS Fatigue scores at baseline and Week 24, along with change from baseline, were summarized by treatment and visit using descriptive statistics. In addition, the applicant determined response thresholds for the Fatigue scores using an anchor-based approach involving comparing changes in the scores to patient-reported assessment of overall change over time. Patients who had a larger improvement from baseline at Week 24 than the threshold values were considered as responders.

(b) (4)

Analyses were performed in evaluable patients. For the summary analysis at baseline and Week 24, the evaluable patients were the ones who had scores at the visits. For the response analysis, the evaluable patients were the ones who had scores at both baseline and Week 24 so that a change in score was available for the determination of response.

Imputations were not performed for missing data.

Reviewer Comments:

- *For the Fatigue scores, the use of an anchor-based approach to justify a threshold for meaningful change is acceptable. This approach is detailed in the applicant's Evidence Dossier, and will be reviewed by the clinical outcome assessment reviewer Dr. Campbell.*

(b) (4)

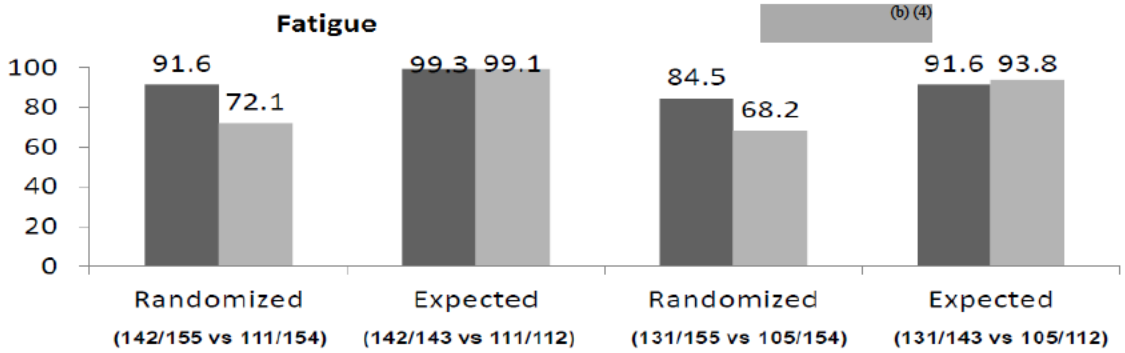
- *The applicant is not proposing efficacy claims for fatigue* (b) (4) *and therefore it is acceptable to have evaluable patients as the primary analysis population for fatigue* (b) (4)

3.2.3 Efficacy Results

3.2.3.1 Completion Rate

At Week 24, fatigue scores were available from 142 patients in the ruxolitinib group, but only from 111 patients in the placebo group. The corresponding completion rate in the intent-to-treat (ITT) population of randomized patients was 92% versus 72%. But if data were to be described in the expected population of patients who were still on study and on randomized treatment at Week 24 (therefore were expected to provide information about experience with fatigue for the randomized treatment), then the completion rate would be as high as 99% for both groups. For inactivity score, it was a similar situation. The completion rate in the randomized patients was lower in the placebo group compared to the ruxolitinib group because more patients in the placebo group were no longer on randomized treatment at Week 24; however, the completion rate in the expected patients was high and comparable between ruxolitinib and placebo groups.

Figure 1: Completion Rate, Ruxolitinib versus Placebo



Reviewer Comment:

The placebo group had a lower instrument completion rate in the randomized patients compared to the ruxolitinib group, mainly because there were 42 patients in the placebo group compared to 12 patients in the ruxolitinib group who had discontinued from study or discontinued from randomized treatment (including crossover from placebo to ruxolitinib) by Week 24.

3.2.3.2 Summary of Scores

Table 1 display the mean and standard deviation for fatigue (b) (4) scores at baseline, Wek 24, and change from baseline to Week 24 by treatment groups. Ruxolitinib and placebo groups appeared to be comparable at baseline with respect to fatigue (b) (4). The mean changes in the placebo group from baseline to Week 24 were closer to 0, in comparison with the mean changes in the ruxolitinib group. However, the variations among scores were big relative to the mean changes to make meaningful comparisons between the groups.

Table 1: Mean (Standard Deviation) of Fatigue (b) (4) Score

	Baseline		Week 24		Change (Week 24 - baseline)	
	Ruxolitinib	Placebo	Ruxolitinib	Placebo	Ruxolitinib	Placebo
Fatigue						
Total	20.9 (5.1)	21.0 (5.1)	17.9 (5.3)	20.8 (5.8)	-2.9 (5.1)	-0.1 (4.4)
Symptom	9.7 (2.5)	9.7 (2.5)	8.1 (2.6)	9.6 (2.6)	-1.6 (2.6)	-0.1 (2.2)
Impact	11.2 (3.0)	11.2 (3.0)	9.8 (3.0)	11.2 (3.4)	-1.3 (3.0)	-0.1 (2.7)
Inactivity	3.9 (2.6)	3.8 (2.5)	2.6 (2.4)	4.3 (2.9)	-1.2 (1.9)	0.6 (2.3)

Reviewer Comment:

The two treatment groups were highly comparable on the distribution of scores at baseline. Besides the similar means and standard deviations shown in Table 1, patient responses to the instruments at baseline covered the entire scoring range with no evidence of a floor effect (defined as having ≥25% of patients at the minimum possible score).

3.2.3.3 Applicant's Clinically Meaningful Change Analysis

The applicant's clinically meaningful change analysis compared the ruxolitinib and the placebo groups in the proportion of patients who had an improvement of greater than or equal to a clinically meaningful threshold from baseline at Week 24. These patients were referred to as responders by the applicant.

For fatigue scores, the responder thresholds were 4.53, 2.53, and 2.18 for 7-item total score, 3-item symptom score, and 4-item impact score, respectively. The thresholds for fatigue scores were developed by applicant using an anchor-based approach, which will be summarized and discussed by Dr. Michelle Campbell in her review. Table 2 shows the applicant's clinically meaningful change analysis result. The reported proportion of responders in fatigue was 35% versus 14% for ruxolitinib versus placebo.

Table 2: Clinically Meaningful Change Analysis in Fatigue

	Ruxolitinib			Placebo		
	7-item Short Form	3-item Symptom	4-item Impact	7-item Short Form	3-item Symptom	4-item Impact
Proportions of responders	50/142 (35.2%)	55/142 (38.7%)	55/142 (38.7%)	16/111 (14.4%)	15/111 (13.5%)	17/111 (15.3%)
Odds ratio	3.23	4.05	3.50			
p-value[a]	0.0002	< 0.0001	< 0.0001			

[a] p-value from the Mantel-Haenszel chi-square test

(b) (4)

Reviewer Comments:

- *As previous communicated to the applicant, the applicant's analysis was not a pre-specified alpha-adjusted analysis* (b) (4) *The reported p-values were not to be included in the label.*
- *The PROMIS Fatigue 7-item short form was initially developed without subscales. It was not clear whether or not the content validity for the symptom and impact subscales was comparable to the total scale. Subject to the review by Dr. Campbell, the proposed additional description on* (b) (4) *might not be acceptable.*
- *There was a concern with the content validity* (b) (4) (b) (4) *. The recommendation would be not to describe the* (b) (4) *in the label.*

Reviewer Comments (continued):

- *The placebo group had more patients discontinued from study or treatment by Week 24. This could indicate informative missing related to treatment efficacy. This reviewer examined all the data available in the patients who discontinued treatment prior to Week 24, 7 patients in the ruxolitinib group and 13 patients in the placebo group had met the responder threshold for fatigue (>=4.53 reduction in score from baseline) at least one visit prior to treatment discontinuation. As a worse case analysis, if none of those 7 patients in the ruxolitinib group were considered as responders, but all of those 13 patients in the placebo group were considered to be responders, the proportion of responders in the randomized patients would be 32.3% (50 out of 155 patients) for the ruxolitinib group compared to 18.8% (29 out of 154 patients) for the placebo group. The difference in proportions of responders between the two groups remained to be significant for this worse case analysis with an estimated odds ratio=2.05 and Mantel-Haenszel chi-square test p-value=0.007.*

3.2.3.4 Fatigue Results with Adjustment for Transfusion

The review division previously pointed out to the applicant that the differential transfusion rates between treatment arms would be a review issue with inclusion of fatigue data in the label. On average, patients in the ruxolitinib arm received 0.96 units/patient/month with 27% of the patients being transfusion dependent, compared to patients in the control arm received 0.77 units/patient/month with 14% of the patients being transfusion dependent (source: clinical review by Dr. Albert Deisseroth, dated 07/01/2011). It was not clear whether or not the increased transfusions in ruxolitinib arm had led to reduced fatigue.

