CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202192Orig1s017

Trade Name:	JAKAFI® tablets, for oral use
Generic or Proper Name:	ruxolitinib
Sponsor:	Incyte Corporation
Approval Date:	May 24, 2019
Indication:	Jakafi is an kinase inhibitor indicated for treatment of: • Intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycthemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults. • Polycthemia vera in adults who have had an inadequate response to or are intolerant of hydroxyurea. • Steroid-refractory acute graft-verus-host disease in adult and pediatric patients 12 years and older.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 202192/S-017

SUPPLEMENT APPROVAL

Incyte Corporation
Attention: Ronald Falcone, PhD
Group Vice President, Regulatory Affairs
1801 Augustine Cut-Off
Wilmington, DE 19803

Dear Dr. Falcone:

Please refer to your supplemental new drug application (sNDA) dated August 24, 2018, received August 24, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jakafi® (ruxolitinib) tablets, 5, 10, 15, 20 and 25 mg.

We acknowledge receipt of your major amendment dated February 24, 2019, which extended the goal date by three months.

This Prior Approval supplemental new drug application provides for a new indication for ruxolitinib for treatment of steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years and older.

APPROVAL & LABELING

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

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (Prescribing Information and Patient 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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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 (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, 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

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information 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 *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[3]

You must submit final promotional materials and Prescribing Information, 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 FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

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

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

If you have any questions, call Suria Yesmin, Senior Regulatory Project Manager, at 301-348-1725.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALBERT B DEISSEROTH
05/24/2019 01:05:36 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202192Orig1s017

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

Indications and Usage (1.3)	05/2019
Dosage and Administration (2.3)	05/2019

INDICATIONS AND USAGE

Jakafi is a kinase inhibitor indicated for treatment of

- intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults. (1.1)
- polycythemia vera in adults who have had an inadequate response to or are intolerant of hydroxyurea. (1.2)
- steroid-refractory acute graft-versus-host disease in adult and pediatric patients 12 years and older (1.3)

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.

Acute Graft Versus Host Disease (2.3)

- The starting dose of Jakafi is 5 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

- In myelofibrosis and polycythemia vera, the most common hematologic adverse reactions (incidence > 20%) are thrombocytopenia and anemia. The most common nonhematologic adverse reactions (incidence >10%) are bruising, dizziness, and headache. (6.1)
- In acute graft versus host disease, the most common hematologic adverse reactions (incidence > 50%) are anemia, thrombocytopenia, and neutropenia. The most common nonhematologic adverse reactions (incidence > 50%) are infections and edema. 6.3)

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 except in patients with acute graft versus host disease. (2.4,7)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: Reduce Jakafi starting dose or avoid treatment as recommended. (2.5,8.6)
- Hepatic Impairment: Reduce Jakafi starting dose or avoid treatment as recommended. (2.5,8.7)
- Lactation: Advise not to breastfeed. (8.2)

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

Revised: 05/2019

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 intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults.

1.2 Polycythemia Vera

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

1.3 Acute Graft Versus Host Disease

Jakafi is indicated for treatment of steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years and older.

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

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

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.

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 dose modifications in Section 2.1 (*Dose Modification Guidelines for Hematological Toxicity for Patients with Myelofibrosis Starting Treatment with a Platelet Count of 100 X 109/L or Greater)* 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.

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 (*see Dose Modification Based on Insufficient Response with Myelofibrosis Starting Treatment with a platelet count of 100 X 109/L or Greater)*, 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.

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.

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.

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 Acute Graft Versus Host Disease

The recommended starting dose of Jakafi is 5 mg given orally twice daily. Consider increasing the dose to 10 mg twice daily after at least 3 days of treatment if the ANC and platelet counts are not decreased by 50% or more relative to the first day of dosing with Jakafi.

Tapering of Jakafi may be considered after 6 months of treatment in patients with response who have discontinued therapeutic doses of corticosteroids. Taper Jakafi by one dose level approximately every 8 weeks (10 mg twice daily to 5 mg twice daily to 5 mg once daily). If acute GVHD signs or symptoms recur during or after the taper of Jakafi, consider retreatment.

Dose Modification Guidelines for Patients with Acute Graft Versus Host Disease

Evaluate blood parameters before and during treatment with Jakafi. Dose reductions should be considered for platelet counts, ANCs or bilirubin value as described in Table 7. Patients who are currently receiving Jakafi 10 mg twice daily may have their dose reduced to 5 mg twice daily; patients receiving 5 mg twice daily may have their dose reduced to 5 mg once daily. Patients who are unable to tolerate Jakafi at a dose of 5 mg once daily should have treatment interrupted until their clinical and/or laboratory parameters recover.

Table 7: Dose Modifications for Patients with Acute GVHD

Laboratory Parameter	Dosing Recommendations
Clinically significant thrombocytopenia after supportive measures	Reduce dose by 1 dose level. When platelets recover to previous values, dosing may return to prior dose level.
ANC less than 1 X 10^9/L considered related to Jakafi	Hold Jakafi for up to 14 days; resume at 1 dose level lower upon recovery.
Total Bilirubin elevation, no liver GVHD	3.0–5.0 × ULN: Continue Jakafi at 1 dose level lower until recovery. >5.0–10.0 × ULN: Hold Jakafi for up to 14 days until bilirubin ≤ 1.5 × ULN; resume at current dose upon recovery Total bilirubin > 10.0 × ULN: Hold Jakafi for up to 14 days until bilirubin ≤ 1.5 × ULN; resume at 1 dose level lower upon recovery.
Total Bilirubin elevation, liver GVHD	>3.0 × ULN: Continue Jakafi at 1 dose level lower until recovery.

2.4 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)*], according to Table 8.

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 except in patients with acute GVHD.

Table 8: Dose Modifications for Concomitant Use with 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 MF or 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
For patients with acute GVHD:	
Ketoconazole	5 mg once daily
Other CYP3A4 inhibitors*	No dose adjustment

*With coadministration of itraconazole, monitor blood counts more frequently for toxicity and adjust the dose of Jakafi if necessary.

2.5 Dose Modifications for Renal or Hepatic 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 9.

Patients with End Stage Renal Disease on Dialysis

Modify the Jakafi dosage for patients with end stage renal disease (ESRD) on dialysis according to Table 9. 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)*].

Table 9: 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 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)*]
ESRD (CLcr less than 15 mL/min) on dialysis	100 to 200 X 10^9/L	15 mg once after dialysis session
	Greater than 200 X 10^9/L	20 mg once after dialysis session
Patients with PV		
Moderate (CLcr 30 to 59 mL/min) or Severe (CLcr 15 to 29 mL/min)	Any	5 mg twice daily
ESRD (CLcr less than 15 mL/min) on dialysis	Any	10 mg once after dialysis session
Patients with acute GVHD		
Moderate (CLcr 30 to 59 mL/min) or Severe (CLcr 15 to 29 mL/min)	Any	5 mg once daily
ESRD (CLcr less than 15 mL/min) on dialysis	Any	5 mg once after dialysis session

ESRD = end stage renal disease, and CLcr = creatinine clearance

Hepatic Impairment

Modify the Jakafi dosage for patients with hepatic impairment according to Table 10.

Table 10: 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
Patients with acute GVHD		
Mild, Moderate, or Severe based on NCI criteria	Any	No dose modification needed
Stage 3 or 4 liver GVHD	Any	Monitor blood counts more frequently for toxicity and consider 5 mg once daily

2.6 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), 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), 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. Use active surveillance and prophylactic antibiotics according to clinical guidelines.

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 (2.6)*], 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 clinically significant 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 reactions were thrombocytopenia and anemia [*see Table 12*]. Thrombocytopenia, anemia and neutropenia are dose-related effects. The three most frequent nonhematologic adverse reactions were bruising, dizziness and headache [*see Table 11*].

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

Table 11 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 11: 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 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 12 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 12: 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. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi.

Table 13 presents the most frequent nonhematologic treatment emergent adverse events occurring up to Week 32.

Table 13: 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 14.

Table 14: 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

6.3 Clinical Trial Experience in Acute Graft-Versus-Host Disease

In a single-arm, open-label study, 71 adults (ages 18-73 years) were treated with Jakafi for acute GVHD failing treatment with steroids with or without other immunosuppressive drugs [see *Clinical Studies (14.3)*]. The median duration of treatment with Jakafi was 46 days (range, 4-382 days).

There were no fatal adverse reactions to Jakafi. An adverse reaction resulting in treatment discontinuation occurred in 31% of patients. The most common adverse reaction leading to treatment discontinuation was infection (10%). Table 15 shows the adverse reactions other than laboratory abnormalities.

Table 15: Acute Graft Versus Host Disease: Nonhematological Adverse Reactions Occurring in ≥ 15% of Patients in the Open-Label, Single-Cohort Study

	Jakafi (N=71)	
Adverse Reactions[a]	**All Grades[b] (%)**	**Grade 3-4 (%)**
Infections	55	41
Edema	51	13
Hemorrhage	49	20
Fatigue	37	14
Bacterial infections	32	28

	Jakafi (N=71)	
Adverse Reactions[a]	**All Grades[b] (%)**	**Grade 3-4 (%)**
Dyspnea	32	7
Viral infections	31	14
Thrombosis	25	11
Diarrhea	24	7
Rash	23	3
Headache	21	4
Hypertension	20	13
Dizziness	16	0

[a] Selected laboratory abnormalities are listed in Table 16 below
[b] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03

Selected laboratory abnormalities during treatment with Jakafi are shown in Table 16.

Table 16: Acute Graft Versus Host Disease: Selected Laboratory Abnormalities Worsening from Baseline in the Open-Label, Single Cohort Study

	Jakafi (N=71)	
	Worst grade during treatment	
Laboratory Parameter	**All Grades[a] (%)**	**Grade 3-4 (%)**
Hematology		
Anemia	75	45
Thrombocytopenia	75	61
Neutropenia	58	40
Chemistry		
Elevated ALT	48	8
Elevated AST	48	6
Hypertriglyceridemia	11	1

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03
NA = Not applicable

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 except in patients with acute GVHD *[see Dosage and Administration (2.4)]*.

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 (2.4)]*. In patients with acute GVHD, reduce Jakafi dose as recommended only when coadministered with ketoconazole, and monitor blood counts more frequently for toxicity and adjust the dose if necessary when coadministered with itraconazole. *[see Dosage and Administration (2.4)]*.

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 child, 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 for treatment of myelofibrosis or polycythemia vera in pediatric patients have not been established.

The safety and effectiveness of Jakafi for treatment of steroid-refractory acute graft-versus-host disease (GVHD) have been established for treatment of children 12 years and older. Use of Jakafi in pediatric patients with steroid-refractory acute GVHD us supported by evidence from an adequate and well-controlled trial of Jakafi in adults *[see Clinical Studies (14.3)]* and additional pharmacokinetic and safety data in pediatric patients.

Jakafi was evaluated in a single-arm, dose-escalation study (NCT01164163) in 27 pediatric patients with relapsed or refractory solid tumors (Cohort A) and 20 with leukemias or myeloproliferative neoplasms (Cohort B). The patients had a median age of 14 years (range, 2 to 21 years) and included 18 children (age 2 to <12 years), and 14 adolescents (age 12 to <17 years). The dose levels tested were 15, 21, 29, 39, or 50 mg/m^2 twice daily in 28-day cycles with up to 6 patients per dose group.

Overall, 38 (81%) patients were treated with no more than a single cycle of Jakafi, while 3, 1, 2, and 3 patients received 2, 3, 4, and 5 or more cycles, respectively. A protocol-defined maximal tolerated dose was not observed, but since few patients were treated for multiple cycles, tolerability with continued use was not assessed adequately to establish a recommended Phase 2

dose higher than the recommended dose for adults. The safety profile in children was similar to that seen in adults.

Juvenile Animal Toxicity Data

Administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at exposures that are at least 27% the clinical exposure at the maximum recommended dose of 25 mg twice daily.

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.

Clinical studies of Jakafi in patients with acute GVHD did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

8.6 Renal Impairment

Total exposure of ruxolitinib and its active metabolites increased with moderate (CLcr 30 mL/min to 59 mL/min) and severe (CLcr 15 mL/min to 29 mL/min) renal impairment, and ESRD on dialysis *[see Clinical Pharmacology (12.3)]*. Reduce Jakafi dose as recommended *[see Dosage and Administration (2.5)]*.

8.7 Hepatic Impairment

Exposure of ruxolitinib increased with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment *[see Clinical Pharmacology (12.3)]*. Reduce Jakafi dose as recommended in patients with MF or PV and any hepatic impairment *[see Dosage and Administration (2.5)]*.

Monitor blood counts more frequently for toxicity and consider 5 mg once daily for patients with Stage 3 or 4 liver GVHD *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

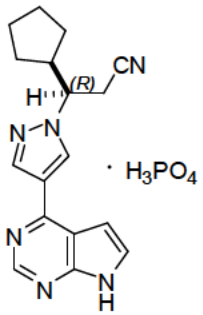
There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated

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).

JAK-STAT signaling pathways play a role in regulating the development, proliferation, and activation of several immune cell types important for GVHD pathogenesis. In a mouse model of acute GVHD, oral administration of ruxolitinib was associated with decreased expression of inflammatory cytokines in colon homogenates and reduced immune-cell infiltration in the colon.

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 maximal plasma concentration (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 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 (% coefficient of variation, CV) was 17.7 L/h in women and 22.1 L/h in men with MF (39%).

Ruxolitinib clearance (%CV) was 12.7 L/h (42%) in patients with PV.

Ruxolitinib clearance (%CV) was 11.9 L/h (43%) in patients with acute GVHD.

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. No clinically relevant effect in ruxolitinib pharmacokinetics were observed with regards to any hepatic impairment (total bilirubin >ULN and any aspartate transferase) in patients with acute GVHD.

Patients with Renal Impairment

Following oral administration of a single dose of Jakafi 25 mg, the total AUC of ruxolitinib and its active metabolites increased by 1.3-,1.5-, and 1.9-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to that in subjects with normal renal function (CLcr ≥ 90 mL/min). Also, the total AUC of ruxolitinib and its active metabolites increased by 1.6-fold in subjects with ESRD after dialysis) compared to that in subjects with normal renal function (CLcr ≥ 90 mL/min). The pharmacokinetics of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure with renal impairment. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out.

Patients with Hepatic Impairment

Following oral administration of a single dose of Jakafi 25 mg, the AUC of ruxolitinib increased in subjects with mild (Child-Pugh A) by 1.9-fold, moderate (Child-Pugh B) by 1.3-fold, and severe (Child-Pugh C) hepatic impairment by 1.7-fold compared to that in subjects with normal hepatic function.

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 (2.4) 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 (2.4) 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)]*.

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 (NCT00952289) 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 (NCT00934544) 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

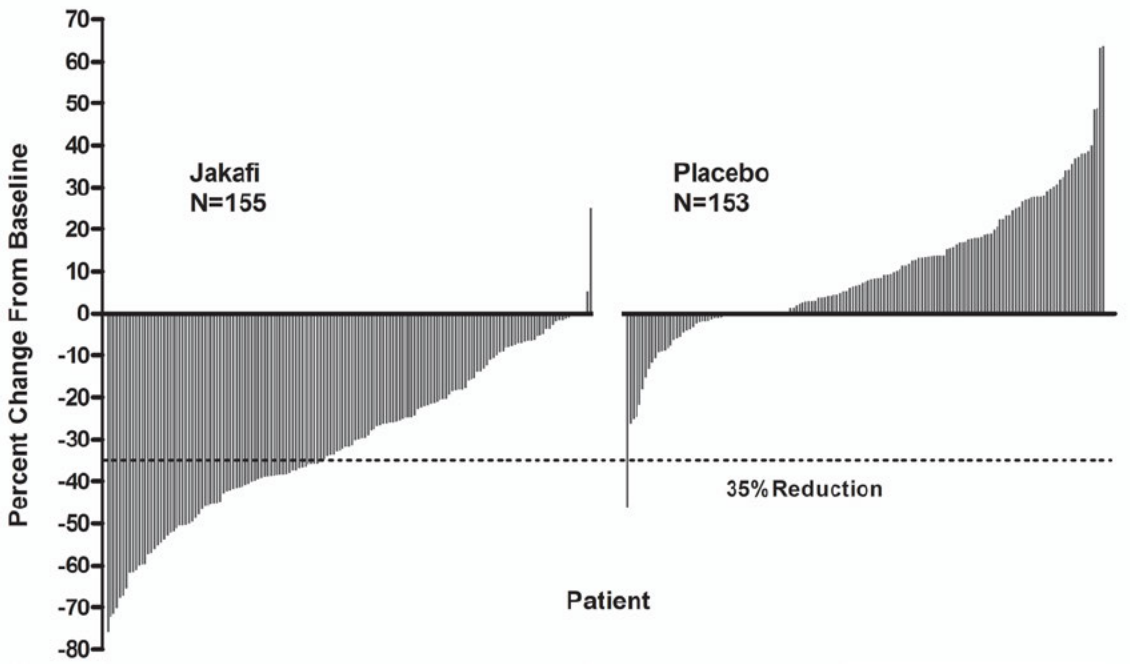
Efficacy analyses of the primary endpoint in Studies 1 and 2 are presented in Table 17 below. A significantly larger proportion of patients in the Jakafi group achieved a 35% or greater reduction in spleen volume from baseline in both studies compared to placebo in Study 1 and best available therapy in Study 2. A similar proportion of patients in the Jakafi group achieved a 50% or greater reduction in palpable spleen length.

Table 17: 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.

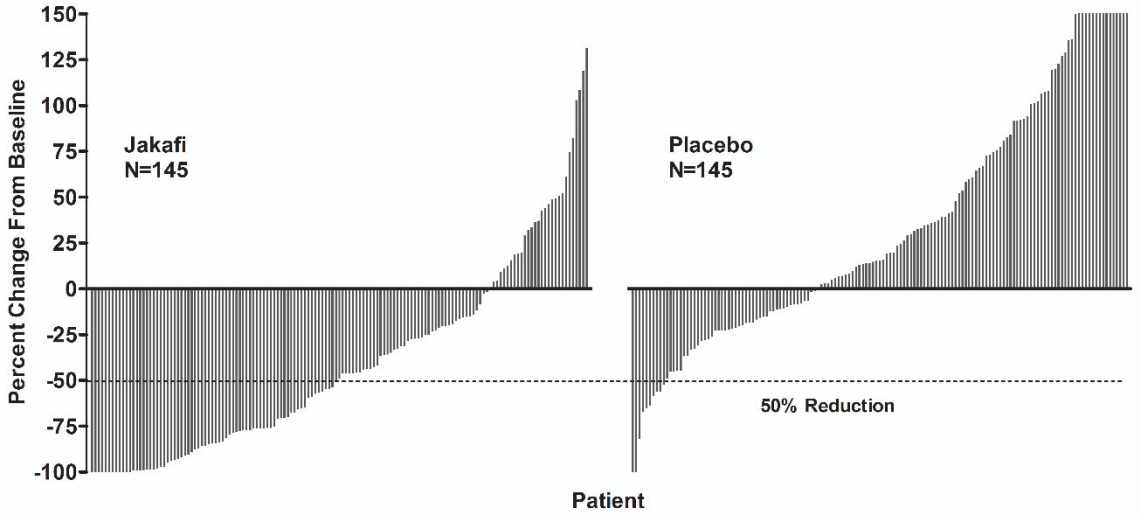
Table 18 presents assessments of Total Symptom Score from baseline to Week 24 in Study 1 including the proportion of patients with at least a 50% reduction (ie, improvement in symptoms). At baseline, the mean Total Symptom Score was 18.0 in the Jakafi group and 16.5 in the placebo group. A higher proportion 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 18: 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.