The applicant performed a subgroup analysis comparing response rate between ruxolitinib and placebo groups by transfusion status (responders defined as meeting the clinically meaningful change thresholds as listed in section 3.2.3.3). The result was statistically significant for both transfusion positive and transfusion negative patients. In patients who received transfusions with the first 24 weeks of treatment (n=68), the response rate was 27.9% versus 4.0% for ruxolitinib group versus placebo group, odds ratio = 9.29, p-value from the Mantel-Haenszel test = 0.023. In patients who did not receive transfusions with the first 24 weeks of treatment (n=185), the response rate was 38.4% versus 17.4% for ruxolitinib group versus placebo group, odds ratio = 2.95, p-value from the Mantel-Haenszel test = 0.002. The Breslow-Day test for difference in response rate results between subgroups was not statistically significant.

The applicant also performed a tipping point analysis, which re-classified transfusion positive responders in the ruxolitinib group as non-responders. This re-classification reduced the estimated response rate in the ruxolitinib group by 8.4% from 35.2% to 26.8%, but the difference with the response rate of 14.4% in the placebo group was still statistically significant.

Reviewer Comment:

The benefit of ruxolitinib on fatigue was suggested after accounting for transfusions. However, with the very different odds ratios estimated within transfusion subgroups and the 8.4% decrease in response rate by ruxolitinib after responder re-classification, the magnitude of benefit was uncertain.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

With this labeling supplement submission, the applicant is proposing to add language to the Clinical Studies section of labeling to describe treatment benefit by ruxolitinib as related to fatigue [redacted] (b) (4)

The proposed additional labeling language is based on additional exploratory analyses that utilized patient data through the first 24 weeks of primary treatment period in COMFORT-1, a double-blind placebo-controlled registration trial which supported the initial approval of ruxolitinib as a treatment for patients with myelofibrosis.

The applicant's proposal to add fatigue [redacted] (b) (4) results from COMFIRT-1 was discussed with the Agency in 2016. The Agency acknowledged that fatigue [redacted] (b) (4) are relevant concepts to patients with myelofibrosis; however, there were important issues that should be addressed, including: (1) analyses were lack of statistical rigor (i.e., pre-specification and alpha-allocation) to support an efficacy claim; (2) clinical meaningfulness of observed differences between ruxotilinib and placebo groups was unclear; (3) potential confounding effects from high transfusions by the ruxotilinib group; and (4) concerns regarding content validity.

In this submission, the applicant addressed issue 1 by not including any p-values in proposed labeling language, and addressed issue 3 by showing additional subgroup and tipping point analyses supporting a benefit of ruxolitinib on fatigue after accounting for transfusions. This reviewer considers the applicant's proposal to describe the data without making a claim to be acceptable. This reviewer also considers the applicant's analyses for transfusions on fatigue to be acceptable. However, the different results from transfusion accounted analyses suggested transfusions did have an impact on fatigue, and therefore the magnitude of ruxolitinib benefit was uncertain.

For issues 2 and 4, the applicant provided an Evidence Dossier including justifications for clinically meaningful difference thresholds and content validity of the instruments. Please refer to review on those justifications by Dr. Campbell.

4.2 Conclusions and Recommendations

This labeling supplement submission is based on exploratory analyses, whose results will not be used to make any efficacy claims. If content validity is considered adequate by Dr. Campbell, information on improvement in fatigue by ruxolitinib may be described in the label. However, considering that the observed differences in response rates between study arms could in part due to imbalances in the number of patients receiving transfusions, recommendation would be either not to present the response rates or present them with a caveat statement regarding the higher rate of transfusions in the ruxolitinib group. [redacted] (b) (4)

APPENDIX: PROMIS Fatigue Scale Short Form [redacted] (b) (4)

PROMIS Fatigue Scale 7-Item Short Form

	In the past 7 days…	
PROMIS 3-item Symptom Scale	1. How often did you feel tired?	Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐
	2. How often did you experience extreme exhaustion?	Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐
	3. How often did you run out of energy?	Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐
PROMIS 4-item Impact Scale	4. How often did your fatigue limit you at work (include work at home)?	Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐
	5. How often were you too tired to think clearly?	Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐
	6. How often were you too tired to take a bath or shower?	Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐
	7. How often did you have enough energy to exercise strenuously?	Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐


(b) (4)

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09/07/2017

THOMAS E GWISE
09/07/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202192Orig1s014

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 6, 2017

To: Rosa Lee-Alonzo, PharmD, Regulatory Project Manager, Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: Addendum to OPDP Labeling Comments for Jakafi (ruxolitinib)

NDA: 202192/Supplement 014

In response to DHP's consult request dated December 28, 2016, OPDP provided initial comments on September 25, 2017, for the proposed labeling (package insert (PI)) for Jakafi.

This addendum is for OPDP's additional comment (below) for Section 14.1 Myelofibrosis of the proposed PI (attached) to provide further context on the type of data being presented. The additional Section 14.1 comment was conveyed to DHP via SharePoint on October 6, 2017.

OPDP's additional comment on the proposed labeling is based on the draft PI received by a link to SharePoint via electronic mail from DHP (Rosa Lee-Alonzo) on October 4, 2017, and is provided below.

> We have concerns with removing the deleted language:
> "However, these analyses are limited by a higher rate of red blood cell transfusions in the Jakafi treatment arm in the first 8-12 weeks of treatment."
> Without this language, the data being presented may misleadingly suggest that it was a pre-specified endpoint and not acquired through an exploratory analysis. We have concerns that this data may be presented in promotion without any indication that this was an exploratory analysis. Please consider including language that this was an exploratory analysis to provide further context of the data.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/

ROBERT L NGUYEN
10/06/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 25, 2017

To: Rosa Lee-Alonzo, PharmD, Regulatory Project Manager, Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Jakafi (ruxolitinib)

NDA: 202192/Supplement 014

In response to DHP consult request dated December 28, 2016, OPDP has reviewed the proposed product labeling (PI) for Jakafi. This supplement (S014) provides changes regarding effect on the concept of fatigue.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Rosa Lee-Alonzo) on September 12, 2017, and are provided below.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/