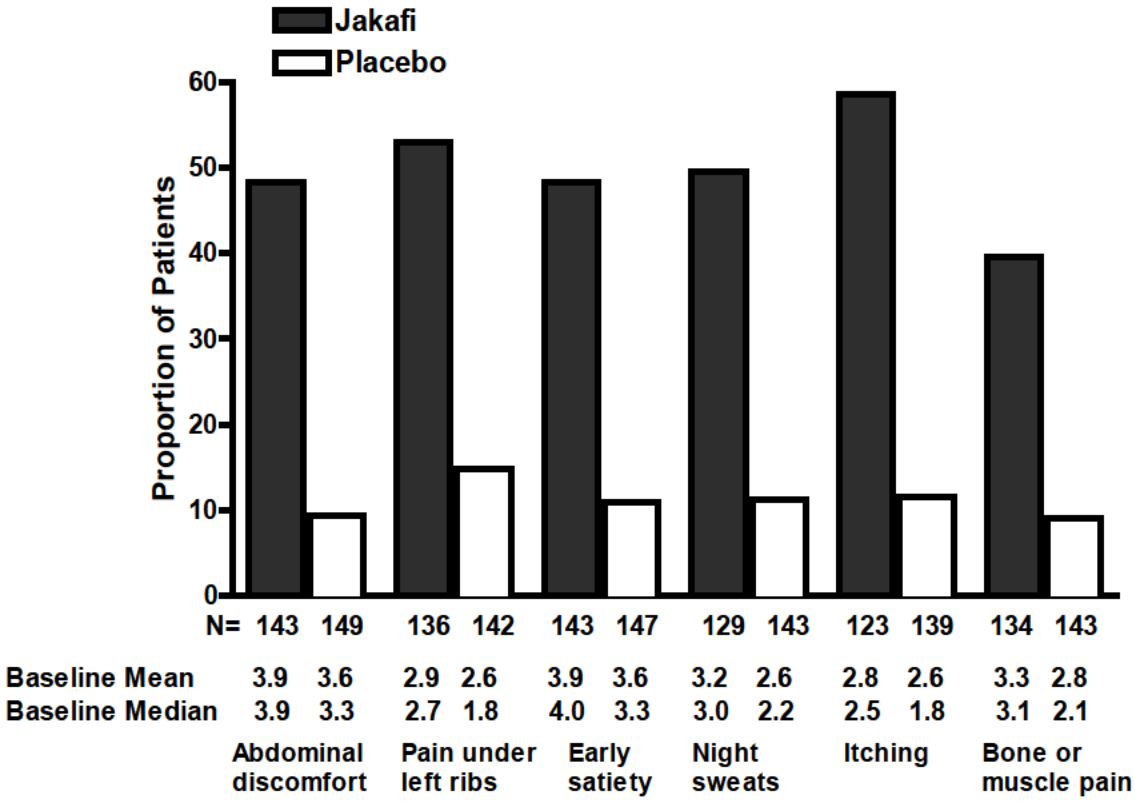
Figure 2: Percent Change from Baseline in Total Symptom Score at Week 24 or Last Observation for Each Patient (Study 1)



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



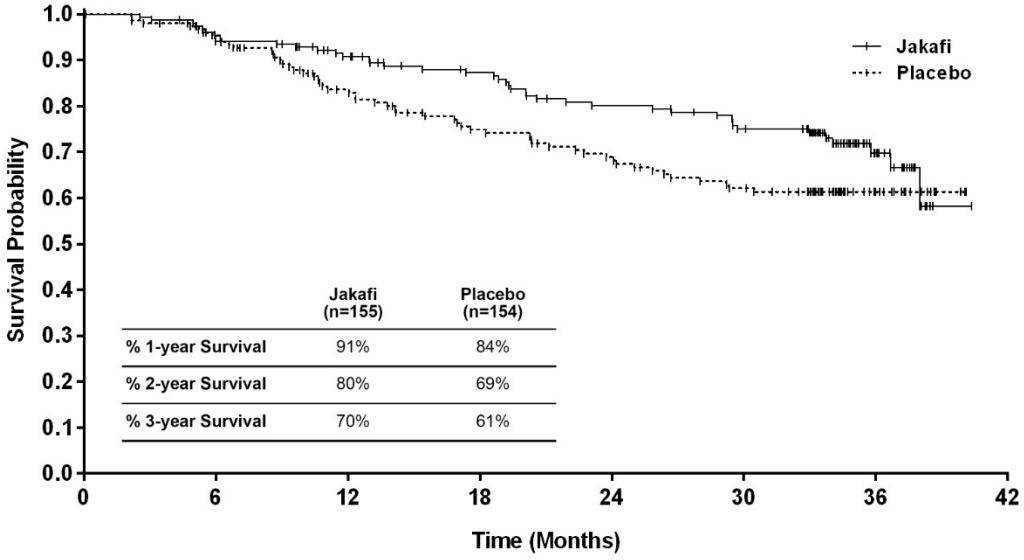
Individual score range = 0 to 10

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.

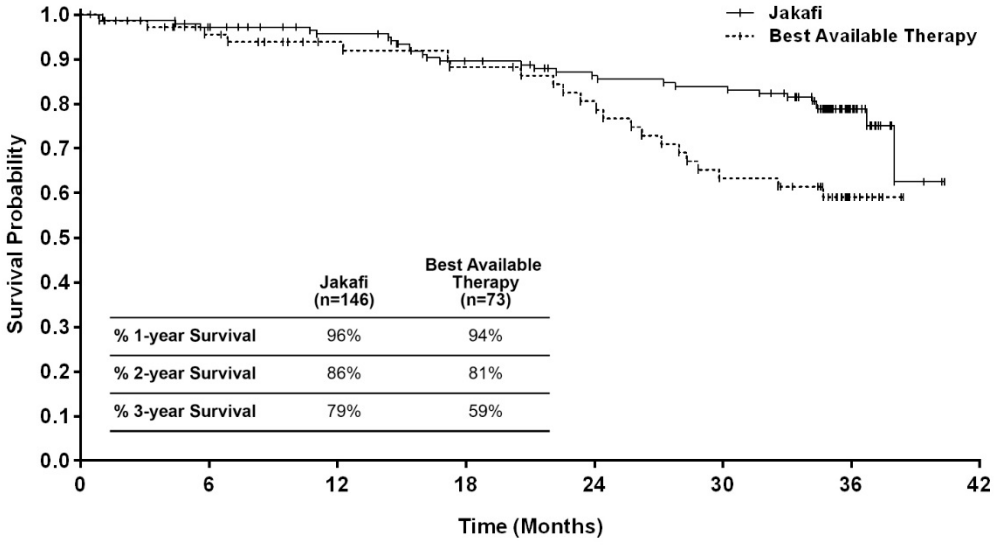
Figure 4: Overall Survival - Kaplan-Meier Curves by Treatment Group in Study 1



	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 (NCT01243944) 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 19. 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 19: 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%)

	Jakafi (N=110)	**Best Available Therapy** (N=112)
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.

14.3 Acute Graft Versus Host Disease

Study 4 (NCT02953678) was an open-label, single-arm, multicenter study of Jakafi for treatment of patients with steroid-refractory acute GVHD Grades 2 to 4 (Mount Sinai Acute GVHD International Consortium (MAGIC) criteria) occurring after allogeneic hematopoietic stem cell transplantation. Jakafi was administered at 5 mg twice daily, and the dose could be increased to 10 mg twice daily after 3 days in the absence of toxicity.

There were 49 patients with acute GVHD refractory to steroids alone. These patients had a median age of 57 years (range, 18-72 years), 47% were male, 92% were Caucasian, and 14% were Hispanic. At baseline, acute GVHD was Grade 2 in 27%, Grade 3 in 55%, and Grade 4 in 18%; 84% had visceral GVHD; the median MAGIC biomarker score was 0.47 (range, 0.10-0.92); and the median ST2 level was 334 mcg/L (range, 55-1286 mcg/L). The median duration of prior corticosteroid exposure at baseline was 15 days (range: 3 – 106 days).

The efficacy of Jakafi was based on Day-28 overall response rate (ORR) (complete response, very good partial response or partial response by Center for International Blood and Marrow Transplant Research (CIBMTR) criteria) and the duration of response. The ORR results are presented in Table 20; Day-28 ORR was 100% for Grade 2 GVHD, 40.7% for Grade 3 GVHD, and 44.4% for Grade 4 GVHD. The median duration of response, calculated from Day-28 response to progression, new salvage therapy for acute GVHD or death from any cause (with progression being defined as worsening by one stage in any organ without improvement in other organs in comparison to prior response assessment) was 16 days (95% CI 9, 83). Also for the Day-28 responders, the median time from Day-28 response to either death or need for new therapy for acute GVHD (additional salvage therapy or increase in steroids) was 173 days (95% CI 66, NE).

Table 20: Day-28 Overall Response Rate for Patients with Steroid-Refractory Acute GVHD in Study 4

	Refractory to Steroids Alone (n=49)
Overall Response (%) (95% CI)	28 (57.1%) (42.2, 71.2)
Complete Response	15 (30.6%)
Very Good Partial Response	2 (4.1%)
Partial Response	11 (22.4%)

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
1801 Augustine Cut-off
Wilmington, DE 19803

Patient Information
JAKAFI® (JAK-ah-fye)
(ruxolitinib)
tablets

What is Jakafi?

Jakafi is a prescription medicine used to treat:

- adults with certain types of myelofibrosis (MF).
- adults with polycythemia vera (PV) who have already taken a medicine called hydroxyurea and it did not work well enough or they could not tolerate it
- adults and children 12 years of age and older with acute graft versus host disease (GVHD) who have taken corticosteroids and they did not work well enough.

It is not known if Jakafi is safe or effective in children for treatment of myelofibrosis or polycythemia vera.

Before taking Jakafi, tell your healthcare provider about of your medical conditions, including if you:

- have an infection
- have or had tuberculosis (TB), or have been in close contact with someone who has TB
- have or had hepatitis B
- have or have had liver problems
- have or have had kidney problems or are on dialysis. If you are on dialysis, Jakafi should be taken after your dialysis
- have high level of fat in your blood (high blood cholesterol or triglycerides)
- have had skin cancer in the past
- are pregnant or plan to become pregnant. It is not known if Jakafi will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Jakafi passes into your breast milk. Do not breastfeed during treatment with Jakafi and for 2 weeks after the final dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Taking Jakafi with certain other medicines may affect how Jakafi works. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take Jakafi?

- Take Jakafi exactly as your healthcare provider tells you.
- Do not change your dose or stop taking Jakafi without first talking to your healthcare provider.
- You can take Jakafi with or without food.
- Jakafi may also be given through certain nasogastric tubes.
  - Tell your healthcare provider if you cannot take Jakafi by mouth. Your healthcare provider will decide if you can take Jakafi through a nasogastric tube.
  - Ask your healthcare provider to give you specific instruction on how to properly take Jakafi through a nasogastric tube.
- If you miss a dose of Jakafi, take your next dose at your regular time. Do not take 2 doses at the same time.
- If you take too much Jakafi call your healthcare provider or go to the nearest hospital emergency room right away.
- You will have regular blood tests during your treatment with Jakafi. Your healthcare provider may change your dose of Jakafi or stop your treatment based on the results of your blood tests.

What are the possible side effects of Jakafi?

Jakafi can cause serious side effects including:

Low blood cell counts. Jakafi may cause low platelet counts (thrombocytopenia), low red blood cell counts (anemia), and low white blood cell counts (neutropenia). If you develop bleeding, stop Jakafi and call your healthcare provider. Your healthcare provider will do a blood test to check your blood cell counts before you start Jakafi and regularly during your treatment with Jakafi. Tell your healthcare provider right away if you develop or have worsening of any of these symptoms:

- unusual bleeding
- bruising
- tiredness
- shortness of breath
- fever

Infection. You may be at risk for developing a serious infection during treatment with Jakafi. Tell your healthcare provider if you develop any of the following symptoms of infection:

- chills
- aches
- fever
- nausea
- vomiting
- weakness
- painful skin rash or blisters

Skin cancers. Some people who take Jakafi have developed certain types of non-melanoma skin cancers. Tell your healthcare provider if you develop any new or changing skin lesions during treatment with Jakafi.

Cholesterol increases. You may have changes in your blood cholesterol levels. Your healthcare provider will do blood tests to check your cholesterol levels during treatment with Jakafi.

The most common side effects of Jakafi in adults with certain types of MF and PV include:

- low platelet counts (thrombocytopenia)
- low red blood cell counts (anemia)
- bruising
- dizziness
- headache

The most common side effects of Jakafi in people with acute graft versus host disease (GVHD) include:

- low red blood cell counts (anemia)
- low platelet counts (thrombocytopenia)
- low white blood cell counts (neutropenia)
- infections
- fluid retention

These are not all the possible side effects of Jakafi.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Incyte Corporation at 1-855-463-3463.

How should I store Jakafi?

- Store Jakafi at room temperature 68°F to 77°F (20°C to 25°C).

Keep Jakafi and all medicines out of the reach of children.

General information about the safe and effective use of Jakafi.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information. Do not use Jakafi for a condition for which it is not prescribed. Do not give Jakafi to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information that is written for healthcare professionals.

What are the ingredients in Jakafi?

Active ingredient: ruxolitinib phosphate

Inactive ingredients: microcrystalline cellulose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxypropyl cellulose

Manufactured for: Incyte Corporation, 1801 Augustine Cut-off, Wilmington, DE 19803

U.S. Patent Nos. 7598257; 8415362; 8722693; 8822481; 8829013; 9079912; 9814722; 10016429

For more information call 1-855-463-3463 or go to www.jakafi.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: May 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202192Orig1s017

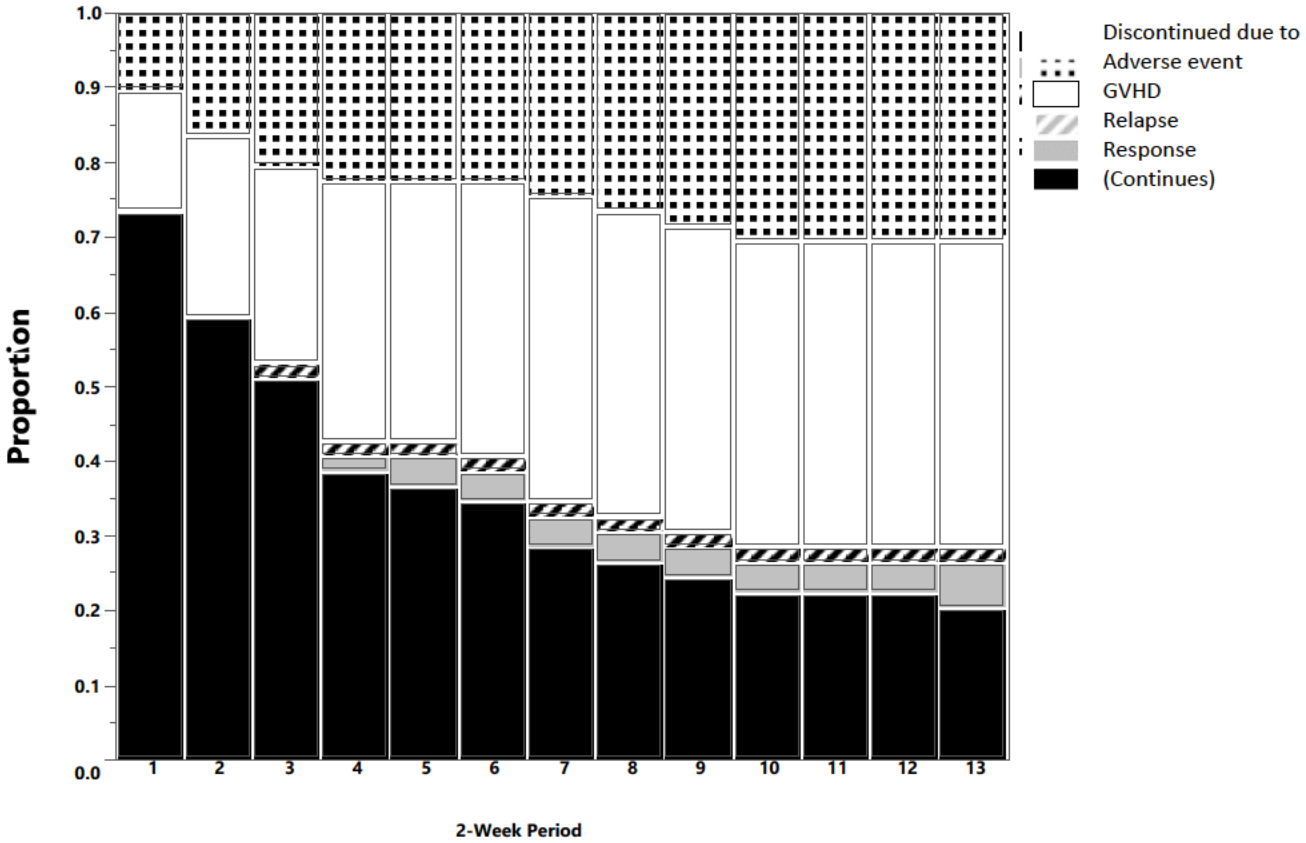
MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multidisciplinary Review and Evaluation Addendum

Application Number	**NDA 202192 S-017**
Application Type	SE1
Priority or Standard	Priority
Received Date	8/24/2018
PDUFA Goal Date	5/24/2019
Office/Division	OHOP/DHP
Review Completion Date	5/26/2019
Applicant	Incyte Corporation
Established Name	Ruxolitinib
Trade Name	Jakafi
Pharmacologic Class	Kinase inhibitor
Formulations	Tablet (5 mg, 10 mg, 15 mg, 20 mg, 25 mg)
Dosing Regimen	5 mg BID with increase to 10 mg BID after 3 days in the absence of toxicity

Figure 11: Proportion of Patients Discontinuing by Reason Over Time



Source: FDA analysis
Includes only the 49 patients who failed steroids alone.

The legend for Figure 11 in the original multidisciplinary review did not format correctly upon completion of the review. The figure with the properly formatted legend is above.

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/s/

DONNA PRZEPIORKA
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Applicant Proposed Indication/Population	For treatment of patients with acute graft versus host disease (GVHD) who have had an inadequate response to corticosteroids
Recommendation on Regulatory Action	Regular Approval
Recommended Indication/Population	For treatment steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years and older.

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GI	gastrointestinal
GRMP	good review management practice
GVHD	Graft versus host disease
HSCT	allogeneic hematopoietic stem cell transplantation
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

ITT	intent to treat
MAGIC	Mount Sinai acute GVHD international consortium
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NRM	non-relapse mortality
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PBSC	peripheral blood stem cell
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PV	polycythemia vera
REG3α	regenerating islet-derived 3α
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
ST2	suppression of tumorigenicity 2
TEAE	treatment emergent adverse event
VGPR	very good partial response

1 Executive Summary

1.1 Product Introduction

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

Jakafi is approved for treatment of patients with intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF, and for treatment of patients with polycythemia vera (PV) who have had an inadequate response to or are intolerant of hydroxyurea. Supplement 017 was submitted for the proposed indication of treatment of patients with acute graft versus host disease (GVHD) who have had an inadequate response to corticosteroids.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of ruxolitinib under 21 CFR 314.105 for the treatment of steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years and older using ruxolitinib 5 mg BID as the starting dose with the target of increasing to 10 mg BID after 3 days in the absence of toxicity. The recommendation is based on the Day-28 overall response rate (ORR) and demonstration of durability of the responses in Study INCB 18424-271 (Study 271; REACH1; NCT02953678).

Study 271 was an open-label, single-arm, multicenter study of ruxolitinib for treatment of patients with steroid-refractory acute GVHD Grades 2 to 4 (Mount Sinai Acute GVHD International Consortium (MAGIC) criteria) occurring after allogeneic hematopoietic stem cell transplantation. Ruxolitinib was administered at 5 mg twice daily, and the dose could be increased to 10 mg twice daily after 3 days in the absence of toxicity. The statistical analysis plan (SAP) prespecified that the results needed to exclude a 40% ORR rate; additionally, a 60% ORR rate was considered clinically meaningful. There was one planned futility analysis when 35 patients (50% of the accrual target) completed the Day-28 visit. The results of the futility analysis did not trigger the rule, and the study was continued. The final analysis was ORR was

to be performed when enrollment was met and all subjects completed the Day 28 response assessments or discontinued earlier. Additional follow-up through Day-180 was needed to establish durability of the responses.

For the purposes of establishing efficacy in the intended population, FDA's analysis included only patients with acute GVHD progressed after 3 days of treatment with methylprednisolone 2 mg/kg/day equivalent, did not improve after 7 days of treatment with methylprednisolone 2 mg/kg/day equivalent, progressed to a new organ after treatment with methylprednisolone 1 mg/kg/day equivalent for skin and upper GI GVHD, or recurred during or after a steroid taper, and no treatment of acute GVHD other than corticosteroids was used. There were 49 patients with acute GVHD refractory to steroids alone in the analysis population. These patients had a median age of 57 years (range, 18-72 years), 47% were male, 92% were Caucasian, and 14% were Hispanic. At baseline, acute GVHD was Grade 2 in 27%, Grade 3 in 55% and Grade 4 in 18%; 84% had visceral GVHD; the median MAGIC biomarker score was 0.47 (range, 0.10 - 0.92); and the median ST2 level was 334 mcg/L (range, 55 - 1286 mcg/L). The median duration of prior corticosteroid exposure at baseline was 15 days (range: 3 – 106 days).