ROBERT L NGUYEN
09/25/2017

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA CONSULT TRACKING NUMBER	C-2016-312
IND/NDA/BLA NUMBER	NDA 202192
REFERENCED IND FOR NDA/BLA	IND 077456
ESTABLISHED NAME/TRADE NAME	Ruxolitinib/Jakafi®
SPONSOR/APPLICANT	Incyte
INDICATION	Treatment of immediate or high risk primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia-myelofibrosis
MEETING TYPE (A/B/C/WRO)	Not applicable
LETTER DATE/SUBMISSION NUMBER	12/15/2016
PDUFA GOAL DATE	10/15/2017
DATE OF CONSULT REQUEST	12/27/2016
REVIEW COMPLETION DATE	09/08/2017
REVIEW DIVISION	Division of Hematology Products
MEDICAL REVIEWER/TEAM LEADER (TL)	Rosanna Setse/Virginia Kwitkowski
REVIEW DIVISION PM	Rosa Lee-Alonzo
COA REVIEWER	Michelle Campbell
COA TL/SECONDARY REVIEWER	Selena Daniels
ASSOCIATE DIRECTOR, COA STAFF	Elektra Papadopoulos
INSTRUMENT(S)	1. Patient-Reported Outcomes Measurement Information System (PROMIS®) Fatigue 7-Item Short Form [redacted (b) (4)]
COA TYPE	PRO
ENDPOINT(S) CONCEPT(S)	Fatigue [redacted (b) (4)]
INTENDED POPULATION(S)	Adults with intermediate or high risk myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia-myelofibrosis
Please check all that apply:	☐Rare Disease/Orphan Designation ☐Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Hematology Products (DHP) regarding NDA 202192. The applicant has completed a phase 3 trial of their drug development program. This request for consultation is for a NDA supplement for the inclusion of claims of benefit related to fatigue (b) (4) (b) (4). The indication of ruxolitinib is the treatment of patients with intermediate or high-risk myelofibrosis including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

The applicant used the following patient-reported outcome (PRO) assessments in their phase 3 clinical trials in adult patients with immediate or high-risk primary myelofibrosis.

Instrument name	Concept(s)	Endpoint	Copy of Instrument
PROMIS® Fatigue 7-item short	Fatigue	Exploratory	Appendix A
(b) (4)			

PROMIS®: Patient-Reported Outcomes Measurement Information System

The applicant proposed the following PRO-related labeling claim:

(b) (4)

See Section 1.4 for the proposed claim in its entirety.

The review concludes the following:

PROMIS Fatigue 7-item Short Form

The evidence provided by the applicant supports that the PROMIS® Fatigue 7-item short form (PROMIS® Fatigue) is fit for purpose in the context of this particular drug development program to measure fatigue-related symptoms and impacts in adult patients with immediate or high-risk primary myelofibrosis, including post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. The applicant established content validity of this measure in the target population through qualitative research (i.e., a review of literature, interviews with key opinion leaders and with patients), as well as the other measurement properties (construct validity, reliability, ability to detect change). Further, the applicant supported their responder threshold using anchor-based methods (a score reduction of 4.5 or more from baseline to week 24 in PROMIS Fatigue total score) supplemented with cumulative distribution function (CDF) plots. While the PROMIS® Fatigue total score is a composite that combines both symptoms and impacts, all individual items showed general improvement (i.e. items moved in the correct

direction) and there is no item driving the result, which mitigates the concern of the use of a total score.

(b) (4)

Best Practices When Developing COA Endpoint Measurement Strategy:
For future medical product development, if a claim of superiority in a particular PRO concept is sought, we recommend that the PRO hypothesis is pre-specified and tested within the statistical hierarchy of hypothesis testing in the clinical trial and controlled for type 1 error. Further, statistical analysis methods, including a threshold for meaningful change, should be prospectively defined, especially procedures for handling missing values. We recommend sponsors to engage FDA early (e.g., Pre-IND) and throughout drug development to discuss COA endpoint strategy to ensure the selected instruments are fit-for-purpose and are well-defined and reliable for the contexts of use prior to initiation of pivotal studies.

B. BACKGROUND

Ruxolitinib

Ruxolitinib is indicated for the treatment of patients with intermediate or high risk primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPVMF), and post-essential thrombocythemia myelofibrosis (PET-MF). It is an inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs), and has been shown in clinical trials to achieve a rapid, marked and durable reduction in spleen size, circulating inflammatory cytokine levels, and symptoms, including abdominal discomfort, pain under the left ribs, early satiety, night sweats, itching, and bone or muscle pain. In 2011, ruxolitinib became the first product to be approved by the FDA for myelofibrosis and the first JAK inhibitor to be approved for any indication.

Patients with Myelofibrosis

One of the most disabling components of myelofibrosis (MF) is splenomegaly. Splenomegaly along with elevated cytokine levels are believed to contribute to the debilitating signs and symptoms that characterize MF. Patients with MF report a variety of symptoms such as night sweats, itching, feeling of fullness (early satiety), fatigue and a variety of daily pains and discomforts in their abdomen, under their ribs, and in their bones and muscles. Patients also describe impacts in activity that include reduced function, including physical and social function, as well as emotional well-being, among others. Collectively, these MF-symptom related experiences contribute to a reduced overall quality of life in this patient population (Mesa et al 2007).

Materials reviewed:

- ***AT 2016-088_IND 077456_Kovacs*** *dated 1/4/2017 (**DARRTS Reference ID 4008177**)*
- PRO evidence dossier
- INCB18424-351 Clinical study report (dated 27 April 2011)
- INCB 18424-351 Clinical study report US-specific addendum for fatigue (b) (4) (dated 06 Dec 2016)

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

1.1 Clinical Trial Population

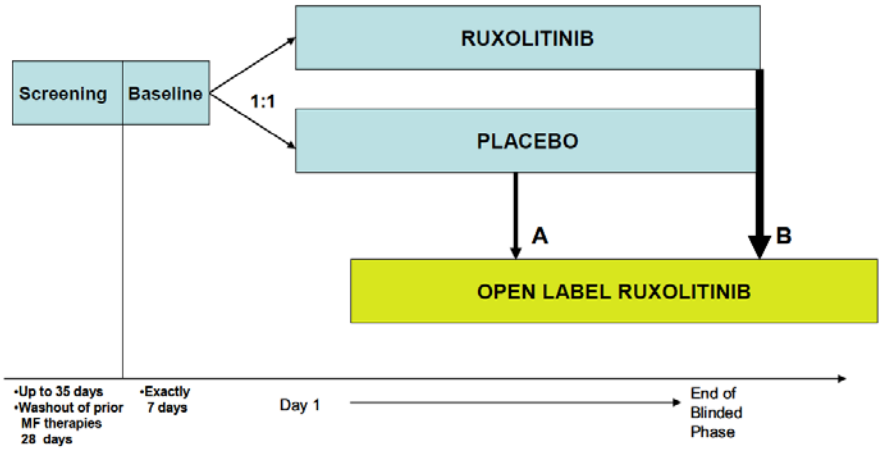
Patients with intermediate or high risk PMF including PPV-MF, and PET-MF.

1.2 Clinical Trial Design

Study INCB 18424-351 (COMFORT-I) was a randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ruxolitinib to placebo in subjects with PMF, PPV-MF, or PET-MF. Subjects must have been 18 years or older with a diagnosis of MF, and for

whom treatment was indicated. Subjects were also required to have had a life expectancy of at least 6 months, and a spleen length determined by palpation of at least 5 cm below the left costal margin. In addition, subjects must have been either resistant or refractory to, intolerant of, or in the Investigator's opinion not candidates for available therapy. Figure 1 presents the study design schema.

Figure 1: Study Design Schema



A: Subjects meeting protocol-defined criteria could be unblinded and if found to be randomized to placebo, could cross over to receive open-label ruxolitinib prior to primary analysis (early crossover).
B: When ALL subjects had completed Week 24 (or discontinued) and half of the subjects remaning in the study had completed Week 36, the database was frozen, primary analyses were conducted, and the study would be unblinded so that all subjects could continue on open-label ruxolitinib.

An overview of the schedule of PRO assessments is provided in Table 2 (on next page). All scheduled study visits will be conducted on dialysis days, including the End-of-Treatment (or Early Termination) and Follow-up Visits.