The FDA-adjudicated Day-28 ORR as 57.1% (95% CI: 42.2, 71.2); Day-28 ORR was 100% for Grade 2 GVHD, 41.4% for Grade 3 GVHD and 44.4% for Grade 4 GVHD. The median follow-up for responders was 5.2 months (range, 1.1 - 14.4 months). The median duration of response, calculated from Day-28 response to progression, new salvage therapy for acute GVHD or death from any cause (with progression being defined as worsening by one stage in any organ without improvement in other organs in comparison to prior response assessment) was 0.5 months (95% CI 0.3, 2.7 months). Also for the responders, the median time to either death or need for new therapy for acute GVHD (additional salvage therapy or increase in steroids) was 5.7 months (95% CI 2.2, NE).

It can be challenging to establish efficacy in a single-arm trial. In this case, however, where the disease is life-threatening, there are no available therapies, the efficacy endpoint is objective, the activity of the drug is established in other diseases, and there is a substantial safety database, FDA was inclined to accept the results of Study 271 as the sole basis of efficacy in this application. The Day-28 ORR of 57.1% with a lower bound of 42.2% was considered adequate. Although the median DOR is quite short, the definition of DOR does not take into account that GVHD may flare and resolve without additional treatment. The additional measure of median time to either death or need for new therapy for acute GVHD of 5.7 months is considered a meaningful representation of durability of the response.

On the basis of biology of GVHD and mechanism of action of ruxolitinib, the efficacy of ruxolitinib for pediatric patients with this indication can be extrapolated from adequate and well-controlled studies in adults.

1.3 Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Steroid-refractory acute GVHD that goes untreated is nearly uniformly fatal.	Patients with steroid-refractory acute GVHD have a poor prognosis.
Current Treatment Options	• There are no therapies approved for treatment of steroid-refractory acute GVHD. • Immunosuppressive drugs are used off-label, but the risks and benefits of drugs used off-label are not well-characterized. • There is no accepted optimal second-line therapy.	There is a need for therapies for patients with steroid-refractory acute GVHD.
Benefit	• In Study 271, 49 adults with steroid-refractory acute GVHD were treated with ruxolitinib starting at 5 mg BID in addition to continuing background therapy, including corticosteroids. • Day-28 ORR as 57.1% (95% CI: 42.2, 71.2) • The median duration of response was 0.5 months (95% CI 0.3, 2.7 months) • The median time to either death or need for new therapy for acute GVHD was 5.7 months (95% CI 2.2, NE)	The magnitude of ORR and durability of response to treatment demonstrates that ruxolitinib is active in this disease.
Risks and Risk Management	• The safety population included 71 adults on Study 271. • A fatal infection occurred in 14% and a fatal hemorrhage in 4%. • The most common adverse reactions were infections, edema, hemorrhage, fatigue, bacterial infections, dyspnea, viral infections, thrombosis, diarrhea, rash and headache. • The most common laboratory abnormalities were anemia, thrombocytopenia and neutropenia. • Patients on the protocol were monitored for safety events and received prophylactic antibiotics.	The major potential risks of cytopenias, infections and hemorrhage can be mitigated through labeling.

Patients with steroid-refractory acute GVHD have a poor prognosis. In Study 271, 57.1% achieved ORR at Day 28; although the DOR was short (0.5 months), the alternate measure of durability using time to death or new therapy was clinically meaningful at 5.7 months.

The major toxicities of ruxolitinib stem are the cytopenias and immunosuppression. Although these effect may be contributing factors in infection and hemorrhage, with the high background rate of these event in patients with GVHD and in the absence of a randomized control for comparison, it was not possible to clearly confirm a causal association. Hence, there were no deaths that could be attributed directly to ruxolitinib. Close monitoring of blood counts is routine practice in this population, but the risk of infections noted warrants adding a recommendation for active surveillance and prophylactic antibiotics to the warning about infections.

On the basis of biology of GVHD and mechanism of action of ruxolitinib, the efficacy of ruxolitinib for pediatric patients with this indication can be extrapolated from the adult

experience, and safety of ruxolitinib is described in labeling down to age 2 years. However, the formulation (5 mg tablets) limits the use to patients comparable in size to adults; traditionally, this is 12 years of age.

Given the observed response rate, and with the labeling modifications in place, the clinical benefit of ruxolitinib appears to outweigh the risks for treatment of steroid-refractory acute GVHD in adult and pediatric patients 12 years and older.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application

						Section where discussed, if applicable
□	The patient experience data that was submitted as part of the application, include:					
	□	Clinical outcome assessment (COA) data, such as				
			□	Patient reported outcome (PRO)		
			□	Observer reported outcome (ObsRO)		
			□	Clinician reported outcome (ClinRO)		
			□	Performance outcome (PerfO)		
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)				
	□	Patient-focused drug development or other stakeholder meeting summary reports				
	□	Observational survey studies designed to capture patient experience data				
	□	Natural history studies				
	□	Patient preference studies (e.g., submitted studies or scientific publications)				
	□	Other: (Please specify)				
□	Patient experience data that was not submitted in the application, but was considered in this review.					
X	Patient experience data was not submitted in the application.					

Donna Przepiorka, MD, PhD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

The Center for International Blood and Marrow Transplant Research (CIBMTR) estimates there are approximately 8000 allogeneic blood and bone marrow transplantations performed in the United States annually according to 2017 data (D'Souza A et al, 2018). Acute GVHD after transplantation results when donor T cells and inflammatory cytokines attack recipient target tissues such as skin, gut and liver. There are several generally accepted risk factors for the development of aGVHD identified**.** Risk factors include degree of donor vs. recipient HLA disparity, gender disparity as well as the source of the graft, conditioning regimen intensity and aGVHD prophylaxis regimen used (Jagasia et al 2012). Acute GVHD affects approximately 10-50% of allogeneic hematopoietic stem cell transplant recipients. Therefore, approximately 800-4000 patients will experience aGVHD in the United States each year. A more precise incidence of aGVHD is difficult to ascertain as there is known intra- and inter-institution variability in diagnosis and management of aGVHD.

The standard-of-care first-line treatment for Grades 2 - 4 aGVHD is methylprednisolone 2 mg/kg/day in divided doses (Martin et al. 2012). Patients are often treated for several weeks and tapered over several months (Deeg 2007). Approximately 25-40% of patients have a complete response to such therapy. Therefore, 60-75% of patients (up to 3000 patients per year assuming 75% of up to 4000 patients) do not respond to upfront steroid therapy.

Patients who do not respond within 7 days or have progression of aGVHD after 3 days are defined as having steroid-refractory (SR-aGVHD) (Martin et al. 2012). Patients with SR-aGVHD have poor prognosis, especially those with grade III or IV disease. It is estimated that SR-aGVHD is responsible for 70% of deaths post allogeneic hematopoietic stem cell transplantation (Weisdorf et al. 1990). Serum biomarkers, such as ST2 and REG3alpha, have also been shown to be prognostic (Major-Monfried et al. 2018).

For treatment of aGVHD, CR+PR at day 28 is a recognized efficacy endpoint (NIH-FDA aGVHD Endpoint Workshop, 2009; Pavletic, 2012), and response criteria have been established (Martin et al. 2009).

2.2 Analysis of Current Treatment Options

There are no drugs approved specifically for the treatment of SR-aGVHD. Many immuno-suppressive agents have been evaluated in an investigational capacity or by off-label use for SR-aGVHD (Martin et al. 2012). There is no evidence at this time to suggest that any of the agents evaluated are more efficacious than the others. An analysis of 29 studies of therapy for SR-

aGVHD revealed that the weighted average 6-month OS was 49%, the overall response (CR+PR) was asymptotically 58%, and the asymptotic CR rate was 32% (Martin et al. 2012). There were only 2 studies in this series that reported Day-28 response with response specifically excluding further systemic treatment. In these 2 studies included 101 patients; the CR rate was 20%, CR+PR 18-54%, and 6-month OS 44%.

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Ruxolitinib was approved on 11/16/11 for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera and for patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea on 12/4/14. Ruxolitinib (Jakafi) is marketed in the United States and as "Jakavi" abroad.

3.2 Summary of Presubmission/Submission Regulatory Activity

Significant regulatory activities relevant to the development program for treatment of aGVHD are summarized in the table below.

Date	Summary of Regulatory Activity
6/16/16	IND 077456 SPA for INCB 184240271 pivotal phase II trial received
6/22/16	(b) (4)
7/29/16	Agency issued no agreement letter for SPA
9/27/16	Type A meeting SPA
9/27/16	Type B meeting ruxolitinib clinical development plan for GVHD
10/10/16	Revised Protocol INCB 184240271 received
11/03/16	Orphan Drug Designation granted for treatment of graft-versus-host disease
12/1/16	FDA requested expanded access protocol
4/28/17	Expanded access protocol INCB 18424-MA-GD-301 submitted
5/26/17	Expanded access protocol INCB 18424-MA-GD-301 approved
6/30/17	Expanded access protocol INCB 18424-MA-GD-301 amended
5/27/18	Type B meeting- Agency provided pre-sNDA comments regarding PK plan
5/31/18	Agency agreed to the revised PK plan
8/24/18	Supplement 17 submitted for the indication of SR-aGVHD

Key advice for the clinical development included:

- The Agency issued a no agreement letter for an SPA request. The Agency addressed 7 key points regarding study design, including acceptable inclusion criteria, ruxolitinib dose modifications and endpoints. [Type A SPA Meeting 9/27/2016]

- The Agency addressed how raw data regarding GVHD staging and grading should be submitted to ensure that enrollment criteria and response assessment could be recapitulated at key time points. [Type B meeting 5/27/2018]

- The Agency also agreed that the sNDA could be submitted when all the subjects in the pivotal study, INCB 18424 271, completed 3 months of follow-up. The proposal to submit the additional duration of response data with at least 6 months of follow-up along with the 4-month safety report was also deemed acceptable. [Type B meeting 5/27/2018]

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

Three clinical study sites (sites 015, 016 and 033) and the Applicant were inspected by OSI. The study sites were selected based on the number of patients enrolled and the large treatment effect size at the site. The regulatory classification for these inspections was No Action Indicated (NAI). OSI concluded that the study data from these clinical sites are considered to be reliable in support of the requested indication. See Section 8.1.1 regarding the systematic data integrity issues identified by the review team and corrected in the major amendment.

4.2. Product Quality

There in no new product quality information in this supplement. The Applicant claimed a categorical exclusion from the requirements to prepare an environmental assessment or an environmental impact statement in accordance with 21 CFR 25.31(b), and the Product Quality Review team recommended that the categorical exclusion be granted.

4.3 Devices and Companion Diagnostic Issues

There are no proposed companion or complementary diagnostics for the new indication.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

The Pharmacology/Toxicology data for ruxolitinib supporting the approval and labeling of Ruxolitinib was reviewed under NDA 202192. The ruxolitinib prescribing information (label) contains the relevant nonclinical data needed for prescribing. For the current supplement 17 (S-017), the Applicant is proposing a new indication for the treatment of patients with acute graft versus host disease (GVHD) who have had an inadequate response to corticosteroids and labeling revisions in support of new indication. Nonclinical study reports include evaluation of preclinical activity and pharmacodynamic activity of ruxolitinib in a MHC-mismatched mouse model of GVHD in support of labeling revisions.

GVHD was induced in BALB/c mice using a single acute dose of 8 Gy of total body irradiation followed by IV injection of bone marrow and splenic cells from a donor C57BL/6 or BALB/c mice to allogeneic group or syngeneic recipients, respectively. Vehicle or ruxolitinib (60 mg/kg twice a day) were administered orally on Day -3 (prophylactically) or Day 14 (therapeutically). In the allogeneic animals dosed with ruxolitinib, a significantly reduced weight loss and reduced overall GVHD scores were observed compared to allogeneic vehicle control group. Statistically significant reductions in the levels of cytokines and pharmacodynamic biomarkers (modulation of JAK/STAT3/STAT5 signaling) were observed in the ruxolitinib-treated group. Switching treatment to ruxolitinib from corticosteroids treatment had improved body weight gain, lower average overall GVHD scores, and increase in percent survival compared to vehicle control-treated animals.

5.2 Referenced NDAs, BLAs, DMFs

NDA 202192

5.3 Pharmacology

The Applicant submitted a summary of results of several non-GLP experiments conducted to investigate the effects of ruxolitinib on preclinical activity and pharmacodynamics in a MHC-mismatched mouse model of acute GVHD. It is not clear from the report the number of studies, dosing groups and number of animals in each group used in the studies.

Report title: Summary Report: Evaluation of the Preclinical Efficacy and Pharmacodynamic Activity of Ruxolitinib in a MHC-Mismatched Mouse Model of Acute Graft-Versus-Host Disease

Major histocompatibility complex (MHC) is a cluster of highly polymorphic genes that encode proteins involved in antigen presentation and are important for enabling the immune system to differentiate between self and foreign tissues. MHC class I enables presentation of mainly endogenous antigens to CD8+ T cells, whereas MHC class II enables presentation of mainly exogenous antigens to CD4+ T cells. Most mouse models of aGvHD (Table 1) involve the transplantation of T-cell-depleted bone marrow supplemented with varying numbers and phenotypic classes of donor lymphocytes (either splenocytes or lymph node T cells) into lethally irradiated recipients. (Schroeder and DiPersio 2011).[1]

Table 1: Characteristics MHC-mismatched of mouse model of graft-versus-host disease

Table 1. Mouse models of aGvHD

Donor strain	Recipient strain	Conditioning regimen	Genetics	Main T-cell type contributing to phenotype	Cell type and dose	Outcome	Reference example(s)
MHC mismatched							
C57/Bl6 ($H2^b$)	BALB/c ($H2^d$)	900 cGy	Mismatched for MHCI, MHCII and miHAs	$CD4^+$ and $CD8^+$	Splenic T cells ($0.5\text{-}2\times10^6$) and TCD donor BM cells	Systemic disease by 10-21 days; lethal	van Leeuwen et al., 2002

(Excerpted from Schroeder and DiPersio 2011)

Janus kinases (JAKs) are intracellular signaling molecules that regulate GVHD. A variety of cytokines that signal through the JAK signaling pathways play a role in regulating the development, proliferation, and activation of several immune cell types important for GVHD pathogenesis, including dendritic cells, macrophages, T cells, B cells, and neutrophils (*Schroeder and DiPersio 2011)*.

GVHD was induced in BALB/c mice using a single acute dose of 8 Gy of total body irradiation (TBI) on Day -1.

Day-0: The syngeneic recipients (vehicle and ruxolitinib D-3) were given an intravenous injection of a combination of splenocytes and T-cell–depleted bone marrow cells from BALB/c mice in sterile 1× PBS. The allogeneic group (vehicle and ruxolitinib D-3 and D14) received bone marrow and splenic cells obtained from donor male C57BL/6 or BALB/c mice. Animals were dosed with vehicle or ruxolitinib (60 mg/kg BID) by oral gavage. Blood samples were collected twice a week and plasma was separated for FACS analysis.

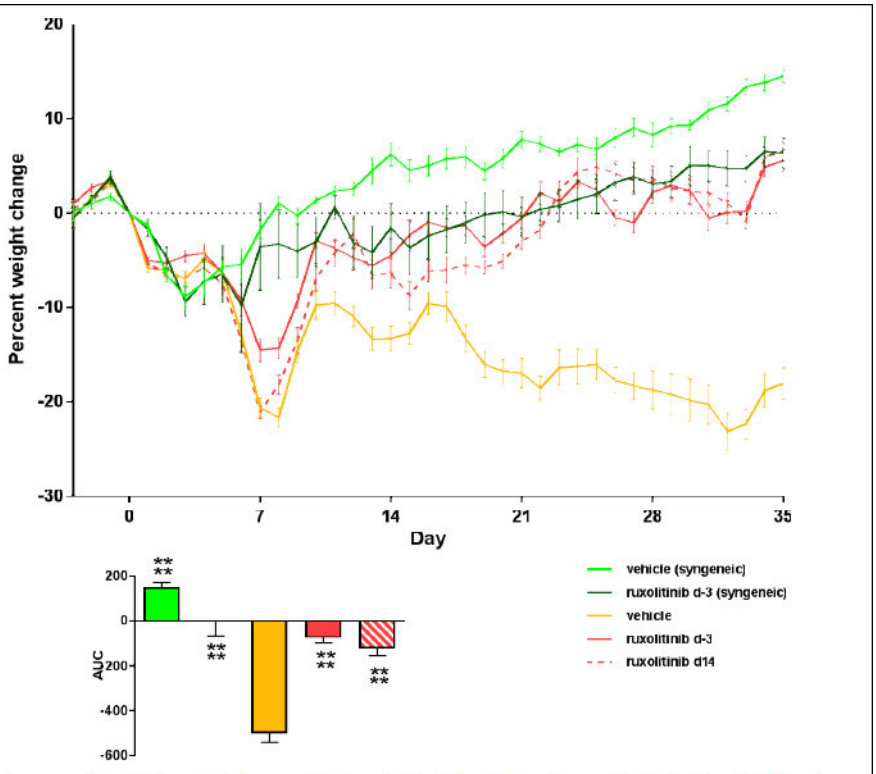
All animals were monitored daily for weight change, survival, GVHD score (activity, posture, fur

[1] Schroeder M.A. and DiPersio J.F. Mouse models of graft-versus-host disease: advances and limitations. Disease Models & Mechanisms 4, 318-333 (2011).

texture, and skin integrity of the mice that develop disease including body weight loss) and incidence of diarrhea and bloody stool. Colon tissues were collected from all surviving animals to measure inflammatory protein levels of IFNγ, IL-1β, and TNFα in the tissue homogenates and immunohistochemistry (IHC) for CD3, CD4, CD8, pSTAT3, and pSTAT5.

Animals were made refractory to corticosteroids by administration of prednisolone (at 1.0, 0.3, and 0.1 mg/kg) starting on Day 14. Treatment 1 (vehicle, prednisolone [0.1, 0.3 or 1 mg/kg], or ruxolitinib [60 mg/kg BID]) was administered from Day 14 until disease became refractory (Day 31). Following onset of refractory period, Treatment 1 was halted and Treatment 2 (vehicle or ruxolitinib 60 mg/kg BID) began and was continued until the conclusion of the study (Day 56). Animals were sacrificed on Day 56.

Figure 1: Percent Body Weight Change in GVHD Mouse Models Treated with Ruxolitinib



Animals were weighed daily and their percent body weight relative to Day -4 was calculated. The AUC (inset) was calculated to enable effective comparison of groups by statistical test.
****$p \leq 0.0001$ in comparison to allogeneic vehicle group, all evaluations as determined by 1-way ANOVA with Holm-Šidák's multiple comparison post-test used discern statistically significant differences between groups. Data are presented as mean ± SEM.