Table 1. Schedule of Assessments

Evaluation	Pre-Randomization		All Subjects on Study (± 7 Day Window for Study Visits)							
	Day -42 to Day -8 **Screen**	Day -7 to Day -1 **Baseline**	Day 1	Week 2,6,20, 30, and q12 Weeks **Lab-only Visits**	2-4 Days Before Week 4 **Study Visit**	Wk 4 **Study Visit**	Wk 8 **Study Visit**	Wk 12 **Study Visit**	Wk 16 **Study Visit**	Wk 24 **Study Visit**	Wk 36 **Study Visit**
Informed consent / Eligibilty criteria	X	X	X								
Medical history	X										
Prior and Concomitant medications	X	X	X			X	X	X	X	X	X
Transfusion history/status	X	X	X			X	X	X	X	X	X
Physical examination, body weight (a)	X	X				X	X	X	X	X	X
Vital signs (a)	X	X				X	X	X	X	X	X
ECOG performance status	X					X	X	X	X	X	
EORTC QLQ-C30 questionnaire		X				X	X	X	X	X	
PROMIS HAQ, PROMIS Fatigue and BPI questionnaires		X				X	X	X	X	X	
PGIC question						X	X	X	X	X	
Complete Screening Symptom Form (b)	X										
Complete Early Cross over Symptom Form (c)						X	X	X	X	X	X
12-lead ECG	X	X				X			X	X	
Serum chemistry tests (d)	X	X			X		X	X	X	X	X
Lipid Panel		X				X (d)		X		X	
Hematology	X	X		X	X		X	X	X	X	X
PT and PTT	X					X				X	
Pregnancy test (d)	X	X				X	X	X	X	X	X
Serology / HIV laboratory tests	X										
Urinalysis	X					X				X	
Blood sample for CD34+ cell count	X	X						X		X	
Blood sample for JAK2 mutation		X								X	
Blood sample for plasma PD markers		X				X				X	
Blood Sample for determination of pSTAT3 (e)			X			X					
Blood sample for plasma level of INCB018424						X (f)	X	X (f)	X	X	X
(b) (4)											
MRI of abdomen (i)		X						X		X	X
Measurement of spleen by palpation (j)	X	X				X	X	X	X	X	X
Contact IVRS (k)	X		X			X	X	X	X	X	X
Randomize subject			X								
Drug accountability assessment						X	X	X	X	X	X
Administer study drug during Clinic Visit			X			X		X			
Dispense study drug and Subject Reminder Card			X			X	X	X	X	X	X
Record Adverse Events	X	X	X		X	X	X	X	X	X	X

Evaluation	All Subjects on Study (± 7 Day Window)			Subjects who Cross Over (± 7 Day Window)			Subjects Taking CYP Inducer	All Subjects on Study	
	Week 48 **Study Visit**	Weeks 60, 84, 108 and q24 Weeks **Study Visit**	Weeks 72, 96, 120 and q24 Weeks **Study Visit**	Cross Over **Study Visit**	2 and 6 Weeks After Cross Over **Lab-only Visits**	4 Weeks After Cross Over **Study Visits**	At the first visit while on therapy For ≥ 2 Weeks **Study Visit**	End of Study **Study Visit**	28 ± 7 days after last dose **Follow-Up**
Informed consent / Eligibility criteria									
Medical history									
Prior and Concomitant medications	X	X	X	X		X		X	X
Transfusion history/status	X	X	X	X		X		X	X
Physical examination, body weight (a)	X	X	X	X		X		X	X
Vital signs (a)	X	X	X	X		X		X	X
ECOG performance status	X		X			X		X	
EORTC QLQ-C30 questionnaire	X		X			X		X	
PROMIS HAQ, PROMIS Fatigue and BPI questionnaires								X	
PGIC question								X	
Complete Screening Symptom Form (b)	X								
Complete Early Cross Symptom form (c)									
12-lead ECG	X		X					X	X
Serum chemistry tests,	X	X	X	X		X		X	X
Lipid panel	X		X					X	
Hematology	X	X	X	X	X	X		X	X
PT and PTT	X		X					X	
Pregnancy test (d)	X	X	X	X		X		X	X
Serology / HIV laboratory tests									
Urinalysis	X		X			X		X	X
Blood sample for CD34+ cell count	X		X			X		X	
Blood sample for JAK2 mutation	X		X					X	
Blood sample for plasma PD markers	X					X		X	
Blood Sample for determination of pSTAT3 (e)							X		
Blood sample for plasma level of INCB018424	X	X	X			X (f)	X (f)		
(b) (4)									
MRI of abdomen (i)	X	X (i)	X						
Measurement of spleen by palpation (j)	X	X	X	X		X		X	X
Contact IVRS (k)	X	X	X	X		X			
Randomize subject									
Drug accountability assessment	X	X	X	X		X		X	
Administer study drug during Clinic Visit				X		X			
Dispense study drug and Subject Reminder Card	X	X	X	X		X			
Record Adverse Events	X	X	X	X		X		X	X

Refer to the INCB 18424-351 clinical study report for more details on the study design and results.

1.3 Endpoint Hierarchy and Definition

Table 2 displays the endpoints from the COMFORT I trial reflecting the inclusion of fatigue [redacted]

Table 2. Revised Efficacy Endpoints Model for Ruxolitinib in Myelofibrosis

Concept	Endpoint	Measurement Basis
	Primary	
Spleen volume →	Proportion of subjects achieving ≥ 35% reduction in spleen volume from Baseline to Week 24 as measured by MRI/CT scan	Objective clinical measurement
	Secondary	
Spleen volume →	Duration of maintenance of a ≥ 35% reduction from baseline in spleen volume	Objective clinical measurement
MF symptoms →	Proportion of subjects who have ≥ 50% reduction in Total Symptom Score from Baseline to Week 24 as measured by the modified MFSAF v2.0 diary	Patient reported outcome
MF symptoms →	Change in Total Symptom Score from Baseline to Week 24 as measured by the modified MFSAF v2.0 diary	Patient reported outcome
Overall Survival →	Improvement in Overall Survival	Objective clinical measurement
	Proposed	
Fatigue →	*Change in PROMIS 3-item Symptoms and PROMIS 4-item Impacts scores*	*Patient reported outcome*
[redacted]		

Reviewer's comments: [redacted] *To determine whether patients experienced a clinical benefit, the applicant also evaluated the proportion of patients who achieved a meaningful score change PROMIS® Fatigue . The applicant proposed a threshold of meaningful change of 4.5 points.*

1.4 Labeling or promotional claim(s) based on the COA

The applicant proposed the following PRO-related supplemental labeling claims in Section 14.1 of the package insert:

[redacted]

(b) (4)

Reviewer's comments: The proposed response rates are based on the proportion of patients who achieved a meaningful score change in PROMIS® Fatigue (i.e., a score reduction of 4.5 or more from baseline to week 24 in PROMIS Fatigue total score). (b) (4) *However, based on discussion with Clinical they do not think this is a concern and prefer to include this data in the label. This reviewer recommends that if the response rates are included in the labeling that it is based on the total score as how it was scored in the COMFORT-I trial. Further, the responder definition should be included to interpret the response rates.*

Table 3 shows the linking of labeling language and concepts to instruments for ruxolitinib.

Table 3. Linking of labeling language and concepts to instruments

(b) (4)

(b) (4)

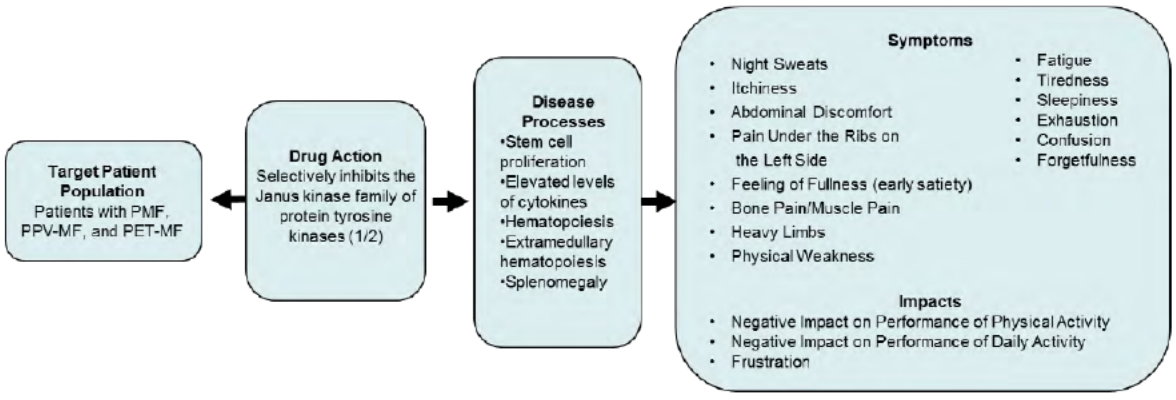
Reviewer's comments: Although PROMIS® Fatigue appears to be adequate to measure fatigue-related symptoms and impacts without (e.g., false or misleading claims); it was not a pre-specified endpoint nor tested within the statistical hierarchy of hypothesis testing. Therefore, this reviewer recommends that if the PRO findings from PROMIS® Fatigue are included in labeling, the data remains descriptive and not include any p-values.

(b) (4)

2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

Figure 2 illustrates the conceptual model of MF symptom concepts.

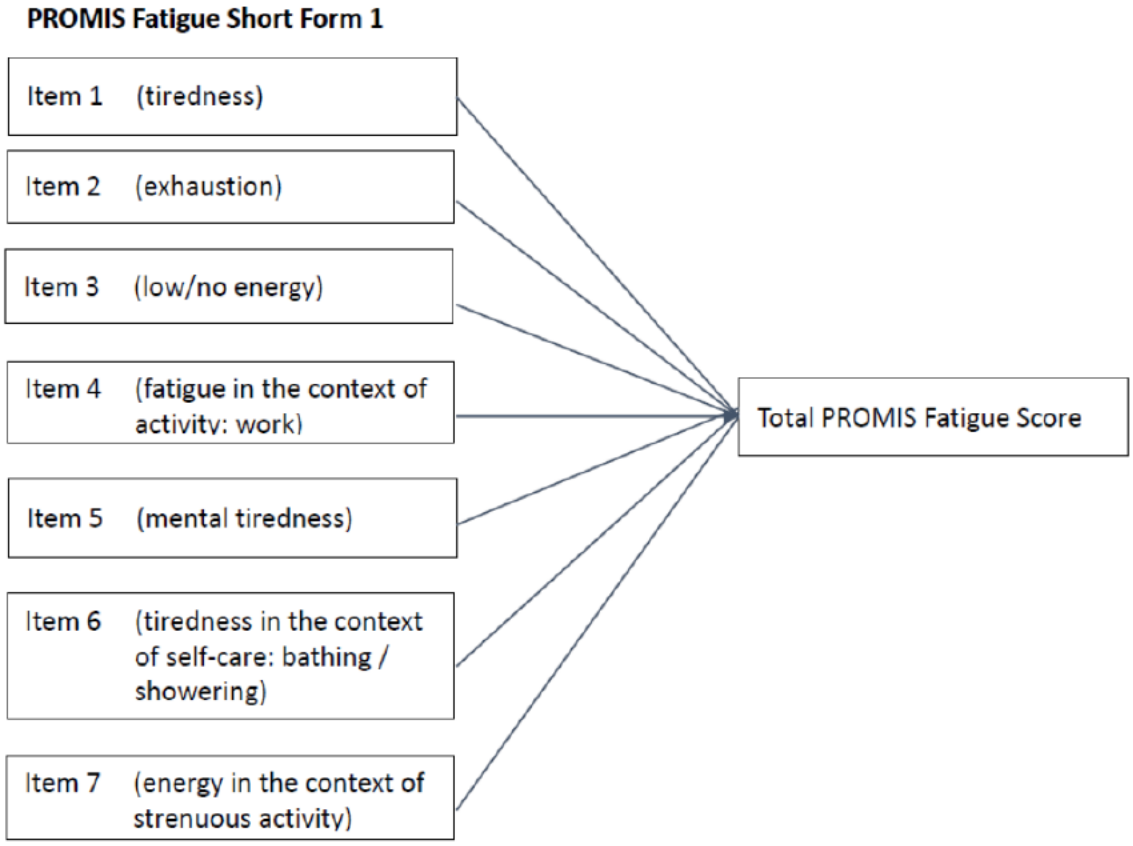
Figure 2. Ruxolitinib conceptual model of MF symptom concepts



The concepts of interest for the instruments are depicted in conceptual frameworks shown in Table 4 and Figure 3.

(b) (4)

Figure 3. Ruxolitinib conceptual model of MF symptom concepts



3 CLINICAL OUTCOME ASSESSMENTS

Patient-Reported Outcomes Measurement Information System (PROMIS®) Fatigue

The PROMIS® Fatigue short form contains 7 frequency items (see Appendix A). Each of the items uses a 5-point response option with scores of 1 (Never) to 5 (Always) with Item 7 (energy) requiring reverse scoring. PROMIS® Fatigue includes a recall period of 7 days and was administered to patients on paper at baseline and the Week 4, 8, 12, 16 and 24 visits.

(b) (4)

4 CONTENT VALIDITY

The following information has been submitted for review:

☒Literature review and/or publications
☒Documentation of expert input
☒Qualitative study protocols and interview guides for focus group or patient interviews
☐Chronology of events for item generation, modification, and finalization (item tracking matrix)
☒Qualitative study summary with evidence to support item relevance, item stems and response options, and recall period
☒Qualitative support for meaningful change
☐Quantitative study summary with evidence to support item retention and scoring
☒Transcripts (if available)

A synopsis of the findings from the developmental activities completed to support the content validity of PROMIS® Fatigue (b) (4) are summarized below:

- Literature review – The applicant completed a literature which identified fatigue was ranked as one of the most important and burdensome symptoms affecting MF patients' quality of life, as well as the importance of the impact of fatigue (b) (4) (b) (4). Also, fatigue can be a consequence of splenomegaly.
- Documentation of expert input–Three key opinion leaders who participated in the COMFORT trials all endorsed the concept of fatigue in MF. The key opinions leaders endorsed the concept of fatigue in MF and that their patient use the following term to describe their fatigue as "physical weakness", "low or drained energy" "tiredness". (b) (4)
- Patient input – Two rounds of qualitative patient interviews were conducted and included a total of 28 MF patients. The first round of interviews contained 15 patients with self-reported physician-diagnosed MF prior to the initiation of the COMFORT I trial and a second round of interview with 13 patients with clinician- confirmed diagnoses of either PMF, PPV-MF, or PET-MF who were experiencing symptom(s) related to their disease at the time of screening after COMFORT I trial was complete.

PROMIS® Fatigue

Fatigue was reported to be one of the most frequently reported MF symptoms, with physical fatigue and low energy as the primary symptom category elicited in the second set of patient interviews. Symptoms related to physical fatigue were experienced by 100% of the interviewed patients. Mental fatigue was the second most predominant category. Within this category, the most predominant symptom expressed by MF patients was forgetfulness, which was found in 62% of the patients. Table 5 provides some exemplary patient quotes.