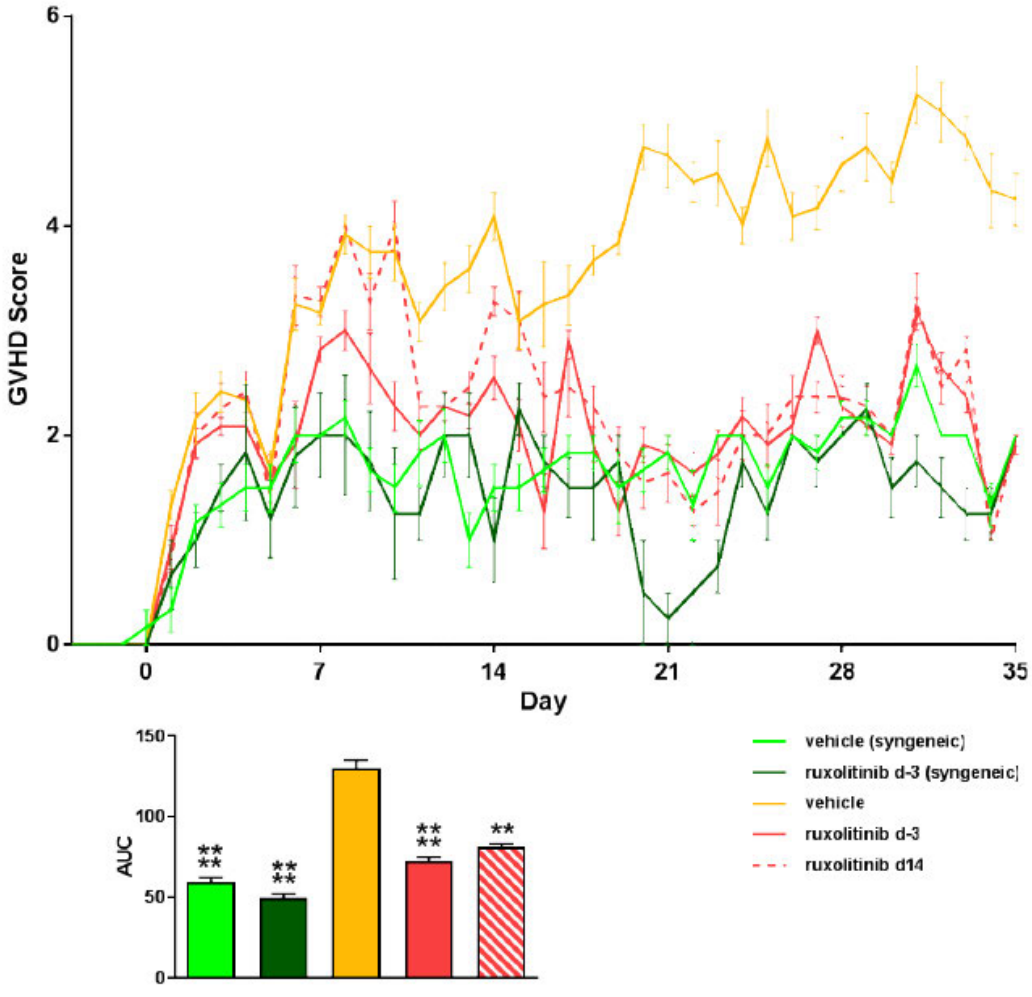
(Excerpted from Applicant's NDA)

GVHD Scores:

The report did not provide the details of the GVHD scores for activity, posture, fur texture, and skin integrity of the mice that develop disease. In patients, skin appears to be the most

common and the first affected organ during GVHD, characterized by a maculopapular rash[2].

Figure 2: Change in GVHD Score in GVHD Mouse Models Treated with Ruxolitinib



Animals were scored daily from Day 0 until the study conclusion. The AUC (inset) was calculated to enable effective comparison of groups by statistical test.
**p ≤ 0.01, ****p < 0.0001 as assessed by Kruskal-Wallis test with Dunn's multiple comparison test comparing all groups to the allogeneic vehicle group (Group 3). Data are presented as mean ± SEM.

(Excerpted from Applicant's NDA)

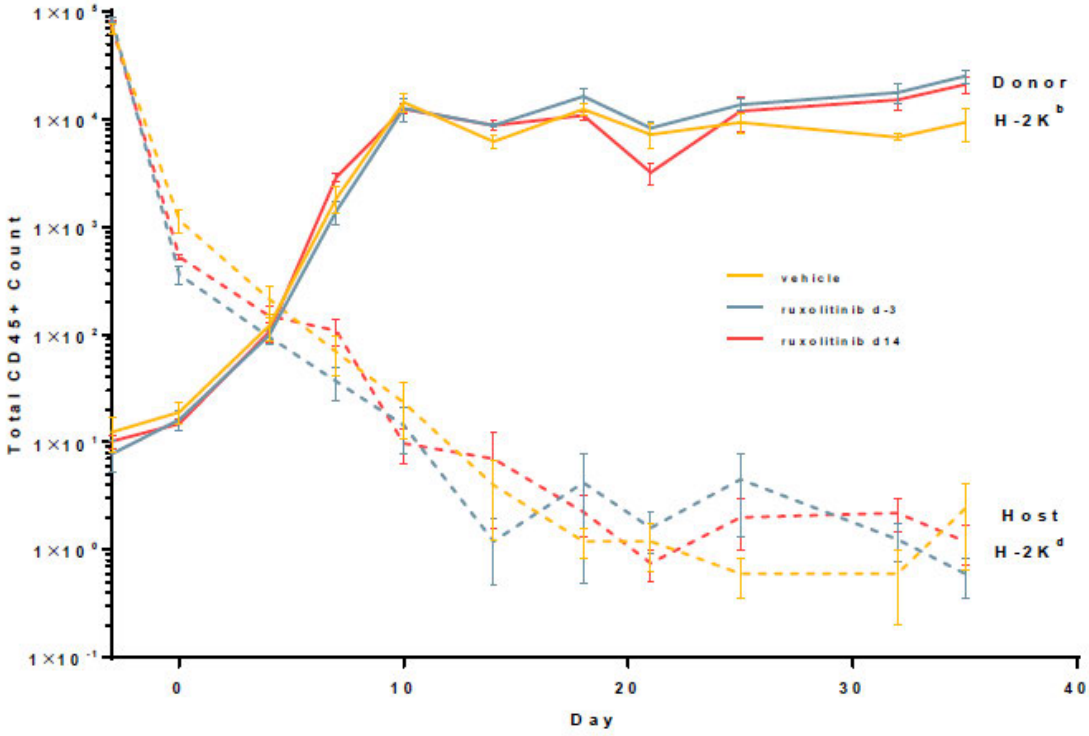
Engraftment

The blood was centrifuged to collect plasma, and the pellet was resuspended and processed for

[2] Riesner K. et al (2016) A preclinical acute GVHD mouse model based on chemotherapy conditioning and MHC-matched transplantation. Bone Marrow Transplantation 51, 410–417.

fluorescent activated cell sorting (FACS) analysis to assess engraftment. Cells were analyzed for the proportion of donor and host leukocytes (CD45, H-2Kb, and H-2Kd). The results show donor leukocytes (CD45+, H-2Kb) steadily increased between Day 0 (day of transfer) and Day 10, plateauing at approximately in number compared to host leukocytes (CD45+, H-2Kd).

Figure 3: Peripheral Blood FACS Analysis for host leukocytes and donor



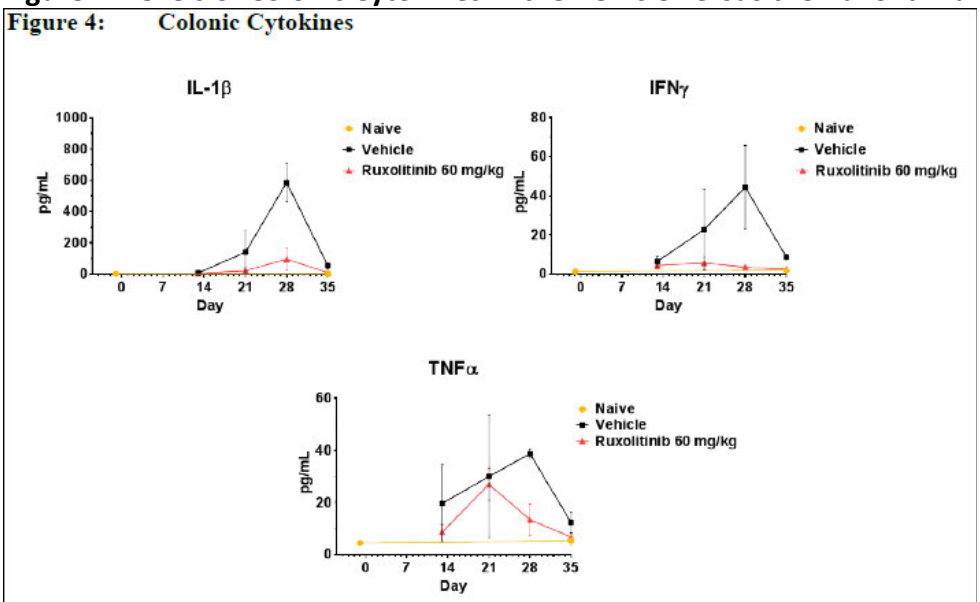
Blood was collected by retro-orbital bleed analyzed for the proportion of donor and host leukocytes (CD45, H-2K^b, H-2K^d) by flow cytometry. Data are presented as mean ± SEM.

(Excerpted from Applicant's NDA)

Cytokines

The levels of cytokines were significantly reduced in ruxolitinib treated animals compared to vehicle controls.

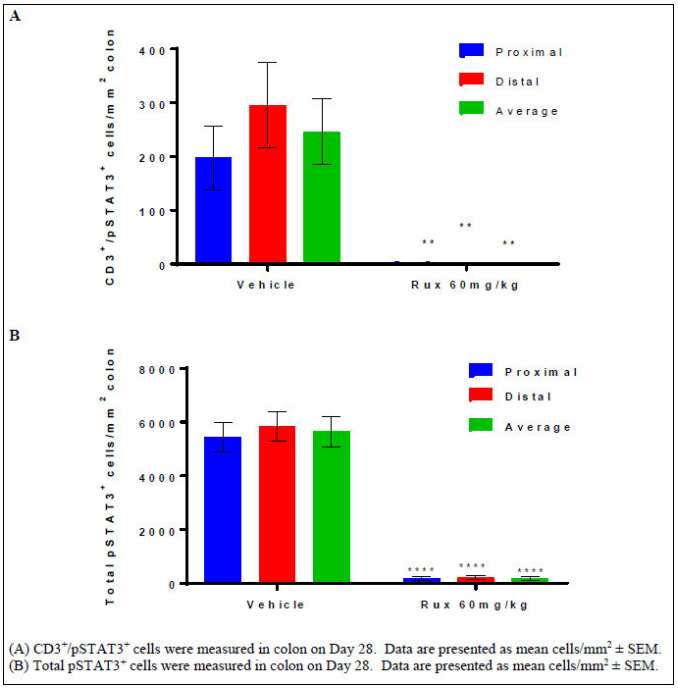
Figure 4: Levels of Colonic Cytokines in the Vehicle versus the Ruxolitinib-Treated Animals



(Excerpted from Applicant's NDA)

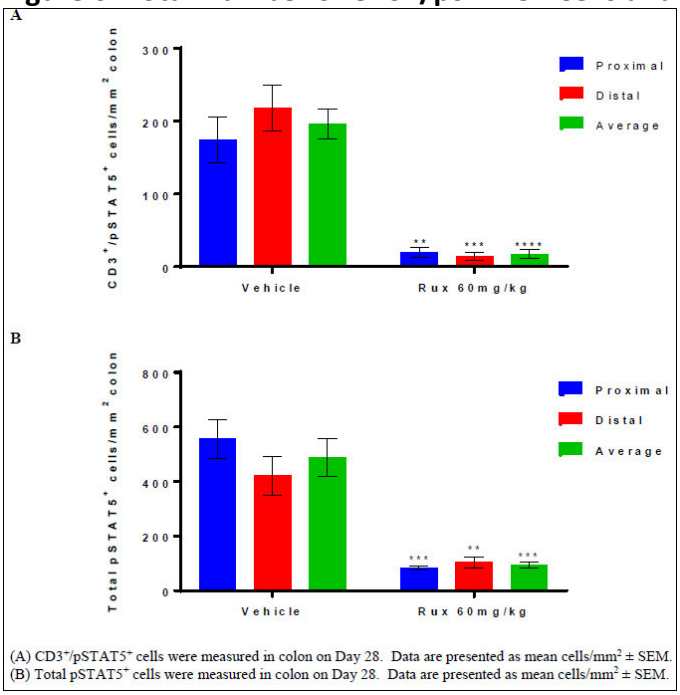
Colon Immunohistochemistry and Pharmacodynamics

Figure 5: Total Number of CD3+/pSTAT3+ Cells and pSTAT3+ Cells



(Excerpted from Applicant's NDA)

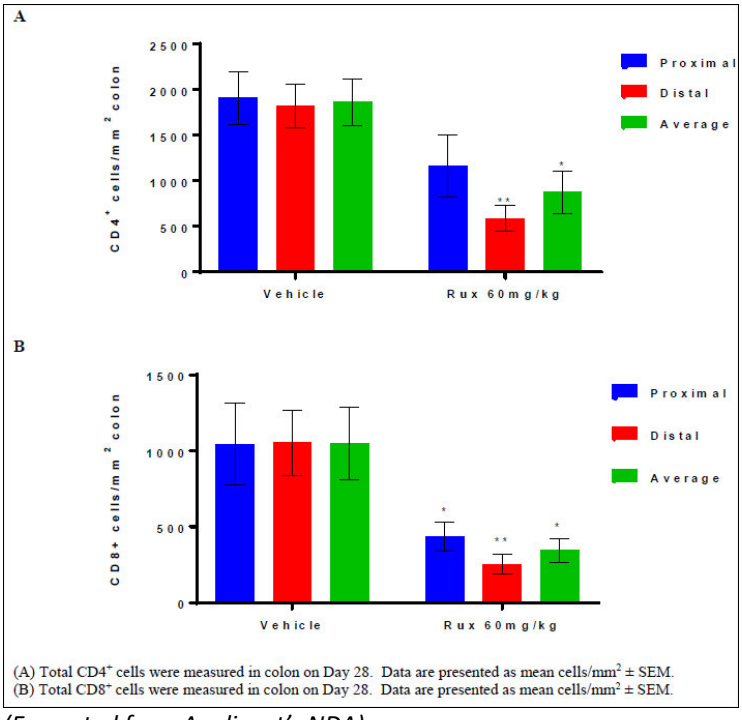
Figure 6: Total Number of CD3+/pSTAT5+ Cells and pSTAT5+ Cells



(A) $CD3^+/pSTAT5^+$ cells were measured in colon on Day 28. Data are presented as mean cells/mm^2 ± SEM.
(B) Total $pSTAT5^+$ cells were measured in colon on Day 28. Data are presented as mean cells/mm^2 ± SEM.

(Excerpted from Applicant's NDA)

Figure 7: Total Number of CD4+ Cells and CD8 Cells

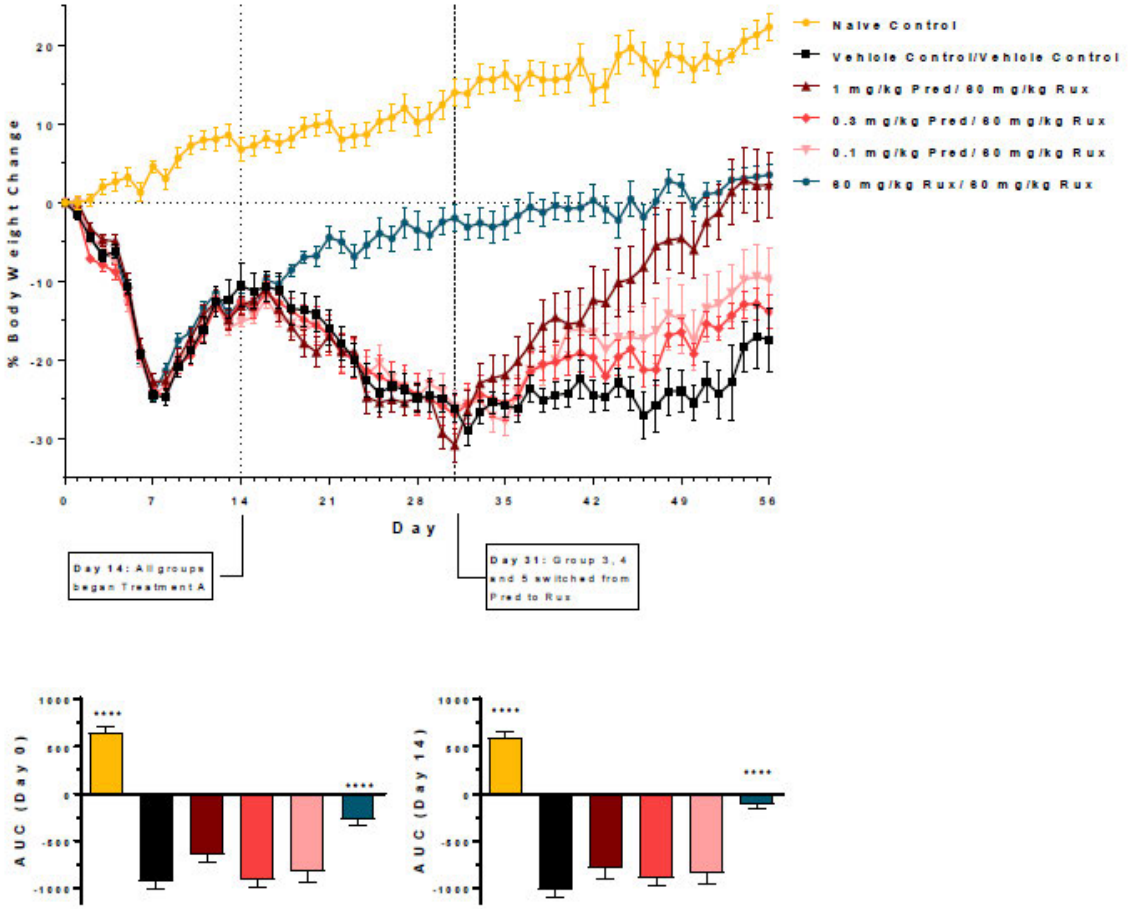


(A) Total $CD4^+$ cells were measured in colon on Day 28. Data are presented as mean cells/mm^2 ± SEM.
(B) Total $CD8^+$ cells were measured in colon on Day 28. Data are presented as mean cells/mm^2 ± SEM.

(Excerpted from Applicant's NDA)

Corticosteroid Refractory Model (Body Weight Change)

Figure 8: Percent Body Weight Change (Corticosteroid Refractory Model)

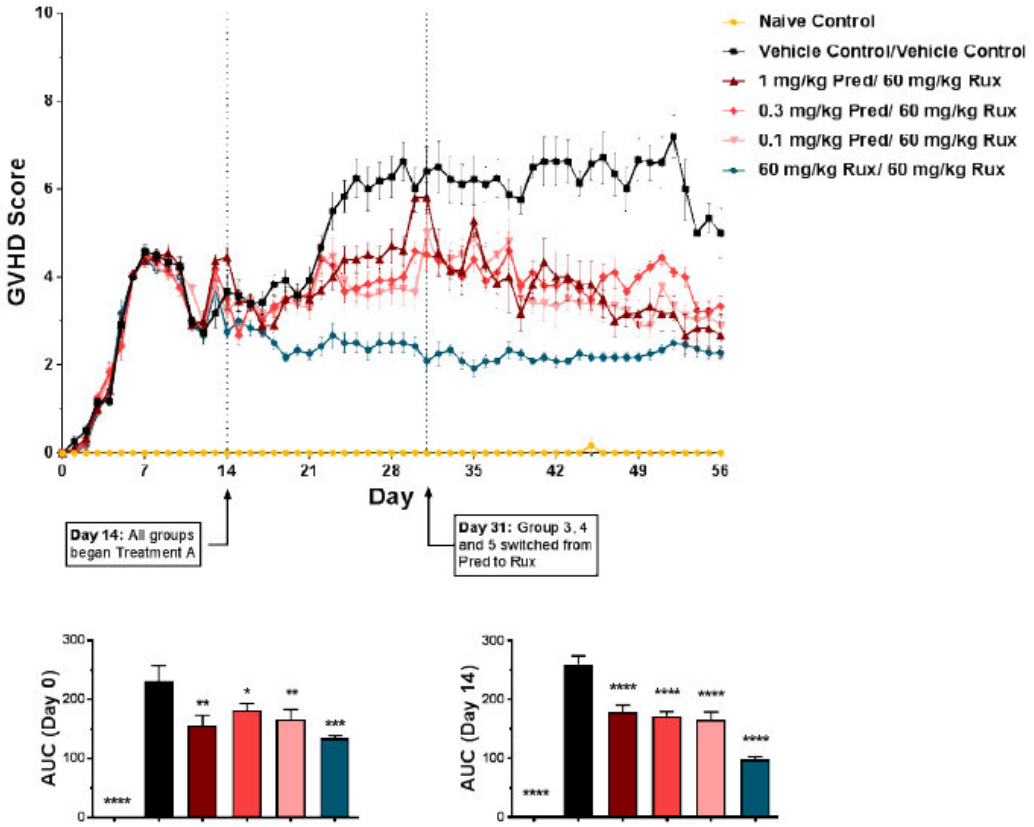


Animals were weighed daily and their percent body weight relative to Day 0 was calculated. The AUC (inset) was calculated from Days 0-56 or Days 14-56 to enable effective comparison of groups by statistical test.
****$p < 0.0001$ as determined by 1-way ANOVA with Holm-Šidák's multiple comparison post-test used to discern statistically significant differences between groups. Data is presented as mean ± SEM.