Table 5. Patient statements related to fatigue symptom and linked to PROMIS® Fatigue symptom concepts

Link to PROMIS Fatigue Item Concept	Patient Description of Symptom
Tiredness	• *Basically, I feel tired all day. I really do. And when it gets too bad, I sit down and I rest a while, even though I may not be doing anything…* • *When I feel exhausted, I feel tired and I feel like I must sit down and rest. If I am doing something, I will have to stop.* • *Well when I first got, I remember being always real tired.* • *Feel like you need a nap, but when you wake up you don't feel any better; very draining.*
Exhaustion	• *If I am out in the stores or something, I can become exhausted, tired.* • *Exhausting, very exhausting. I sleep for an hour, wake up, sit there, and just drop right back off again. And be to the point where, I think something about, would be a problem. The weakness. I just don't have any strength.*

Link to PROMIS Fatigue Item Concept	Patient Description of Symptom
	• *The normal fatigue is just a feeling of exhaustion, um, not wishing to do my normal activities.*
Low / no energy	• *Well say for instance I have company and I am serving coffee and cake or whatever. My energy starts going down. I will start good but then as I keep going and progress, the energy starts weening from me.* • *Run down means like I am not energetic. Like, I love to walk and lately I haven't been able, I could probably if I wanted. But it is just that. I can't get it in me to say like "Okay. I am going to take off." Before, I would just take off. Like I am just like (sigh).* • *No energy to do anything, I always want to sit down* • *General malaise. Weakness, fatigue, maybe a little nausea. Just not having enough energy is it. Have some headaches.*

Reviewer's comments: The applicant has supported the content validity of PROMIS® Fatigue in the target population through qualitative research as well as literature review and

expert clinician input. Based on the review of the qualitative data, this reviewer feels that fatigue is a symptom of the disease that is important to patients.

(b) (4)

(b) (4)

(b) (4)

Reviewer's comments:
Based on review of the qualitative data, this reviewer does not believe the applicant has sufficiently established content validity (b) (4) *as patients interpreted this concept inconsistently.*

(b) (4)

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

PROMIS® Fatigue

The measurement properties for PROMIS® fatigue in the general population has been described in the in the literature.

Additionally, the applicant performed additional supportive analyses in the MF population. A synopsis of these results are described below.

Reviewer's comments: Initially, there was some concern in regards to combining symptoms and impacts in a total score. As such, the Agency had suggested the applicant to evaluate whether individual items of the PROMIS® Fatigue scale contributed similarly to change in the total score and to understand which item(s) may be driving the result. (b) (4) *Although the applicant provided this data, the data of most importance for review was the item-level analyses. The results presented below are for the 7-item total score.*

Item characteristics
Table 7 shows the item and total score characteristics at baseline visit of COMFORT-I trial.

Table 7. PROMIS® Fatigue floor and ceiling effects at baseline.

In the past 7 days…	N	Minimum	Maximum	Mean	Std. Deviation	% Floor	% Ceiling
Item 1: How often did you feel tired?	304	1	5	3.74	0.83	1%	18%
Item 2: How often did you experience extreme exhaustion?	304	1	5	2.72	1.01	12%	3%
Item 3: How often did you run out of energy?	303	1	5s	3.25	0.91	3%	6%
Item 4: How often did your fatigue limit you at work (include work at home)?	302	1	5	3.19	1.02	6%	9%
Item 5: How often were you too tired to think clearly?	304	1	5	2.31	0.98	24%	1%
Item 6: How often were you too tired to take a bath or shower?	304	1	5	1.86	0.98	48%*	1%
Item 7: How often did you have enough energy to exercise strenuously?	300	1	5	3.87	1.19	5%	40%*

*Exceeds standard of 25%

Reviewer's comments: There was some evidence of skew on only two of the seven items in the PROMIS® Fatigue assessments. Specifically, Item 6 (How often were you too tired to take a bath or shower?) exceeded a 25% threshold for floor effects, and Item 7 (How often did you have enough energy to exercise strenuously?) exceeded the 25% threshold for ceiling effects. These results were not as concerning as the results showed general improvement in most of the items.

Test-retest reliability
Test-retest reliability was assessed with a cohort of "stable" subjects (n=88) from COMFORT-I defined as having a Patient Global Impression of Change (PGIC) score of 4 (unchanged) at Week 4. The intraclass correlation coefficient (ICC) for baseline and Week 4 scores with this

sample was 0.85. Similarly, test-retest reliability was assessed with a cohort of "stable" subjects (n=30) for the subset of patients having a PGIC score of 4 (unchanged) between week 16 and 24. The ICC using this time period was 0.92 for the 7-item total score.

Reviewer's comments: The test-retest reliability estimates fall within the acceptable range.

Internal consistency
Table 8 provides the results of internal consistency reliability estimates.

Table 8. Internal consistency reliability for PROMIS® Fatigue

	Baseline	**Week 24**
	Cronbach alpha*	Cronbach alpha*
PROMIS® Fatigue	0.86 (n= 298)	0.88 (n= 251)

*Standardized

Reviewer's comments: The internal consistency reliability estimates fall within the acceptable range.

Construct validity

- Convergent validity
  Convergent validity was assessed by correlating the PROMIS® Fatigue scale total score at baseline with spleen volume, MFSAF v2.0 total symptom score (TSS), Inactivity and EORTC functional status indicators, specifically the EORTC Fatigue, Physical Function, Role Function, and Social Function scales. Resulting correlations are shown in Table 9.

Table 9. Convergent validity for PROMIS® Fatigue

		PROMIS® Fatigue
Spleen Volume at Baseline	Pearson Correlation	0.13*
	N	235
Spleen Volume at Baseline	Pearson Correlation	0.44**
	N	235
Worst Inactivity	Pearson Correlation	0.64**
	N	284
EORTC Fatigue at Baseline	Pearson Correlation	0.73**
	N	275
EORTC Physical Function at Baseline	Pearson Correlation	-0.66**
	N	275
EORTC Role Function at Baseline	Pearson Correlation	-0.64**
	N	273

EORTC Social Function at Baseline	Pearson Correlation	-0.57**
	N	274

*Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

Reviewer's comments: The applicant noted that the resulting correlations were as expected based on their hypotheses; however, those hypotheses were not explicitly described in the evidence dossier. Based on the results, PROMIS® Fatigue total score does have a moderate to high positive correlation with the EORTC Fatigue items. Further, there was moderate to high negative correlation with measures that related to activity (EORTC Physical Function domain, EORTC Role Function domain), which is logical as fatigue impairment results in inactivity.

- Known-groups validity
  Known-Groups validity was evaluated by examining two criterion variables – spleen volume and the MFSAF TSS as indicators of overall disease severity. Baseline scores on both variables were split at the median, defining two distinct clinical groups. Significant differences on the PROMIS® Fatigue scale total score were found across larger and smaller spleen volume groups, with the larger spleen volume group reporting significantly more fatigue symptoms and impacts. Similar findings were found for the TSS median-split groups. Results are shown in Table 10 and 11.

Table 10. Known-groups validity for PROMIS® Fatigue by spleen volume median groups at baseline

		N	Mean	Standard Deviation
PROMIS® Fatigue (raw score)	Spleen Volume ≤ Median	126	19.74	5.11
	Spleen Volume ≥ Median	126	22.05	5.08
	Total	252	20.89**	5.22

**Group mean differences: p<.001
Note: The higher the score on PROMIS® Fatigue Shore Form 7a indicated more severe fatigue.

Table 11. Known-groups validity for PROMIS® Fatigue by MFSAF TSS median groups at baseline

		N	Mean	Standard Deviation
PROMIS® Fatigue (raw score)	TSS ≤ Median	121	18.86	5.25
	TSS ≥ Median	125	22.82	4.45
	Total	246	20.87**	5.24

** Group mean differences: p<.001

Note: The higher the score on PROMIS® Fatigue Shore Form 7a indicated more severe fatigue.