(Excerpted from Applicant's NDA)

Corticosteroid Refractory Model (GVHD Score)

Figure 9: Change in GVHD Score (Corticosteroid Refractory Model)



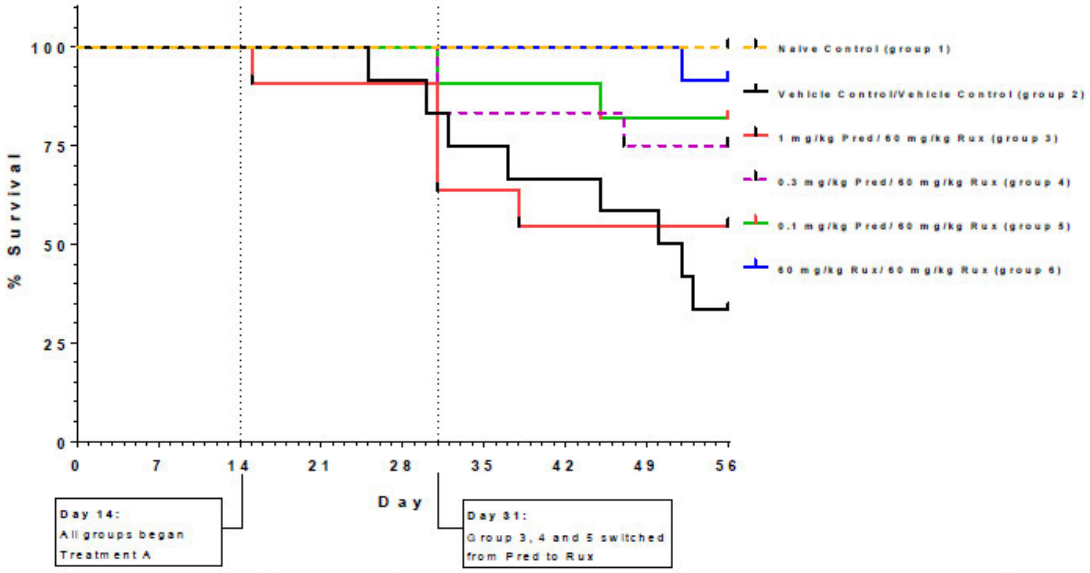
Animals were scored daily according to the protocol shown from either Day 0 or Day 14 until study conclusion on Day 56. The AUC was calculated to enable effective comparison of groups by statistical test.
* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, **** = $p < 0.0001$, as assessed by analysis with Kruskal-Wallis with Dunn's post-hoc test comparing all groups to the vehicle group. Data is presented as mean ±SEM.

(Excerpted from Applicant's NDA)

Overall Survival

Treatment with 60 mg/kg BID ruxolitinib led to a significant increase in percent survival as compared to vehicle-treated animals.

Figure 10: Percent Survival (Day 56) in Ruxolitinb-Treated Animals Compared to Vehicle Control



P-values

	Naïve Control	Veh/Veh	1 mg/kg Pred/ Rux	0.3 mg/kg Pred/ Rux	0.1 mg/kg Pred/ Rux	Rux/ Rux
Naïve Control		0.0141	0.0469	0.1973	0.1997	0.4795
Vehicle Control/Vehicle Control	0.0141		0.7201	0.0591	0.072	0.0024
1 mg/kg Pred/ 60 mg/kg Rux	0.0469	0.7201		0.1631	0.2038	0.0205
0.3 mg/kg Pred/ 60 mg/kg Rux	0.1973	0.0591	0.1631		0.939	0.2571
0.1 mg/kg Pred/ 60 mg/kg Rux	0.1997	0.072	0.2038	0.939		0.253
60 mg/kg Rux/ 60 mg/kg Rux	0.4795	0.0024	0.0205	0.2571	0.253	

Survival was tracked for the duration of the study until Day 56 and percent survival for all groups was plotted. Survival data was analyzed using Log-rank (Mantel-Cox) test, and p-values between groups are displayed in the table. Significant differences are shaded in blue.

(Excerpted from Applicant's NDA)

Secondary Pharmacology

Not applicable

Safety Pharmacology

Not applicable

5.4 ADME/PK

Not applicable

5.5 Toxicology

5.5.1 General Toxicology

Not applicable

5.5.2 Genetic Toxicology

In Vitro Assays in Mammalian Cells
Not applicable

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Not applicable

Other Genetic Toxicity Studies
Not applicable

5.5.3 Carcinogenicity

Not applicable.

5.5.4 Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development
Not applicable

Embryo-Fetal Development
Not applicable

Prenatal and Postnatal Development

Not applicable

5.5.5 Other Toxicology Studies

Not applicable

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Primary Reviewer

Christopher Sheth, PhD.
Team Leader

6 Clinical Pharmacology

6.1 Executive Summary

JAKAFI (ruxolitinib) is a Janus Associated Kinases (JAK) 1 and 2 inhibitor that received approval on November 16, 2011 for the treatment of patients with intermediate or high-risk myelofibrosis (MF), and on December 4, 2014 for the treatment of patients with polycythemia vera (PV) who have had an inadequate response to or are intolerant of hydroxyurea. The approved starting doses for the MF indication are 20 mg twice daily (BID) at baseline platelet count (BPC) >200 x 10^9/L, 15 mg BID at BPC 100-200 x 10^9/L, and 5 mg BID at BPC 50 to <100 x 10^9/L, and for the PV indication is 10 mg BID.

The current review includes evaluation of Supplement 17 submitted to support the proposed indication of acute graft versus host disease (aGVHD) who have had an inadequate response to corticosteroids.

The following key questions were addressed in the review of this efficacy supplement:

- Is the proposed ruxolitinib dosing regimen for the aGVHD indication supported by the pharmacokinetics (PK), efficacy, and safety data in Study INCB 18424-271 (REACH-1)?
- Is the PK of ruxolitinib similar between patients with aGVHD and MF?
- What is the effect of strong CYP3A inhibitors, and fluconazole (CYP3A and CYP2C9 dual inhibitor) on the PK and safety of ruxolitinib and appropriate dose adjustment of ruxolitinib?
- What is the effect of renal and hepatic baseline impairment on the PK and safety of ruxolitinib and appropriate dose adjustment of ruxolitinib?
- What is the effect of liver involvement on the PK and safety of ruxolitinib and appropriate dose adjustment of ruxolitinib?

Recommendations
The proposed JAKAFI starting dosing regimen of 5 mg BID in patients with aGVHD with the dose titration schema based on safety and efficacy is acceptable. From a Clinical Pharmacology standpoint, the sNDA is approvable provided the Applicant and the FDA reach an agreement regarding the labeling language for patients with aGVHD.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness[†]	Trial INCB 18424-271 (REACH-1) (phase 2, patients with aGVHD who had an inadequate response to corticosteroids) demonstrated that overall response rate (ORR) at Day 28 was 54.9% (95% CI: 42.7, 66.8) with a complete response rate of 26.8%.
General dosing instructions	Starting dose of 5 mg orally twice daily, with or without food. A dose increase to 10 mg twice daily should be considered after at least 3 days of treatment if the hematologic parameters are stable.

Dosing in patient subgroups (intrinsic and extrinsic factors)	• Dose adjustment to ruxolitinib 5 mg once daily with co-administration of ketoconazole. Monitor blood counts more frequently for toxicity and dose adjust if necessary with co-administration of itraconazole. No dose adjustments for co-administration of other CYP3A inhibitors. • Dose adjustment to ruxolitinib 5 mg once daily is recommended in patients with moderate (CLcr 30 to 59 mL/min) to severe (CLcr 15 to 29 mL/min) renal impairment, and ruxolitinib 5 mg after a dialysis session in patients with end stage renal disease (ESRD) on dialysis. • No dose adjustments are recommended for patients with mild to severe hepatic impairment based on NCI criteria. • For patients with Stage 3 or 4 liver GVHD, monitor blood counts more frequently for toxicity and consider dose adjustment to ruxolitinib 5 mg once daily.
Labeling	• Dose reduction to 5 mg once daily only when co-administered with of ketoconazole. Monitor blood counts more frequently for toxicity and dose adjust if necessary with coadministration of itraconazole. No dose adjustment with other CYP3A inhibitors. • No restriction of co-administration of fluconazole doses greater than 200 mg in patients with aGVHD. • Reduce dose to ruxolitinib 5 mg once daily with moderate to severe renal impairment and ruxolitinib 5 mg after a dialysis session in patients with ESRD on dialysis. • No dose adjustment is necessary in patients with mild to severe hepatic impairment based on NCI criteria. • Monitor blood counts more frequently for toxicity and consider dose reduction to ruxolitinib 5 mg once daily for patients with Stage 3 or 4 liver GVHD.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable.

Post-Marketing Requirements and Commitments

There are no post-marketing requirements or commitments.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

JAKAFI (ruxolitinib) is a Janus Associated Kinases (JAK) 1 and 2 Inhibitor. The PK of ruxolitinib was previously reviewed and described in the clinical pharmacology reviews under original NDA 202192 (DARRTS IDs 3034751 and 3656455). The current submission provides assessments of exposure-response relationships for efficacy and safety and an updated population PK (popPK) analyses of ruxolitinib in patients with aGVHD from the REACH-1 study. The following is a summary of the clinical PK of ruxolitinib when JAKAFI is administered in patients with MF (original NDA) and aGVHD:

- Bioavailability of ruxolitinib is 95%. The increases in the area under the concentration-time curve (AUC) and peak concentrations (C_{max}) of ruxolitinib were dose proportional over a single dose of 5 to 25 mg. Time to C_{max} (T_{max}) was within 1 to 2 hours post-dose. No effect of food on PK of ruxolitinib.
- The mean elimination half-life of ruxolitinib is ~3 hours and of ruxolitinib + metabolites is ~5.8 hours.
- Ruxolitinib is eliminated predominately via metabolism with 74% of total dose excreted in urine and 22% excreted via feces. Unchanged drug accounted for <1% of the excreted total dose.
- Based on popPK analyses, ruxolitinib clearance (CL/F) in patients with aGVHD (11.9 L/h 43% CV) was approximately 50% of that in patients with MF (17.7 L/h in women and 22.1 L/h in men with MF (39% CV)).
- No clinically relevant differences in ruxolitinib PK with regard to age, race, sex, weight, or hepatic impairment (HI) based on NCI criteria.
- Exposure of a single dose of ruxolitinib 25 mg increased with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) HI as compared with normal hepatic function in subjects. No effect of HI (based on NCI criteria) on PK and safety of ruxolitinib at clinical doses were observed in patients with aGVHD.
- Total exposure of ruxolitinib and its active metabolites increased with moderate (CLcr 30 mL/min to 59 mL/min) and severe (CLcr 15 mL/min to 29 mL/min) renal impairment (RI), and ESRD on dialysis in subjects administered a single dose of ruxolitinib 25 mg.
- Based on popPK analyses, ruxolitinib CL/F in patients with aGVHD decreased with the severity of liver involvement; ruxolitinib CL/F in patients with aGVHD and Stages 1 to 3 and Stage 4 liver involvement were 67% and 8%, respectively, of those in patients with no liver involvement. However, it should be noted that the sample size was limited with only one patient with aGVHD and Stage 4 liver involvement.
- Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9. No effect of strong CYP3A inhibitors (with the exception of ketoconazole and itraconazole) and fluconazole (moderate CYP3A inhibitor and strong CYP2C9 inhibitor) on the PK of ruxolitinib in patients with aGVHD.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

In the current supplement, the Applicant proposes a starting dose of 5 mg twice daily (BID) with possible escalation to 10 mg BID after 3 days, in patients with aGVHD. Per the Applicant, the ruxolitinib dosing regimen for aGVHD was based safety and efficacy in Study INCB 18424-271 (REACH-1). An analysis of overall response rate (ORR) at Day 28 by average reported daily

ruxolitinib dose between Days 1 and 28 in the REACH-1 study supports a starting ruxolitinib dose of 5 mg BID with possible escalation to 10 mg BID after 3 days. PopPK analysis (Appendix 14) indicated that the 5 mg BID dosing regimen in patients with aGVHD is expected to provide similar exposures to 10 mg BID in patients with MF, with a slower absorption rate and about 50% lower clearance (CL/F) in patients with aGVHD compared to patients with MF. Also, patients with aGVHD tend to have low platelet counts at baseline (median 74 × 10^9/L).

In general, the proposed dosing regimen of ruxolitinib 5 mg BID with possible escalation to 10 mg BID after 3 days appears to be safe and effective for patients with aGVHD based on the REACH-1 study.

Therapeutic Individualization

Table 2 lists the recommended starting doses in the approved MF and PV indications and the new indication of aGVHD, with dose modifications based on intrinsic and extrinsic factors.

Table 2: Recommended Starting Doses for Myelofibrosis (MF), Polycythemia vera (PV), and aGVHD

Patient Population	Baseline Platelet x10^9/L	Starting Doses					
		General	Patient Subgroups				
			Strong CYP3A4 inhibitor/ Fluconazole (<200 mg)	Renal Impairment			Hepatic Impairment (CP-A/B/C)
				Moderate	Severe	ESRD on dialysis	
MF (Approved)	>200	20 mg BID	10 mg BID	---		20 mg QD	---
	150-200	15 mg BID		---		15 mg QD	---
	100-150			10 mg BID			10 mg BID
	50-<100	5 mg BID	5 mg QD	5 mg QD		Avoid use	5 mg QD
PV (Approved)	N/A	10 mg BID	5 mg BID	5 mg BID		10 mg QD	5 mg BID
aGVHD	N/A	5 mg BID	5 mg QD*	5 mg QD		5 mg QD	---

*Only for ketoconazole. BID=twice daily. QD=once daily

Dose adjustment to ruxolitinib 5 mg once daily (QD) is proposed for co-administration of ketoconazole but not for other strong CYP3A inhibitors. Monitor blood counts more frequently for toxicity and dose adjust if necessary are proposed for co-administration of itraconazole. No dose adjustment is proposed with other CYP3A inhibitors. Also, dose adjustment to 5 mg QD is proposed for patients with moderate and severe RI and for Stage 3 or 4 liver involvement, and ruxolitinib 5 mg after a dialysis session in patients with ESRD on dialysis. No dose adjustment is recommended for patients with aGVHD and any HI based on NCI criteria, as popPK analyses and safety assessments using data from the REACH-1 study showed that the effect of HI based on NCI criteria was not clinically meaningful in patients with aGVHD.

Outstanding Issues

There are no outstanding issues at this time.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

The Office of Clinical Pharmacology recommends the following labeling concepts in the final package insert:

- Include in Section 2.4 Dose Modifications for Concomitant Use with Strong CYP3A4 Inhibitors or Fluconazole, that there are no restrictions on fluconazole at doses > 200 mg in patients with aGVHD. Include in Table 8 Dose Modifications for Concomitant Use with Strong CYP3A4 Inhibitors or Fluconazole, dose adjustment to ruxolitinib 5 mg QD for ketoconazole, monitor blood counts more frequently for toxicity and dose adjust if necessary with co-administration of itraconazole, and no dose adjustments with other CYP3A inhibitors.
- Include in Table 9 Dose Modifications for Renal Impairment of Section 2.5 Dose Modifications for Organ Impairment, dose adjustment to 5 mg QD for moderate RI in addition to severe RI. Also, specify that the dose adjustment in patients with aGVHD and ESRD on dialysis is 5 mg after a dialysis session.
- In Table 10 Dose Modifications for Hepatic Impairment, specify that no dose adjustment is needed in patients with aGVHD and mild, moderate or severe HI based on NCI criteria, not Child-Pugh. Also, include monitoring blood counts more frequently for toxicity for Stage 3 or 4 liver GVHD in addition to considering dose reduction to 5 mg QD.
- Modify Section 7 Drug Interactions to align with the recommendations in Section 2.4: allow fluconazole doses >200 mg in patients with aGVHD, and ruxolitinib dose reduction only when co-administered with itraconazole and ketoconazole, and not for other strong CYP3A inhibitors.
- Reformat Sections 8.6 Renal Impairment and 8.7 Hepatic Impairment according to the clinical pharmacology labeling guidance. Include a sentence in Section 8.7 that patients with aGVHD with Stage 3 or 4 liver involvement be more frequently monitored for blood counts and dose reduction to 5 mg QD be considered.
- In Section 12.3 Pharmacokinetics, under Elimination, include ruxolitinib clearance in patients with aGVHD. Also, under Specific Populations, include that there is no clinically relevant effect of HI based on NCI criteria on ruxolitinib PK in patients with aGVHD.
- In Section 12.3, modify the 'Renal Impairment' sub-section to state that following oral administration of a single dose of JAKAFI 25 mg, the total AUC of ruxolitinib and its active metabolites increased by 1.3-,1.5-, and 1.9-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function (CLcr ≥ 90 mL/min). Also, the total AUC of ruxolitinib and its active metabolites increased by 1-6-fold in subjects with ESRD after dialysis compared to that in subjects with normal renal function (CLcr ≥ 90 mL/min).

- In Section 12.3, reformat the 'Hepatic Impairment' sub-section to align with the Clinical pharmacology labeling guidance.

6.3.2 Clinical Pharmacology Questions

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?
Yes. As stated in Section 6.2.2, the proposed dosing regimen for patients with aGVHD is generally supported by the PK, efficacy, and safety data in REACH-1.

Upon request, exposure-response analyses were performed by the Applicant using data from REACH-1. The results for efficacy suggest no correlation between ruxolitinib exposures and ORR at Day 28. For safety, no increased rate of TEAE with >20% incidence, including anemia and decreased platelet counts was associated with higher ruxolitinib exposure levels. However, based on the review of the original NDA submission, the exposure-response relationships for safety measures in patients with MF suggest a decrease in platelet count and hemoglobin with increasing ruxolitinib exposure.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?
Yes. Dose adjustment to 5 mg QD is recommended for patients with aGVHD and moderate to severe RI and 5 mg after a dialysis session for patients with ESRD on dialysis based on results from a dedicated renal impairment study, and due to limited number of patients with moderate RI (n=10) and lack of patients with severe RI from the REACH-1 study to inform the updated popPK analyses and safety assessment.

No dose adjustment is recommended for patients with HI according to NCI criteria based on the results of the updated popPK analyses and assessment of safety in patients with aGVHD and HI.

Population PK analyses

Table 3: Estimated Ruxolitinib Clearance By Baseline Renal Impairment (Left) And Hepatic Impairment (right: NCI criteria) in REACH-1.

Renal Fn.	Normal (CLcr ≥90 mL/min)	Mild (CLcr 89-60 mL/min)	Moderate (CLcr 59-30 mL/min)
n	43	18	10
Mean	13.39	10.99	10.78
Median	13.50	10.80	9.73
%CV	43.24	47.59	43.04
Min	2.25	1.11	4.60
Max	29.35	19.41	20.73

Hepatic Fn.	Normal	Mild*	Moderate*	Severe*
n	39	13	7	12
Mean	13.75	12.87	9.47	9.28
Median	13.95	11.23	10.21	9.02
%CV	41.75	38.15	25.45	60.34
Min	4.24	6.00	6.18	1.11
Max	29.35	23.90	12.36	20.42

*Mild= TB ≤ULN and AST >ULN or TB >1 – 1.5xULN and any AST; Moderate= TB >1.5 – 3x ULN and any AST; Severe= TB > 3x ULN and any AST.
CLcr= creatinine clearance, TB=total bilirubin, AST=aspartate transaminase

Source: Based on Applicant's Response to IR, Module 5.3.5.2, SDN 928

Renal Impairment

PopPK analyses showed that creatinine clearance (mild, n=164; moderate, n=101; severe, n=2) had no effect on the PK of ruxolitinib (Appendix 14). Also, comparison of estimated clearance of ruxolitinib in patients with aGVHD and renal dysfunction in REACH-1 showed that the mean ruxolitinib clearance in patients with mild to moderate RI were similar to that for patients with normal renal function (Table 3).