Reviewer's comments: The PROMIS® fatigue total score was compared by fitting one-way analysis of variance (ANOVA) models. The rationale to use the median as the cut-off to distinguish different clinical groups is unclear. The results provide evidence that the measure can differentiate between the two median cutoffs, but it is unknown whether these cutoffs reflect clinically distinct groups.

Ability to detect change

Ability to detect change was assessed using two different approaches to evaluate change in the PROMIS® fatigue scale total score when there was change on other clinical variables suggesting the patients had indeed changed. Specifically, patients were considered to have changed clinical status based on responses to the PGIC and on percent change in spleen volume.

PGIC week 24 scores were partitioned into "improved" (n=117) with PGIC ratings of 1 (very much improved), 2 (much improved), and 3 (minimally improved) and "worsened" (n=116) with PGIC ratings of 5 (minimally worse), 6 (much worse), and 7 (very much worse). Baseline to Week 24 PROMIS® Fatigue total score was evaluated by fitting a general linear model with corresponding baseline score values as covariates. Significant group differences were found in each analysis with the improved groups showing reduction in the symptom, impact, and total fatigue scores while the worsened groups reported increases on the scales (Table 12).

Table 12. Change in PROMIS® Fatigue total score by PGIC Improved and Worsening Groups Baseline to Week 24

	PROMIS® Fatigue
	LS Mean (SE) †
PGIC Group±	
Improved	-3.41 (0.33)***
Worsened	2.52 (0.56)

†LS Mean (least squared mean with baseline value covaried); SE (standard error)
±PGIC Improved (PGIC score 1-3 at Week 24); PGIC Worsened (PGIC 5-7 at Week 24)
*** $p < 0.001$

Note: The higher the score on PROMIS® Fatigue Shore Form 7a indicated more severe fatigue.

Reviewer's comments: The PROMIS® fatigue total score demonstrates the ability to detect change in the MF population. The cumulative distribution function (CDF) plots also provides support for the ability of this measure to detect change. See Section 7.

(b) (4)

Reviewer's comments: Other measurement properties (reliability, construct validity and ability to detect change) are not reviewed until the instrument's content validity has been established. Testing other measurement properties (reliability, construct validity, and ability to detect change), while important, will not replace or rectify problems with content validity.

6 SCORING ALGORITHM

PROMIS® Fatigue

The total raw score for a short form with all questions answered is calculated by summing the values of the response to each question. A t-score can also be calculated which rescales the raw score into a standardized score with a mean of 50, standard deviation (SD) of 10, and 0-100 range by means of a table provided in the scoring manual. If a t-score is reported, a score on PROMIS® Fatigue Shore Form 7a above 50 can be interpreted as above average fatigue (relative to general public population). The higher the score on PROMIS® Fatigue Shore Form 7a indicated more severe fatigue.

(b) (4)

7 INTERPRETATION OF SCORES

PROMIS® Fatigue

The existing literature on the development of the PROMIS® Fatigue suggests a minimally important difference (MID) range of 3.0-5.0 T score points. The published MID data (both raw scores and T-scores) are shown in Table 13.

Table 13. Published values for minimal important difference estimates on PROMIS® Fatigue

Recommended IRT-based T-score MIDs and Raw Score MIDs for PROMIS-Cancer Short Forms in Advanced Cancer Patients

Short Form	T-Score MID Points	T-Score MID Effect Sizes*	Raw Score MID Points	Raw Score MID Effect Sizes§
17-item Fatigue	2.5 – 4.5	0.37 – 0.67	4.0 – 8.0	0.33 – 0.65
7-item Fatigue	3.0 – 5.0	0.39 – 0.65	2.0 – 3.0	0.38 – 0.57
Pain Interference	4.0 – 6.0	0.43 – 0.64	4.0 – 7.0	0.39 – 0.69
Physical Function	4.0 – 6.0	0.45 – 0.67	4.0 – 6.0	0.42 – 0.63
Emotional Distress-Anxiety	3.0 – 4.5	0.40 – 0.60	3.0 – 4.0	0.45 – 0.60
Emotional Distress-Depression	3.0 – 4.5	0.36 – 0.54	3.0 – 4.0	0.43 – 0.57

*Calculated as the T-Score MID divided by the Assessment 1 T-score standard deviation

§Calculated as the Raw Score MID divided by the Assessment 1 Raw Score standard deviation

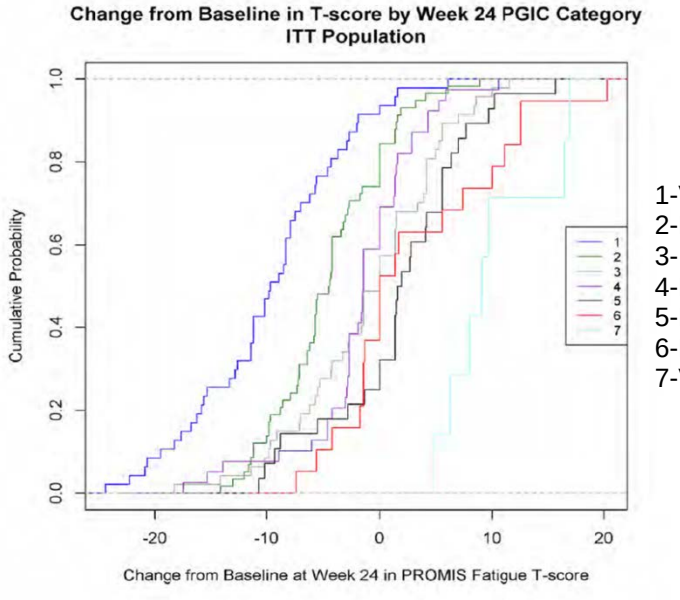
Reviewer's comments: From a regulatory standpoint, we are more interested in what constitutes a clinically meaningful within-patient change in scores (i.e., responder threshold), from the patient perspective, rather than a minimal clinically important difference (MCID) across all patients. Therefore, in previous communication with the applicant, it was suggested that they create CDF plots for the PROMIS® Fatigue scale.

Anchor-based methods
The anchor-based approach to clinically meaningful change employed the PGIC as a well-established measure of patient perception of clinical status change. To have a relatively conservative estimate of meaningful change, the applicant identified a sample of patients selecting either "1" (Very Much Improved) or "2" (Much Improved) irrespective of treatment group assignment, and mean raw change score values were calculated for the total score. The responder threshold using this anchor approach was -4.53 for PROMIS Fatigue total score.

Reviewer's comments: PROMIS® Fatigue when anchored to the PGIC showed separation on the meaningful change.

Cumulative distribution function plots
The applicant was requested by FDA to plot CDF of each anchor response category to help inform the responder threshold for PROMIS® Fatigue. The CDF plots suggests that a meaningful threshold might range from 4-9 points (t-score) when anchored to the "Much improved" and "Very much improved" PGIC response categories (Figure 4).

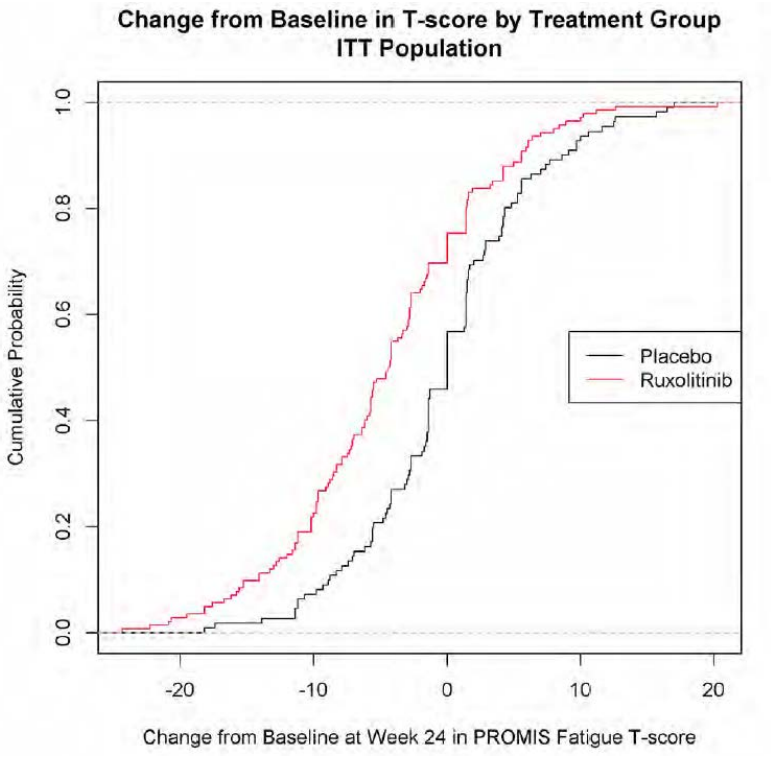
Figure 4. Cumulative distribution function curve: Change from baseline to Week 24 PROMIS Fatigue change scores by PGIC at Week 24



Based on the threshold generated from the CDF plots, the applicants proposed threshold seems reasonable based on the separation between the two treatment arms (Figure 5).

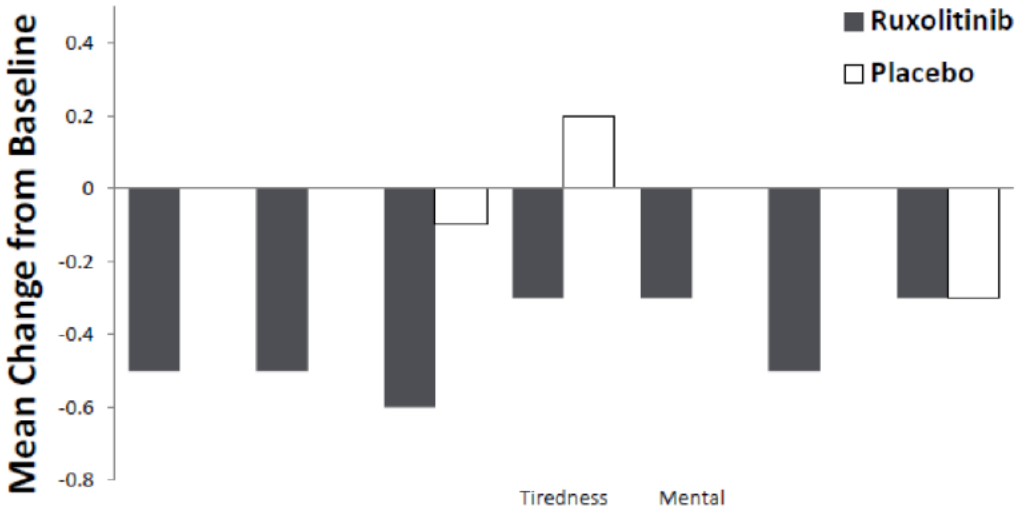
Reviewer's comment: Our confidence in the responder definition would be increased had we also been able to apply additional anchors such as a static current-state global as interpretation of meaningful change often relies on use of more than a single anchor.

Figure 5. Cumulative distribution function curve: Change from baseline to Week 24 PROMIS® Fatigue change scores by treatment arm at Week 24



The applicant also showed that all items in the PROMIS® Fatigue contribute to the total score (Figure 6).

Figure 6. Change from baseline to Week 24 for individual items of PROMIS® Fatigue change scores by treatment arm at Week 24



	Exhaustion	Low/no energy	Tiredness	Tiredness impact on self-care: bathing / showering	Mental tiredness impact on thinking clearly	Fatigue impact on work	Impact on strenuous activity
Ruxolitinib	-0.5	-0.5	-0.6	-0.3	-0.3	-0.5	-0.3
Placebo	0	0	-0.1	0.2	0	0	-0.3
N	142 111	142 110	141 111	142 110	142 111	141 111	140 110

Reviewer's comments: Despite the fact the PROMIS® Fatigue total score combines both symptoms and impacts, all items showed general improvement (i.e. items moved in the correct direction) and there is no item driving the result, which mitigates the concern of the use of a total score. Note: The higher the score on PROMIS® Fatigue Shore Form 7a indicated more severe fatigue.

(b) (4)

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The COMFORT-I trial was conducted at a total of 89 sites in the United States (n=68), Canada

(n=6), and Australia (n=15). A total of 309 MF patients were randomized in the trial and available to contribute data to the efficacy analysis. The majority of these subjects read and spoke in English (N=305) [redacted] (b) (4) Among these 305 subjects, 235 were from the United States, 22 from Canada and 48 from Australia [redacted] (b) (4)

Reviewer's comments: PROMIS® Fatigue has been translated in U.S. Spanish and Canadian French. The translation process appears to be in accordance to ISPOR best practices. [redacted] (b) (4)

8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable

9 REVIEW USER MANUAL

The applicant did not provide a user manual for review.

10 KEY REFERENCES FOR COA

Cella, D., Riley, W., Stone, A., Rothrock, N., Reeve, B., Yount, S., et al. (2010). The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. Journal of Clinical Epidemiology, 63(11), 1179–1194.

Christodoulou, C., Junghaenel, D. U., DeWalt, D. A., Rothrock, N., & Stone, A. A. (2008). Cognitive interviewing in the evaluation of fatigue items: Results from the Patient-Reported Outcomes Measurement Information System (PROMIS). Quality of Life Research, 17(10), 1239–1246.

Riley, W. T., Rothrock, N., Bruce, B., Christodoulou, C., Cook, K., Hahn, E. A., et al. (2010). Patient-Reported Outcomes Measurement Information System (PROMIS) domain names and definitions revisions: further evaluation of content validity in IRT-derived item banks. Quality of Life Research, 19(9), 1311–1321.

DeWalt, D. A., Rothrock, N., Yount, S., & Stone, A. A. (2007). Evaluation of item candidates: the PROMIS qualitative item review. Medical Care, 45(5 Suppl 1), S12–S21.

Reeve, B. B., Hays, R. D., Bjorner, J. B., Cook, K. F., Crane, P. K., Teresi, J. A., et al. (2007). Psychometric evaluation and calibration of health-related quality of life item banks: plans for the Patient-Reported Outcomes Measurement Information System (PROMIS). Medical Care, 45(5 Suppl 1), S22–S31.

D. APPENDICES

Appendix A: PROMIS Fatigue 7-item Short Form (b) (4)

APPENDIX A: PROMIS FATIGUE 7-ITEM SHORT FORM

Incyte Corporation
Clinical Study Report INCB 18424-351

Final
27 April 2011

APPENDIX IX – PROMIS FATIGUE SCALE QUESTIONNAIRE

PROMIS Item Bank v. 1.0 - Fatigue Short - Form 1

Fatigue - Short Form 1

Please respond to each question by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
FATEXP20	How often did you feel tired?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP6	How often did you experience extreme exhaustion?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP18	How often did you run out of energy?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP33	How often did your fatigue limit you at work (include work at home)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP30	How often were you too tired to think clearly?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP21	How often were you too tired to take a bath or shower?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40	How often did you have enough energy to exercise strenuously?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

APPENDIX B: (b) (4)

(b) (4)

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

/s/

MICHELLE L CAMPBELL
09/08/2017

SELENA R DANIELS
09/08/2017

ELEKTRA J PAPADOPOULOS
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