However, Clinical Pharmacology review of the dedicated RI study in the original NDA submission, indicates that the increase in overall exposure with renal impairment is mainly driven by the metabolites but there was no substantial increase in AUC of ruxolitinib with various degrees of RI (DARRTS ID 3034751). Since the renal impairment categories were not consistent with the FDA's renal impairment guidance in the original analysis in the dedicated renal impairment study (INCB 18424-142), the Applicant was requested to revise the renal impairment categories based on creatinine clearance (Cockcroft-Gault) per the FDA's guidance and re-estimate total AUC of ruxolitinib plus active metabolites for each of the renal impairment categories in Study INCB 18424-142. The reanalysis indicated there was 1.5- to 1.9-fold increase in total AUC of ruxolitinib plus active metabolites with moderate (CLcr 30-59 mL/min) to severe (CLcr 15-29 mL/min) RI, respectively, and a 1.6-fold increase with ESRD on dialysis compared to patients with normal renal function (CLcr ≥ 90 mL/min) (Table 4). Also, the change in the PD marker (i.e., pSTAT3 inhibition) was consistent with the increase in metabolite exposure with severity of RI.

Table 4: Summary of Total AUC of Ruxolitinib and Active Metabolites for Renal Impairment Categories (Study INCB 18424-142)

		Total AUC (nM*hr)				Reference=Normal	
RENAL Classification	**n**	**mean**	**median**	**min**	**max**	**Ratio using mean**	**Ratio using ANOVA**
Normal Renal Function (CLcr≥90 mL/min)	5	4479.31	4531.27	3913.97	5012.41	1.00000	
Mild (CLcr 60 - 89 mL/min)	10	5992.61	5943.73	4483.98	7139.00	1.33784	1.32841
Moderate (CLcr 30 - 59 mL/min)	14	6795.26	6693.95	4414.23	10048.22	1.51703	1.48556
Severe (CLcr 15 - 29 mL/min)	3	8698.57	8711.05	8273.37	9111.31	1.94194	1.94664
ESRD, HD predose	4	7194.10	7068.57	6119.49	8519.77	1.60607	1.59303
ESRD, HD postdose	4	7040.91	7254.76	4387.62	9266.48	1.57187	1.52046

Source: Applicant's 1/17/19 response to IR requested

Hepatic Impairment

PopPK analyses showed that HI (mild, n=91; moderate, n=22; and severe, n=12), had no effect on the PK of ruxolitinib (Appendix 14). Furthermore, comparison of estimated clearance of ruxolitinib in patients with aGVHD and hepatic dysfunction in REACH-1 showed that the mean ruxolitinib clearance in patients with GVHD and mild HI was similar to that of patients with aGVHD and normal hepatic function (**Table 3**). The mean ruxolitinib clearance in patients with moderate and severe HI decreased by ~30% compared to patients with normal hepatic function, however, there was considerable overlap in the variability.

Safety Assessments

Table 5: Safety Assessment In Patients With aGVHD and Normal Organ Function And Various Degrees Of Baseline Renal Impairment (Left) And Hepatic Impairment (right: NCI criteria) in Trial REACH-1

Renal Fn	Normal (CLcr ≥90 mL/min)	Mild (CLcr 89-60 mL/min)	Moderate (CLcr 59-30 mL/min)
Adverse Event	(N=43)	(N=18)	(N=10)
% Overall	100	100	100
% Serious	81	72	100
%Grade 3-4	93	100	100
% AEs leading to			
DI	47	33	40
DR	35	28	50
TD	28	39	30
Death	33	44	50

Hepatic Fn	Normal	Mild	Moderate	Severe
Adverse Event	(N=39)	(N=13)	(N=7)	(N=12)
% Overall	100	100	100	100
% Serious	82	69	86	92
%Grade 3-4	97	92	86	100
% AEs leading to				
DI	46	54	0	42
DR	41	23	43	25
TD	28	23	71	25
Death	31	31	57	58

AE= adverse events. DI=dose interruption, DR=dose reduction, TD=treatment discontinuation
*Mild= TB ≤ULN and AST >ULN or TB >1 – 1.5xULN and any AST; Moderate= TB >1.5 – 3x ULN and any AST; Severe= TB > 3x ULN and any AST.
CLcr= creatinine clearance, TB=total bilirubin, AST=aspartate transaminase

Source: Based on Applicant's Response to IR, Module 5.3.5.2, SDN 928

Renal Impairment

Safety assessment indicated no trends in the incidence of serious AEs, Grade 3/4 AEs, and discontinuations due to AEs in patients with aGVHD and mild to moderate RI compared to patients with aGVHD and normal renal function in REACH-1 (**Table 5**). However, an increase in the incidence of dose reduction and deaths due to AEs were observed in patients with moderate RI. Further, the sample size for moderate RI is limited to make a meaningful interpretation, and no patients with baseline severe RI were enrolled in REACH-1.

It should be noted that patients taking moderate or strong CYP3A inhibitors were almost evenly distributed (~50%) among aGVHD patients with normal renal function and RI in the REACH-1 study (data not shown).

Hepatic Impairment

Safety assessment indicated no trends in the incidence of serious AEs, Grade 3/4 AEs, and discontinuations due to AEs in patients with aGVHD and hepatic dysfunction compared to patients with aGVHD with normal hepatic function in REACH-1 (**Table 5**). Although sample size in the HI groups was limited, it was evenly distributed between HI groups and included a sufficient number of patients with severe HI.

It should be noted that patients taking moderate or strong CYP3A inhibitors were almost evenly distributed (~50%) among aGVHD patients with moderate and severe HI and normal hepatic function in the REACH-1 study (data not shown).

Stage 3 or 4 liver GVHD

Consideration of dose adjustment to 5 mg QD is proposed with more frequent monitoring of blood counts and toxicity for Stage 3 or 4 liver involvement as popPK analysis indicates liver involvement is a significant predictor of ruxolitinib clearance, and safety data is sparse.

Table 6: Estimated Ruxolitinib Clearance In Patients with aGVHD and Various Stages Of Liver Involvement In REACH-1.

Parameter	STAGE 0	STAGE 1	STAGE 2	STAGE 3	STAGE 4
n	56	2	4	8	1
mean	13.32	8.45	7.63	10.86	1.11
%CV	40.39	37.87	23.07	54.33	--
min	4.24	6.18	5.40	2.25	1.11
max	29.35	10.71	9.27	20.42	1.11

Source: Based on Applicant's Response to IR, Module 5.3.5.2, SDN 928

PopPK analysis indicated that liver involvement on clearance was a statistically significant predictor of CL/F (Appendix 14). Ruxolitinib CL/F in patients with aGVHD decreased with the severity of liver involvement; the oral clearances of ruxolitinib in patients with aGVHD and Stages 1 to 3 and Stage 4 liver involvement were 67.4% and 8.3%, respectively, of those in patients with aGVHD patients with no liver involvement (**Table 6**). However, it should be noted there was only one patient with aGVHD and Stage 4 liver involvement.

Table 7: Safety Assessment In Patients With aGVHD and Various Stages Of Liver Involvement In REACH-1

	Stage 1	Stage 2	Stage 3	Stage 4
Adverse Event	(n=2)	(n=4)	(n=8)	(n=1)
% Overall	100	100	100	100
% Serious	100	100	100	100
%Grade 3-4	100	100	100	100
% AEs leading to				
DI	0	25	50	0
DR	50	25	25	0
TD	100	0	25	100
Death	50	50	50	100

Source: Based on Applicant's Response to IR, Module 5.3.5.2, SDN 928

No meaningful assessment of safety with liver involvement was possible as the number of patients with aGVHD and Stage 1 to 4 liver involvement were limited in the REACH-1 study (**Table 7**).

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes. Dose reduction to 5 mg QD is proposed with ketoconazole (a strong CYP3A inhibitor) in patients with aGVHD based on results from a drug-drug interaction (DDI) study in healthy subjects that showed ketoconazole increased ruxolitinib AUC by 91% and C_{max} by 33%. More frequent monitoring for toxicity and dose adjustment if necessary are proposed with itraconazole (strong CYP3A inhibitor) as itraconazole is used for anti-fungal therapy, there is no DDI study available with itraconazole, and itraconazole was not co-administered in REACH-1 or in other clinical studies that were used in the popPK analysis. No dose adjustment is recommended for JAKAFI with other CYP3A inhibitors. No restriction of co-administration of fluconazole doses > 200 mg is proposed in patients with aGVHD.

Effect of CYP3A inhibitors on Ruxolitinib:

Ruxolitinib is a CYP3A4 substrate, and to a lesser degree a substrate of CYP2C9. In the REACH-1 study, the majority of patients were taking concomitant drugs that were CYP3A inhibitors during PK visits: 92% of the patients were on anti-fungal therapy, including posaconazole, voriconazole, and fluconazole, and 62% of the patients were on anti-viral therapy, including acyclovir, valaciclovir, ganciclovir, and valganciclovir. 42% of patients were taking strong CYP3A inhibitors. In addition, 56% of the patients were taking multiple CYP3A inhibitors at the same time in the REACH-1 study.

Moderate (n=12) or strong (n=30) CYP3A inhibitors were included as covariates in the popPK analysis (Appendix 14), which indicated no clinically significant effect with moderate (i.e., including fluconazole) or strong CYP3A inhibitors (i.e., posaconazole and voriconazole) on ruxolitinib PK. The popPK analysis indicated that co-administration of moderate or strong CYP3A inhibitors decreased estimated ruxolitinib CL/F by only 15%. This effect is similar to the 21% decrease in clearance observed with erythromycin (a moderate CYP3A inhibitor) but was ~3-fold lower than the 52% decrease in clearance observed with ketoconazole (a strong CYP3A inhibitor) in a dedicated DDI study submitted in the original NDA submission. Also, ketoconazole and itraconazole was not co-administered to patients in the REACH-1 study, and in the other clinical studies used for popPK analysis. The dedicated DDI study demonstrated that ketoconazole increases ruxolitinib AUC 2-fold. No DDI study is available for itraconazole. The Applicant cited literature results indicating that midazolam AUC increases by 16-fold with ketoconazole and 11-fold with itraconazole (Olkkola et al. Clin. Pharmacol. Therap. 55: 481-485, 1994), suggesting that itraconazole may increase ruxolitinib AUC to a clinically meaningful extent.

PopPK analysis also indicated co-administration with anti-CMV therapy did not show a significant impact on ruxolitinib exposures. It is recommended to reduce ruxolitinib to 5 mg

once daily with co-administration of ketoconazole, monitor blood counts more frequently for toxicity and dose adjust if necessary with co-administration of itraconazole, and no dose adjustments with co-administration of other strong CYP3A inhibitors.

Also, in REACH-1 study, 17% of the patients with aGVHD in REACH-1 study were co-administered fluconazole and the daily doses of fluconazole in 8 of 12 patients with aGVHD were > 200 mg (i.e., 400 mg). Considering CYP3A as a covariate in the popPK analysis did not have a clinically meaningful effect on ruxolitinib PK and since majority of patients on fluconazole had doses > 200 mg, it is recommended that fluconazole doses > 200 mg can be co-administered with JAKAFI in patients with aGVHD.

Effect of CYP3A inducers on Ruxolitinib

PopPK analysis (Appendix 14) included 24, 3, and 4 patients on weak, moderate and strong CYP3A inducers, respectively. The limited data indicated that concomitant CYP3A inducers had no effect on the PK of ruxolitinib. Further, a dedicated DDI study submitted in the original NDA submission showed that although rifampin, a strong CYP3A inducer, decreased ruxolitinib exposure (AUC) by 61%, it did not significantly affect the pharmacodynamic (PD) response (i.e., pSTAT3 inhibition).

Almost all patients with aGVHD in REACH-1 were concomitantly administered corticosteroid (prednisone or methyl-prednisolone), which are weak CYP3A4 inducers. PopPK analysis indicated that the co-administration of a corticosteroid has no effect on ruxolitinib PK. The labeling states that no adjustment is recommended with co-administration of strong CYP3A inducers and to monitor patients frequently, adjusting the dose based on safety and efficacy; no change is proposed.

Is the bioanalytical method to assess ruxolitinib concentrations reliable?

Yes. The in-study assay performance was within acceptable limits.
A validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) assay was used to quantitate ruxolitinib serum samples in Study REACH-1. The quantitation range of the assay was 1-1000 nM. The quality controls levels were 3, 50 and 800 nM. All study samples were evaluated in seven analytical runs, and all runs were successful. The in-study accuracy and precision of the assay were 0.02 to 1% of nominal and 2 to 5% CV, respectively. Incurred sample reproducibility (ISR) was demonstrated in 77 study samples: 100% of the ISR samples within 20% of the original values. The maximum duration of frozen storage of study samples (296 days) was within the validated long-term frozen storage stability of 372 days at -60 to -80°C.

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7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

Table 8: Clinical Studies Supporting the Safety and Efficacy

Trial Identity	Trial Design	Study Population	Regimen/ schedule/ route	Study Endpoints	Accrual Target (treated)	No. of Centers and Countries
Study # INCB 18424-271 *(NCT02953678)* (On-going)	Single-arm open-label study	Adults with SR-aGVHD	Ruxolitinib 10 mg PO BID	Primary Endpoint: (ORR) at Day 28, Key Secondary Endpoints: DOR	70 (71)	US: 26 sites

7.2 Review Strategy

The key materials used for the review of efficacy and safety included NDA 202192 and relevant information in the public domain, such as the published literature. This review is based on the prespecified analysis of ORR at the data cut-off date of 4/2/18.

Statistical analyses by the reviewers were performed using SAS (SAS Institute, Inc., Cary, NC) and JMP 13.0 (SAS Institute, Inc., Cary, NC). MedDRA Adverse Events Diagnostic (MAED) (Clinical Trials & Surveys Corporation, Owings Mills, MD) was used to assess for safety signals. Unless stated otherwise, all other p-values are unadjusted for multiplicity and should be interpreted with caution.

8 Statistical and Clinical Evaluation - Efficacy

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study INCB 18424-271

A Single-Cohort, Phase 2 Study of Ruxolitinib in Combination with Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease (REACH1) (NCT02953678)

INVESTIGATIONAL PLAN

Trial Design

Study 271 was an open-label single-arm trial of ruxolitinib for treatment of patients with Grades 2 - 4 aGVHD persisting after treatment with corticosteroids.

Objectives:
Primary Objective: Assess the efficacy of ruxolitinib in combination with corticosteroids in subjects with Grade 2 - 4 steroid-refractory acute GVHD.

Secondary Objectives: Assess additional response and longer-term efficacy outcomes in the study population. Assess the incidence and severity of adverse events (AEs) and serious adverse events (SAEs). Evaluate the pharmacokinetics of ruxolitinib when administered in combination with corticosteroids.

Key Eligibility Criteria:
- Patients 12 years of age or older with Grades 2 - 4 steroid-refractory acute GVHD after first allogeneic HSCT.
- GVHD was graded according to MAGIC criteria (Harrris et al 2016).

- Steroid-refractory was defined as any of the following:

    - Progressive GVHD after 3 days of primary treatment with methylprednisolone ≥ 2 mg/kg/day (or at least 1 mg/kg/day for treatment of skin GVHD alone)
    - GVHD not improved after 7 days of primary treatment with methylprednisolone ≥ 2 mg/kg/day (or at least 1 mg/kg/day for treatment of skin GVHD alone)
    - Patients who demonstrated a response to corticosteroids, but progressed before a 50% decrease from the initial starting dose was achieved.

- Absolute neutrophil count (ANC) ≥ 1.0 Gi/L for 3 consecutive days.

Patients were to be excluded if they had more than 1 prior allogeneic HSCT, received systemic treatment of aGVHD other than corticosteroids, had GVHD overlap syndrome, had relapse of the primary disease for which HSCT was performed, had active infection, had creatinine clearance < 40 mL/min or other severe organ dysfunction, or had any prior treatment with a JAK inhibitor for any reason

Treatment Plan
Treatment consisted of ruxolitinib 5 mg PO BID (escalating to 10 mg PO BID on day 3 in the absence of ≥ 50% decrease in platelet counts and/or ANC relative to Day 1 or other toxicity) in combination with methylprednisolone 2.0 mg/kg/day equivalent. Corticosteroids were to be tapered as tolerated (reduction to 0.2 mg/kg/day by day 28 recommended). The ruxolitinib dose was reduced or discontinued for patients with toxicity or failing treatment. For patients

who achieved CR or VGPR, ruxolitinib was to be continued to study day 180 and tapered thereafter provided corticosteroids have been discontinued for at least 8 weeks.

Monitoring Plan

Table 9: Monitoring Schedule

Clinical Assessments

Item	Section	Screening Phase	Treatment Phase[a]												EOT	Follow-Up Phase	
		-28 to -1	D1	D3	D7	D14	D21	D28	D35	D42	D49	D56[b]	D100	D180	D365[c]		Safety[d]	Survival
Informed consent	7.1	X																
Inclusion/exclusion criteria	3	X																
Contact IVRS	7.2	X	X					X				X	X		X	X		X
Demography/disease history	7.3	X																
Prior/concomitant medications	7.4	X	X													X	X	
Supportive care medications	5.2.2.4	X	X													X	X	
AE assessment	7.5.1	X	X													X	X	
Physical examination	7.5.2	X	X		X	X	X	X	X	X	X	X	X		X	X	X	
Vital signs	7.5.3	X	X		X	X	X	X	X	X	X	X	X		X	X	X	
ECOG performance status	7.5.4	X	X		X	X	X	X	X	X	X	X	X		X	X	X	
12-lead ECG	7.5.5	X	As indicated													X		
Acute GVHD grading and response assessment	7.6.1	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Chronic GVHD assessment	7.6.2												X	X	X	X		
Chimerism assessment	7.6.3	X	As indicated															
PTLD assessment	7.6.4		As indicated															
Dispense study drug	5.1		X					X				X			X			
Study drug compliance	5.3		X					X				X			X	X		
Steroid dose monitoring	5.3		X													X		
Survival follow-up	6.4																	X[e]

ECG = electrocardiogram; PTLD = post-transplant lymphoproliferative disorder.
[a] A ± 2-day window is permitted to facilitate scheduling during the treatment phase.
[b] After Day 56, visits will occur every 28 days and will include all Day 56 assessments.
[c] The Day 365 visit will also serve as the regularly scheduled visit occurring every 28 days after Day 56 (ie, Day 364).
[d] Thirty to 35 days after EOT. For subjects withdrawing due to reasons other than GVHD progression, GVHD status should be assessed every 28 days.
[e] Every 8 weeks ± 7 days.

Laboratory Assessments

Item	Section	Screening Phase	Treatment Phase[a]													EOT	Safety Follow-Up
		-28 to -1	D1[b]	D3	D7	D14	D21	D28	D35	D42	D49	D56[c]	D100	D180	D365[d]		
Chemistry panel	7.5.6.1	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Hematology	7.5.6.2	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Hepatitis screening	7.5.6.4	X															
Serum pregnancy test (childbearing females only)	7.5.6.3	X														X	
Urine pregnancy test[e] (childbearing females only)	7.5.6.3		X														
PK assessment[f]	7.7		X		X	X											
Correlative study blood collection	7.8	X	X		X	X		X				X[g]	X	X	X	X	

[a] A ± 2-day window is permitted to facilitate scheduling during the treatment phase.
[b] Day 1 laboratory assessments do not need to be repeated if screening assessments were performed in preceding 7 days.
[c] After Day 56, visits will occur every 28 days and will include all Day 56 assessments.
[d] The Day 365 visit will also serve as the regularly scheduled visit occurring every 28 days after Day 56 (ie, Day 364).
[e] Urine pregnancy tests are only required if medically indicated and should be confirmed with a serum pregnancy test.
[f] Samples to be collected at predose and at 1 hour ± 15 minutes, at 2 hours ± 30 minutes, and between 4 and 8 hours postdose.
[g] Day 56 only.

Source: Study INCB184240271 Protocol Tables 5 and 6

Statistical Analysis Plan

The endpoint definitions per protocol are shown below:

Primary Objective	**Primary Endpoint**
Assess the efficacy of ruxolitinib in combination with corticosteroids in subjects with Grades II to IV steroid-refractory acute GVHD.	ORR at Day 28, defined as the proportion of subjects demonstrating a CR, very good partial response (VGPR), or PR.
Secondary Objectives	**Secondary Endpoints**
Assess additional response and longer-term efficacy outcomes in the study population.	Key secondary endpoint: Six-month duration of response (DOR), defined as the time from first response until GVHD progression or death. DOR will be assessed when all subjects complete the Day 180 visit.
	ORR, defined as the proportion of subjects demonstrating a CR, VGPR, or PR at Days 14, 56, and 100.
	Three-month DOR, defined as the time from first response until GVHD progression or death, when all subjects complete the Day 84 visit.
	NRM, defined as the proportion of subjects who died due to causes other than malignancy relapse at Months 6, 9, 12, and 24.
	Relapse rate, defined as the proportion of subjects whose underlying malignancy relapses.
	Relapse-related mortality rate, defined as the proportion of subjects whose malignancy relapses and has a fatal outcome.
	Failure-free survival (FFS), defined as the proportion of subjects who are still alive, have not relapsed, have not required additional therapy for acute GVHD, and have not demonstrated signs or symptoms of chronic GVHD, at Month 6.
	OS, defined as the time from study enrollment to death due to any cause.

Source: Protocol INCB 18424-271 Amendment 2 Section 2

The definitions used by the statistical reviewer are:

Primary Endpoint:
The primary endpoint of the study is overall response rate (ORR) at Day 28. The definition of ORR and its individual components are shown below.

Primary Endpoint	**Definition**
Overall Response Rate (ORR) at Day 28	The proportion of subjects demonstrating a complete response (CR), very good partial response (VGPR), or partial response (PR).

Primary Endpoint	**Definition**
Complete response (CR)	A score of 0 for the GVHD grading in all evaluable organs. For a response to be scored as CR at Day 28 or later, the subject must still be in CR on that day and have had no intervening additional therapy for an earlier progression, mixed response (MR), or no response (NR).
Very good partial response (VGPR)	• Skin: No rash, or residual erythematous rash involving < 25% of the body surface, without bullae (residual faint erythema and hyperpigmentation do not count). • Liver: Total serum bilirubin concentration < 2 mg/dL or < 25% of baseline at enrollment. • Gut: ➢ Tolerating food or enteral feeding ➢ Predominantly formed stools ➢ No overt GI bleeding or abdominal cramping ➢ No more than occasional nausea or vomiting
Partial response (PR)	Improvement in 1 stage in 1 or more organs involved with GVHD symptoms without progression in others. For a response to be scored as PR at Day 28 or later, the subject must still be in PR on that day and have had no intervening additional therapy for an earlier progression, MR, or NR.

Key Secondary Endpoints**:**
The key secondary endpoints are duration of response (DOR), non-relapse mortality (NRM), and overall survival (OS). The definitions for these endpoints are shown in table below.

Key Secondary Endpoints:	**Definition**
Duration of Response (DOR)	The time from response at Day 28 to the date of progression, new salvage therapy for aGVHD or death from any cause, with progression being defined as worsening by one stage in any organ without improvement

	in other organs in comparison to the prior assessment (not in comparison to baseline staging).
Non-Relapse Mortality (NRM)	The proportion of subjects who died due to causes other than the underlying malignancy relapse.
Overall Survival (OS)	The time from first day of ruxolitinib treatment to death due to any cause

Sample Size Determination:
Approximately 70 subjects are planned for the final analysis of the primary endpoint of ORR. With the assumed true rate of 60%, a sample size of 70 subjects would provide > 90% probability to have a 95% CI with lower limit of ≥ 40%.

Efficacy Analysis Population:
Steroid-refractory aGVHD are defined as having any of the following:

- Subjects with progressive GVHD (ie, increase in stage in any organ system or any new organ involvement) after 3 days of primary treatment with methylprednisolone ≥ 2 mg/kg per day (or equivalent).
- Subjects with GVHD that has not improved (ie, decrease in stage in at least 1 involved organ system) after 7 days of primary treatment with methylprednisolone ≥ 2 mg/kg per day (or equivalent).
- Subjects who previously began corticosteroid therapy at a lower dose (at least 1 mg/kg per day methylprednisolone) but develop new GVHD in another organ system.
- Subjects who cannot tolerate a corticosteroid taper, that is, begin corticosteroids at 2.0 mg/kg per day, demonstrate, response, but progress before a 50% decrease from the initial staring dose of corticosteroids is achieved.

Failed Steroids Alone Population: Study subjects who have steroid-refractory aGVHD and failed steroids as the only therapy prior to entering the study and received treatment of ruxolitinib.

Failed Steroids +/- Other Population: Study subjects who have steroid-refractory aGVHD and failed steroids with or without additional GVHD therapies prior to treatment with ruxolitinib.

Statistical Hypothesis:

H_0**:** ORR < 0.4
H_a: ORR ≥ 0.4

Statistical Methods:
Since this is a single cohort study, no formal statistical tests are performed. The primary efficacy endpoint, ORR at Day 28, is calculated with a 95% confidence interval (CI). CI is

calculated based on the exact method for a binomial distribution. Subjects who have missing response data at Day 28 (includes withdrawal or death before Day 28) will be considered nonresponders. A positive study outcome is concluded if the lower limit of the 95% CI of the ORR is above the prespecified threshold of 40%.

The secondary endpoint, nonrelapse mortality rate, is analyzed using the same method as ORR. Duration of response is assessed using a Kaplan-Meier method for subjects who achieved a response. The median duration and 95% CI are estimated. Subjects who are still responding at the time of database lock or discontinued will be right-censored at the time of last valid response assessment. For overall survival, the survival time distribution and the median survival is also assessed using a Kaplan-Meier method. Subjects with no observed death or loss to follow-up will be treated as censored at their last date known to be alive.

Interim Analyses for Futility:
An interim analysis to assess futility was performed when 35 subjects (50% of the planned total number of subjects) had completed the Day 28 visit or discontinued treatment. The futility criterion was to claim futility when ≤ 15 subjects responded at the time of the interim analysis. At the interim analysis, 21 of 35 subjects (60.0%) demonstrated a response at Day 28, and the study was continued.

Protocol Amendments

Protocol Amendment 1
Protocol amendment 1 dated 9/12/16 was submitted to 'address regulatory feedback that relates to eligibility criteria, secondary endpoints, graft-versus-host-disease (GVHD) staging and grading criteria, inclusion of an interim analysis, starting dose of ruxolitinib, dose modifications of ruxolitinib in subjects with liver GVHD, and the ability of investigators to taper ruxolitinib.

Protocol amendment 2
Protocol amendment 2 dated 10/4/16 was submitted to 'address regulatory feedback provided after finalization of Amendment 1 that relates to secondary endpoints, dose modifications of ruxolitinib, and guidance to investigators on tapering of ruxolitinib.

STUDY RESULTS

Compliance with Good Clinical Practices

The Applicant attested to compliance with Good Clinical Practice (GCP) (Study 271 Interim CSR Ethics Section). FDA audit of three clinical sites identified no regulatory issues (see Section 4.1 above).

Financial Disclosure

The Applicant submitted a Form FDA 3454 to certify no financial interests and arrangements for 470 investigators. The Applicant three investigators with disclosable financial arrangements; no patients were enrolled at the sites for these three investigators.

Data Quality and Integrity

Using the available raw data in the initial submission of this supplement, FDA was not able to confirm the key derived variables for baseline patient characteristics, prior therapy, response and post-study treatments. In a teleconference 1/7/2019, the data issues were discussed with the Applicant, and FDA recommend collection of additional raw data and re-analyses based on the new information. A new data set with updated data files was received on 2/1/2019; this was considered a major amendment. At the time of completion of this review, the following were the major issues identified with the data in the supplement:

1. To facilitate the assessment of response, the Applicant submitted za.xpt with updated data needed for organ staging (including total bilirubin, presence of grossly bloody stool, severe abdominal pain, skin rash percentage, presence of erythroderma with bullae or desquamation, stool output episodes or volume, presence of persistent nausea, vomiting or anorexia). Taking into account additional explanatory comments, FDA employed an algorithmic approach to derive the organ staging according to Harris, et al (2016). Forty responders were identified. The FDA-adjudicated responses listed in the table below were sent to the Applicant on 12/28/2018 and acknowledged as accepted by the Applicant in a response to IR received 1/17/2019.

Table 10 : FDA-Adjudicated Responses

Subject	Response		Subject	Response
(b) (6)	PR		(b) (6)	PR
	PR			CR
	PR			PR
	PR			CR
	PR			CR
	CR			PR
	CR			CR
	VGPR			PR
	CR			CR
	VGPR			CR
	CR			CR
	PR			CR
	PR			CR
	CR			CR
	PR			PR
	CR			PR
	CR			PR
	VGPR			CR

Table 10 : FDA-Adjudicated Responses

Subject	Response		Subject	Response
(b) (6)	VGPR		(b) (6)	CR
	VGPR			CR

Source: FDA analysis

Compared to the Day-28 assessment response variable (ASSMREP) in adfda.xpt submitted 2/1/2019, FDA identified 7 discrepancies in Day-28 response as listed below.

Table 11 : Response Discrepancies in adfda.xpt

Subject	Applicant's Variable ASSMREP	FDA-Adjudicated Response
(b) (6)	(MR) MIXED RESPONSE	PR
	(VGPR) VERY GOOD PARTIAL RESPONSE	PR
		CR
		CR
	(PR) PARTIAL RESPONSE	NR
	(VGPR) VERY GOOD PARTIAL RESPONSE	PR
	OTHER: TRAUMA FROM MVA	CR

Source: FDA analysis

FDA also noted that the Applicant's response assessment variables (ASSMREP and RESPALFC) in adfda.xpt and adsl.xpt submitted 2/1/2019 did not match each other. For the purposes of this review, the FDA-adjudicated responses will be used to assess the treatment effect.

2. The adsl.xpt file submitted 2/1/2019 was used for this review. FDA identified 2 errors in baseline GVHD grade (variable MAGCRGRD) - patients (b) (6) and (b) (6) were listed as grade 3 and should be grade 4. FDA also identified 2 errors in the categorization for prior salvage therapy (variable PRSALVGE) - patients (b) (6) and (b) (6) were listed as "Without Prior Salvage", but they received basiliximab and vedolizumab, respectively, prior to study, and therefore should be considered as failing 2 or more prior therapies. The Applicant acknowledged these errors in a response to IR received 2/21/2019.

3. The variable HLAM in adsl.xpt had elements that did not appear to coincide with the HLA match score (HLASCORE) and donor (DNRSURCE). For the purposes of categorizing the MHC compatibility of the donors, the HLA match score was used by FDA.

4. Based on a comparison of the listing of GVHD prophylaxis in gvhdv2.xpt, the prior therapies listed in adcm.xpt and the donor information in adsl.xpt, FDA concluded that the prophylaxis data in gvhdv2.xpt was not credible. FDA recommended that the Applicant obtain the prophylaxis used as reported on CIBMTR data collection forms. In a response to IR received 2/1/2019, the Applicant provided a revised listing of the GVHD prophylaxis for each patient based on their review of source documentation. FDA noted that there were still prophylaxis medications listed in adcm.xpt that did not appear in the revised listing nor in the updated variable PROFLAXS in adsl.xpt, especially with regard to use of posttransplant cyclophos-

phamide. Hence, FDA concluded that the GVHD prophylaxis data are not credible and will not be used in the review.

5. Lastly, for the duration of response (DOR), the Applicant used the period from the date of day-28 response (CR, VGPR, or PR) to the date when the event (PD, new anti-GVHD therapy, or death) occured or was censored, and the result is given in AVAL for PARAMCD=DORFDA in adtte.xpt submitted 2/1/2019. However, for this calculation, the Applicant defined PD as increase in organ stage from baseline; FDA clarified for the Applicant that PD should be calculated from the nadir response rather than from baseline. For the DOR calculation, FDA will consider PD from nadir response at or after day 28. Since some of the PD events were flares of GVHD that did not require new therapy, FDA suggested that the Applicant consider assessing time to death or change in treatment as an additional measure of the durability of the treatment effect. The Applicant provided their analysis of this alternative endpoint in a response to IR received 2/21/2019. The data set in the NDA at the time of this review does not reflect the corrected DORFDA calculation, nor does it include the Applicant's derived result for the alternate measure of durability. FDA's analysis utilizes their own calculations for these outcomes.

Patient Disposition:

Between start of the study on 5/7/2014 and data cut-off on 2/22/2018, 84 patients were screened, and 71 patients were enrolled and treated. Of the 71 patients enrolled in the study, 13 did not receive at least 2 mg/kg steroids (+/- 10%) prior to study entry. These patients are not considered have been treated with an adequate dose of steroids and are excluded from FDA's analysis. Of the remaining 58 patients, 49 (84.5%) failed only steroids as the prior therapy for aGVHD (Table 12). These 49 patients are considered in the failed steroids alone population. Nine (15.5%) others failed 2 or more therapies prior to enrollment. These patients are considered in the failed 2 or more therapies population. At the time of data cutoff date of April 02, 2018, 11 patients (19.0%) remained in the study, 30 patients died during the study (12 due to GVHD progression).

Table 12: FDA Primary Endpoint Analysis Population: Disposition

	Ruxolitinib (N=58)
Steroid-refractory population	58 (100.0)
Failed steroids alone as prior therapy	49 (84.5)
Failed 2 or more therapies	9 (15.5)
Number of patients who are still ongoing as the data cutoff date of 04/02/18	11 (19.0)
Number of patients discontinued the study	32 (55.2)

Primary reason for study discontinuation	
Death	30 (51.7)
GVHD progression	12 (20.7)
Other	18 (31.0)
Withdrawal by patients	2 (3.4)

Source: FDA analysis

Baseline Demographic Characteristics:
The summary of the baseline demographic characteristics for both steroid-refractory and failed steroid alone populations is presented in Table 13. For both populations, the majority of the patients were < 65 years old, with a median age of approximately 57 years (range: 18-72 years). Most of the patients were also white and not Hispanic origin. Sex was evenly distributed.

Table 13: FDA Analysis Populations - Demographics

	Ruxolitinib	
	Failed Steroids +/- Other (N = 58)	**Failed Steroids Alone (N = 49)**
Age (years)		
N	58	49
Mean (SD)	52.5 (14.06)	52.3 (14.29)
Median	57.5	57
(Min, Max)	(18, 72)	(18, 72)
Age group (years), n (%)		
< 65 years	49 (84.5)	43 (87.8)
≥ 65 years	9 (15.5)	6 (12.2)
Sex, n (%)		
Female	27 (46.6)	26 (53.1)
Male	31 (53.4)	23 (46.9)
Race, n (%)		
White/Caucasian	54 (93.0)	45 (91.8)
Black/African-American	2(3.5)	2(4.1)
Asian	2 (3.5)	2 (4.1)
Ethnicity, n (%)		
Hispanic	8 (13.8)	7 (14.3)
Not Hispanic	48 (82.8)	41 (83.7)
Not Reported	2 (3.4)	1 (2.0)
ECOG Grade, n (%)		
1	20 (34.5)	17 (34.7)
2	21 (36.2)	18 (36.7)
3	16 (27.6)	13 (26.5)

Table 13: FDA Analysis Populations - Demographics

	Ruxolitinib	
	Failed Steroids +/- Other (N = 58)	**Failed Steroids Alone (N = 49)**
Missing	1 (1.7)	1 (2.1)

Source: FDA analysis

Baseline Disease Characteristics:
The distribution of the patients with various stages of organ involvement (skin rash, lower gastrointestinal (GI), upper GI, liver) are shown in Table 14. All patients had grade II or higher MAGIC grade based on FDA's assessment. The proportion of patients with Grade II, III, or IV were 24.1%, 53.4%, and 22.4%, respectively for the steroids-refractory population and 26.5%, 55.1%, and 18.4%, respectively for the failed steroid alone population.

GVHD that had not improved after 7 days of primary treatment was the most common reason for the steroid refractoriness among the patients (39.7% in the steroid-refractory population and 38.7% in the failed steroid alone population). It is followed by progressive GVHD after 3 days of primary treatment (24.1% in the steroid-refractory population and 22.5% in the failed steroid alone population) and patients that could not tolerate a steroid taper (22.4% in the steroid-refractory population and 22.5% in the failed steroid alone population). Steroid refractory caused by previously began steroid therapy at a lower dose but developed new GVHD in another organ system had 13.8% patients in the steroid-refractory population and 16.3% of patients in the failed steroids alone population.

Acute leukemia/myelodysplastic syndromes (MDS) was the most common underlying malignancy for these patients (67.2% in steroid-refractory population, 65.3% in failed steroids alone population); 82.8% patients in the steroid-refractory population and 79.6% patients in the failed steroids alone population had their allogeneic HSCT using peripheral blood stem cell (PBSC). The median duration of prior corticosteroid exposure was 15 days (range: 3-106).

Table 14: FDA Analysis Population - GVHD Characteristics

	Ruxolitinib	
	Failed Steroids +/- Other (N = 58)	**Failed Steroids Alone (N = 49)**
Skin Rash (stage), n (%)		
Stage 0	27 (46.6)	23 (46.9)
Stage 1	3 (5.2)	3 (6.1)
Stage 2	6 (10.3)	6 (12.2)
Stage 3	19 (32.8)	16 (32.7)
Stage 4	3 (5.2)	1 (2.1)

Table 14: FDA Analysis Population - GVHD Characteristics

	Ruxolitinib	
	Failed Steroids +/- Other (N = 58)	**Failed Steroids Alone (N = 49)**
Lower GI (stage), n (%)		
Stage 0	15 (25.9)	13 (26.5)
Stage 1	7 (12.1)	7 (14.3)
Stage 2	6 (10.3)	5 (10.2)
Stage 3	19 (32.8)	16 (32.7)
Stage 4	11 (19.0)	8 (16.3)
Upper GI (stage), n (%)		
Stage 0	40 (69.0)	33 (67.3)
Stage 1	18 (31.0)	16 (32.7)
Liver (stage), n (%)		
Stage 0	46 (79.3)	38 (77.6)
Stage 1	1 (1.7)	1 (2.0)
Stage 2	4 (6.9)	4 (8.2)
Stage 3	7 (12.1)	6 (12.2)
Stage 4	0	0
MAGIC Grade, n (%)		
Grade II	14 (24.1)	13 (26.5)
Grade III	31 (53.4)	27 (55.1)
Grade IV	13 (22.4)	9 (18.4)
Steroid-Refractory Criteria, n (%)		
Progressive GVHD after 3 days of primary treatment	14 (24.1)	11 (22.5)
GVHD that had not improved after 7 days of primary treatment	23 (39.7)	19 (38.7)
Previously began steroid therapy at a lower dose but developed new GVHD in another organ system	8 (13.8)	8 (16.3)
Patients that could not tolerate a steroid taper	13 (22.4)	11 (22.5)
Underlying Malignancy at Baseline, n (%)		
Acute Leukemia/MDS	39 (67.2)	32 (65.3)
Lymphoma/CLL	9 (15.5)	7 (14.3)
Other	10 (17.3)	10 (20.4)

Table 14: FDA Analysis Population - GVHD Characteristics

	Ruxolitinib	
	Failed Steroids +/- Other (N = 58)	**Failed Steroids Alone (N = 49)**
Type of allo-HSCT, n (%)		
Bone Marrow	9 (15.5)	9 (18.4)
Cord Blood	1 (1.7)	1 (2.0)
PBSC	48 (82.8)	39 (79.6)
Duration of Prior Corticosteroids Exposure (days)		
N	58	49
Mean (SD)	22.4 (22.36)	21.3 (22.37)
Median	15	15
(Min, Max)	(3, 106)	(3, 106)

Source: FDA analysis

Protocol Violations/Deviations

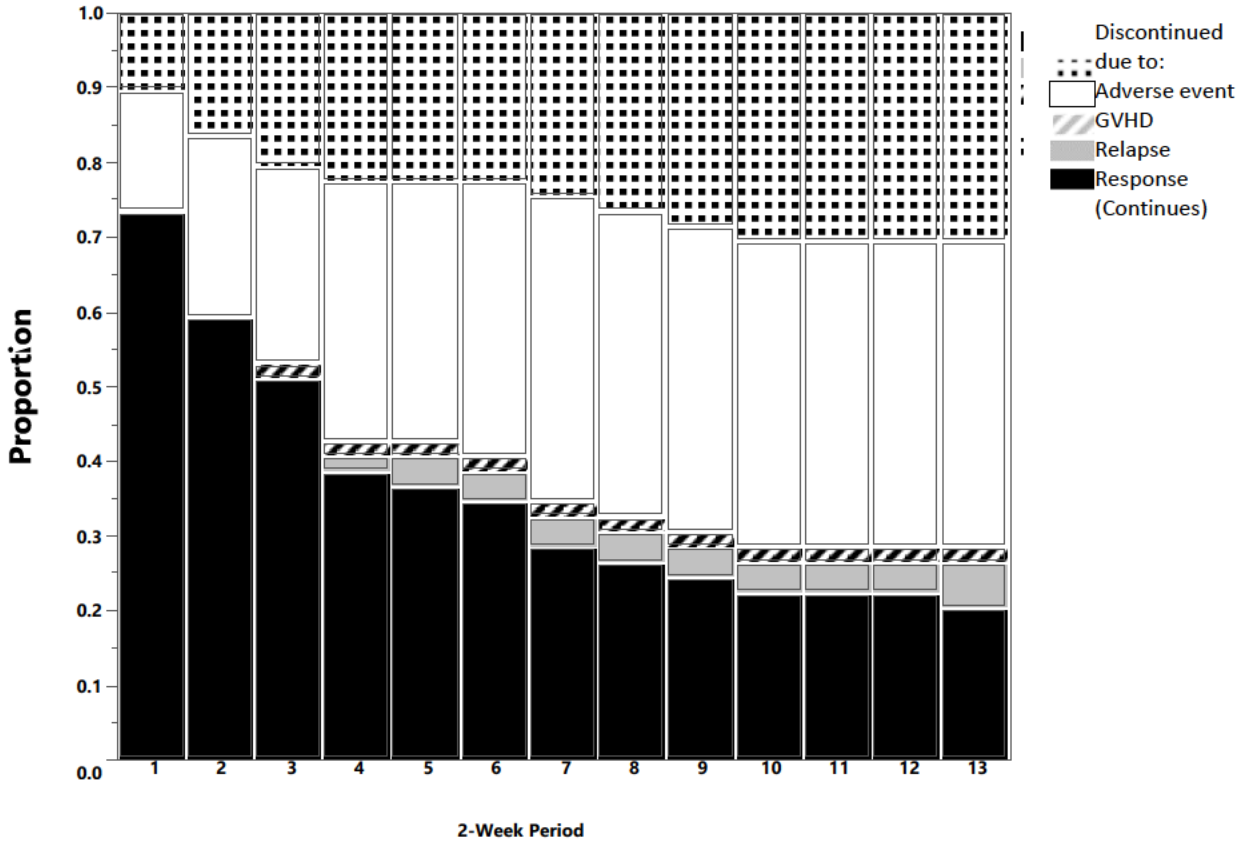
The Applicant reported 213 protocol violations involving 46 patients during the treatment period. There were 36 patients with a missed assessment, 26 with an assessment out of the prespecified window, 7 patients with study treatment noncompliance and 9 with other violations. None of the on-treatment protocol violations were considered major (affecting efficacy outcomes). See also the discussion above regarding the 22 (31%) of enrolled patients who did not meet eligibility due to prior or concurrent use of additional systemic therapies for aGVHD or who did not fail full-dose corticosteroids prior to enrollment.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant indicated that no patient had less than 80% dose intensity. FDA noted this calculation was based on prescribed dose, including dose interruptions and dose reductions for adverse events, etc.

For the 49 patients who failed steroids alone, FDA found that 48 (98%) patients started ruxolitinib at 5 mg BID (1 started at 5 mg daily), and only 28 (57%) increased the ruxolitinib dose to 10 mg BID by study day 7. Based on the plan to treat with 5 mg BID for 3 days followed by 10 mg BID, the median dose intensity was 70% (range 28-100%) during the reported period of treatment; 26 (53%) patients had < 80% dose intensity and 8 (16%) had < 50% dose intensity. Figure 11 below shows the proportion of patients continuing or discontinuing treatment at 2-week intervals on study for the 49 patients who failed steroids alone.

Figure 11: Proportion of Patients Discontinuing by Reason Over Time



Source: FDA analysis
Includes only the 49 patients who failed steroids alone.

Use of additional poststudy treatments were reported for 18 (37%) patients. These included extracorporeal photopheresis in 12, etanercept in 3, infliximab in 3, vedolizumab in 3, antithymocyte globulin (ATG) in 2, basiliximab in 2, mycophenolate mofetil in 2, sirolimus in 1 and tacrolimus in 1.

Efficacy Result - Primary Endpoint

Table 15 presents a summary of the primary endpoint, which is ORR at Day 28, along with its individual components (CR, VGPR, PR). The steroid-refractory population had an ORR of 56.9% with 95% CI of (43.2%, 69.8%). The failed steroids alone population had an ORR of 57.1% with 95% CI of (42.2%, 71.2%). Since the lower limit of the 95% CI is 43.2% and 42.2% for the steroid-refractory and failed steroids alone population respectively, the study has met the predetermined criteria for a positive study outcome (lower limit of the 95% CI for ORR at Day 28 ≥ 40%) for both populations. Therefore, it can be concluded that ruxolitinib is effective in the treatment of steroid-refractory aGVHD.

Table 15: FDA Analysis - Primary Endpoint

	Ruxolitinib	
	Failed Steroids +/- Other (N = 58)	**Failed Steroids Alone (N = 49)**
Number (%) of patients who had an overall response at Day 28 [a]	33 (56.9)	28 (57.1)
95% CI for ORR	(43.2, 69.8)	(42.2, 71.2)
Responders, n (%)		
CR	16 (27.6)	15 (30.6)
VGPR	3 (5.2)	2 (4.1)
PR	14 (24.1)	11 (22.4)
Non-responders [b], n (%)	25 (43.1)	21 (42.9)

[a] Patients who had a CR, VGPR, or PR at Day 28 response assessment or other response assessments within ± 2 days of Day 28, on or before the start of new anti-GVHD therapy (if applicable).
[b] Patients with missing assessment were considered non-responders.
Source: FDA analysis

Subgroup Analyses of the Primary Endpoint

Failed Steroids +/- Other Population:
The ORR at Day 28 and its individual component of CR, VGPR, and PR by baseline demographics, disease characteristics, and relevant biomarkers for the steroid-refractory population are summarized in Table 16. In general, the results from the subgroups support the primary analysis result.

Table 16: FDA Subgroup Analysis - Failed Steroids +/- Other Population

	ORR (CR+VGPR+PR) n (%)	**CR n (%)**	**VGPR n (%)**	**PR n (%)**
Primary Outcome (n=58)	33 (56.9)	16 (27.6)	3 (5.2)	14 (24.1)
Demographics				
Age				
< 65 Years (n=49)	29 (59.2)	15 (30.6)	2 (4.1)	12 (24.5)
≥ 65 Years (n=9)	4 (44.4)	1 (11.1)	1 (11.1)	2 (22.2)
Sex				
Female (n=31)	17 (54.8)	6 (19.4)	1 (3.2)	10 (32.3)
Male (n=27)	16 (59.3)	10 (37.0)	2 (7.4)	4 (14.8)

Table 16: FDA Subgroup Analysis - Failed Steroids +/- Other Population

	ORR (CR+VGPR+PR) n (%)	CR n (%)	VGPR n (%)	PR n (%)
Race				
White (n=54)	31 (57.4)	14 (25.9)	3 (5.6)	14 (25.9)
Black or African American (n=2)	1 (50.0)	1 (50.0)	0	0
Asian (n=2)	1 (50.0)	1 (50.0)	0	0
Ethnicity				
Hispanic (n=8)	5 (62.5)	4 (50.0)	0	1 (12.5)
Not Hispanic (n=48)	27 (56.3)	12 (25.0)	3 (6.25)	12 (25.0)
Not Reported (n=2)	1 (50.0)	0	0	1 (50.0)
Disease Characteristics				
MAGIC Grade				
Grade II (n=14)	14 (100)	9 (64.3)	1 (7.1)	4 (28.6)
Grade III (n=31)	12 (38.7)	5 (16.1)	1 (3.2)	6 (19.4)
Grade IV (n=13)	7 (53.9)	2 (15.4)	1 (7.7)	4 (30.8)
Steroid-Refractory Criteria				
Progressive GVHD after 3 days of primary treatment (n=14)	8 (57.1)	5 (35.7)	2 (14.3)	1 (7.1)
GVHD that had not improved after 7 days of primary treatment (n=23)	12 (52.2)	4 (17.4)	1 (4.3)	7 (30.4)
Previously began steroid therapy at a lower dose but developed new GVHD in another organ system (n=8)	3 (37.5)	1 (12.5)	0	2 (25.0)
Patients that could not tolerate a steroid taper (n=13)	10 (76.9)	6 (46.2)	0	4 (30.8)
Underlying Malignancy at Baseline				
Acute Leukemia /MDS (n=39)	20 (51.3)	10 (25.6)	1 (2.6)	9 (23.1)
Lymphoma/CLL (n=9)	7 (77.8)	4 (44.4)	1 (11.1)	2 (22.2)
Other (n=10)	6 (60.0)	2 (20.0)	1 (10.0)	3 (30.0)

Table 16: FDA Subgroup Analysis - Failed Steroids +/- Other Population

	ORR (CR+VGPR+PR) n (%)	CR n (%)	VGPR n (%)	PR n (%)
Type of allo-HSCT				
Bone Marrow (n=9)	7 (77.8)	3 (33.3)	1 (11.1)	3 (33.3)
Cord Blood (n=1)	1 (100)	0	1 (100)	0
PBSC (n=48)	25 (52.1)	13 (27.1)	2 (4.2)	10 (20.8)
Biomarkers				
ST2 (Log_{10})				
< 5.5 (n=28)	22 (78.6)	13 (46.4)	2 (7.1)	7 (25.0)
≥ 5.5 (n=28)	11 (39.3)	3 (10.7)	1 (3.6)	7 (25.0)
MB Score*				
< 0.291 (n=9)	7 (77.8)	3 (33.3)	2 (22.2)	2 (22.2)
≥ 0.291 (n=47)	26 (55.3)	13 (27.7)	1 (2.1)	12 (25.5)

* MB score, $\hat{p}$, is derived from a published Mount Sinai Acute GVHD International Consortium (MAGIC) prediction model: $Log[-log(1-\hat{p})] = -11.263 + 1.844(log_{10}\ ST2) + 0.577(log_{10}\ REG3\alpha)$ (Hartwell et al. 2018)
Source: FDA analysis

Failed Steroids Alone Population:

The ORR at Day 28 and the individual CR, VGPR, and PR by baseline demographics, disease characteristics, and relevant biomarkers for the failed steroids alone population are summarized in Table 17. Similar to findings from the steroids refractory population, the results from the subgroups support the primary analysis result.

Table 17: FDA Subgroup Analysis - Failed Steroids Alone Population

	ORR (CR+VGPR+PR) n (%)	CR n (%)	VGPR n (%)	PR n (%)
Primary Analysis (n=49)	28 (57.1)	15 (30.6)	2 (4.1)	11 (22.4)
Demographics				
Age				
< 65 Years (n=43)	26 (60.5)	14 (32.6)	2 (4.7)	10 (23.3)
≥ 65 Years (n=6)	2 (33.3)	1 (16.7)	0	1 (16.7)
Sex				
Female (n=26)	14 (53.9)	5 (19.2)	1 (3.8)	8 (30.8)
Male (n=23)	14 (60.9)	10 (43.5)	1 (4.3)	3 (13.0)
Race				
White (n=45)	26 (57.8)	13 (28.9)	2 (4.4)	11 (24.4)

Table 17: FDA Subgroup Analysis - Failed Steroids Alone Population

	ORR (CR+VGPR+PR) n (%)	CR n (%)	VGPR n (%)	PR n (%)
Black or African American (n=2)	1 (50.0)	1 (50.0)	0	0
Asian (n=2)	1 (50.0)	1 (50.0)	0	0
Ethnicity				
Hispanic (n=7)	4 (57.1)	3 (42.9)	0	1 (14.3)
Not Hispanic (n=41)	24 (58.5)	12 (29.3)	2 (4.9)	10 (24.4)
Not Reported (n=1)	0	0	0	0
Disease Characteristics				
MAGIC Grade				
Grade II (n=13)	13 (100)	8 (61.5)	1 (7.7)	4 (30.8)
Grade III (n=27)	11 (40.7)	5 (18.5)	1 (3.7)	5 (18.5)
Grade IV (n=9)	4 (44.4)	2 (22.2)	0	2 (22.2)
Steroid-Refractory Criteria				
Progressive GVHD after 3 days of primary treatment (n=11)	5 (45.5)	4 (36.4)	1 (9.1)	0
GVHD that had not improved after 7 days of primary treatment (n=19)	10 (52.6)	4 (21.1)	1 (5.3)	5 (26.3)
Previously began steroid therapy at a lower dose but developed new GVHD in another organ system (n=8)	3 (37.5)	1 (12.5)	0	2 (25.0)
Patients that could not tolerate a steroid taper (n=11)	10 (90.9)	6 (54.5)	0	4 (36.4)
Underlying Malignancy at Baseline				
Acute Leukemia / MDS (n=32)	17 (53.1)	9 (28.1)	1 (3.1)	7 (21.9)
Lymphoma/CLL (n=7)	5 (71.4)	4 (57.1)	0	1 (14.3)
Other (n=10)	6 (60.0)	2 (20.0)	1 (10.0)	3 (30.0)
Type of allo-HSCT				
Bone Marrow (n=9)	7 (77.8)	3 (33.3)	1 (11.1)	3 (33.3)
Cord Blood (n=1)	1 (100)	0	0	1 (100)
PBSC (n=39)	20 (51.3)	12 (30.8)	1 (2.6)	7 (17.9)

Table 17: FDA Subgroup Analysis - Failed Steroids Alone Population

	ORR (CR+VGPR+PR) n (%)	CR n (%)	VGPR n (%)	PR n (%)
Biomarkers				
ST2 (Log_{10})				
< 5.5 (n=23)	19 (82.6)	12 (52.2)	2 (8.7)	5 (21.7)
≥ 5.5 (n=24)	9 (37.5)	3 (12.5)	0	6 (25.0)
MB Score*				
< 0.291 (n=8)	7 (87.5)	3 (37.5)	2 (25.0)	2 (25.0)
≥ 0.291 (n=39)	21 (53.9)	12 (30.8)	0	9 (23.1)

* MB score, $\hat{p}$, is derived from a published Mount Sinai Acute GVHD International Consortium (MAGIC) prediction model: $Log[-log(1-\hat{p})] = -11.263 + 1.844(log_{10}\ ST2) + 0.577(log_{10}\ REG3\alpha)$ (Hartwell et al. 2018)
Source: FDA analysis

Efficacy Results – Secondary and Other Relevant Endpoints

Table 18 summarizes the results for the secondary and other relevant endpoints. For the 33 responders in the Failed Steroids +/- Other population, the median duration of response was 20 days (95% CI: 13, 83). For the 28 responders in the Failed Steroids Alone population, the median duration of response was 16 days (95% CI: 9, 83).

At the time of the data cutoff, 30 of the 58 patients (51.7%) in the Failed Steroids +/- Other population had died, and the median overall survival is 165 days (95% CI: 62, NE). All reported deaths were from causes other than relapse of the underlying malignancy. The cumulative incidence rate of the nonrelapse mortality rate (NRM) at month 6, 9, and 12 were 48.3% (95% CI: 35.0, 61.8), 50.0% (95% CI: 36.6, 63.4), and 51.7% (95% CI: 38.2, 65.1), respectively.

A total of 24 of the 49 patients (49.0%) in the Failed Steroids Alone population had died, and the median overall survival is 333 days (95% CI: 93, NE). All reported deaths were from causes other than relapse of the underlying malignancy. The cumulative incidence rate of the NRM at month 6, 9, and 12 were 46.9% (95% CI: 32.5, 61.7), 46.9% (95% CI: 32.5, 61.7), and 49.0% (95% CI: 34.4, 63.7), respectively.

The median follow-up time of each population is also presented here. The Failed Steroids +/- Other population has a median follow-up time of 102 days (range: 9, 438) and the failed steroids alone population has 112 days (range: 10, 438).

Table 18: FDA Analysis - Secondary and Other Endpoints

	Ruxolitinib	
	Failed Steroids +/- Other (N = 58)	**Failed Steroids Alone (N = 49)**
Number of Responses, n (%)	33 (56.9)	28 (57.1)
Duration of response (days) (95% CI)		
25th percentile	9 (8, 15)	8 (8, 13)
Median	20 (13, 83)	16 (9, 83)
75th percentile	116 (24, NE)	116 (23, NE)
(Min, Max)	(6, 338)	(6, 338)
Nonrelapse Mortality Rate (NRM), n (%, [95% CI])		
6 months	28 (48.3, [95% CI: 35.0, 61.8])	23 (46.9, [95% CI: 32.5, 61.7])
9 months	29 (50.0, [95% CI: 36.6, 63.4])	23 (46.9, [95% CI: 32.5, 61.7])
12 months	30 (51.7, [95% CI: 38.2, 65.1])	24 (49.0, [95% CI: 34.4, 63.7])
Overall Survival		
Number of Deaths, n (%)	30 (51.7)	24 (49.0)
Median OS (days) (95% CI)	165 (62, NE)	333 (93, NE)
Median follow-up time		
Median (days)	102.5	112
(Range)	(9, 438)	(10, 438)

Source: FDA analysis

Efficacy Results – Exploratory or COA (PRO) endpoints

There were no patient-reported outcomes data submitted.

Additional Analyses Conducted on the Individual Trial

Patients Failing Steroids Alone

Durability of Response: For the 28 responders among the 49 patients failing steroids alone, the median time to either death or need for new therapy for acute GVHD (additional salvage therapy or increase in steroids) was 173 days (95% CI 66, NE).

Chronic GVHD: Four patients were observed to have signs or symptoms of chronic GVHD; the initial observations were made at Study Days 55, 115, 156 and 347.

Patients Failing 2 or More Therapies

There were an additional 9 patients who had failed full-dose steroids and at least one additional therapy. The results in this small subgroup are:

Primary Endpoint: ORR at Day 28: For the 9 study patients who failed at least 2 therapies before enrolled in the study, 5 (55.6%) achieved a response. Of the 5 responses, 1 CR (11.1%), 1 VGPR (11.1%), and 3 PRs (33.3%).

Table 19: FDA ORR Analysis - Failed 2 or More Therapies Population

	Failed >= 2 Therapies (N=9)
Number (%) of patients who had an overall response	5 (55.6)
95% CI for ORR	(21.2, 86.3)
Responders, n (%)	
CR	1 (11.1)
VGPR	1 (11.1)
PR	3 (33.3)
Non-responders, n (%)	4 (44.4)

Source: FDA analysis

Secondary Endpoints:
For the 5 responders, the median duration of response was 22 days (95% CI: 15, 132) (Table 20). 6 of the 9 patients (49.0%) in the failed 2 or more therapies population died. The median overall survival is 49 days (95% CI: 9, NE). All reported deaths were non-relapse mortality. The cumulative incidence rate of the NRM at month 6, 9, and 12 were 55.6% (95% CI: 21.2, 86.3), 66.7% (95% CI: 29.9, 92.5), and 66.7% (95% CI: 29.9, 92.5), respectively.

Table 20: FDA Secondary Endpoint Analysis - Failed 2 or More Therapies Population

	Failed >= 2 Therapies (N=9)
Number of Responses, n (%)	5 (55.6)
Duration of response (days) (95% CI)	
25^{th} percentile	20 (15, 85)
Median	22 (15, 132)
75^{th} percentile	85 (20, 132)
(Min, Max)	(15, 132)

Table 20: FDA Secondary Endpoint Analysis - Failed 2 or More Therapies Population

	Failed >= 2 Therapies (N=9)
Nonrelapse Mortality Rate (NRM), n (%, [95% CI])	
6 months	5 (55.6, [95% CI: 21.2, 86.3])
9 months	6 (66.7, [95% CI: 29.9, 92.5])
12 months	6 (66.7, [95% CI: 29.9, 92.5])
Overall Survival (days)	
Number of Deaths, n (%)	6 (66.7)
Median OS time (95% CI)	49 (9, NE)
Median follow-up time (days)	
Median	49
(Min, Max)	(9, 372)

Source: FDA analysis

8.1.2. Literature Review

A literature search on the parameters ("INCB018424"[All Fields] OR "ruxolitinib"[All Fields]) AND acute[All Fields] AND (graft-vs-host[All Fields] OR GVHD[All Fields] OR allogeneic[All Fields]) yielded 38 citations. Additional citations were sought in recent national meeting abstract collections. There were seven publications identified with efficacy data not overlapping the current submission and relevant to the proposed indication:

Spoerl et al (2014) provided a series of 6 cases of adults (age 38-73 years) treated with ruxolitinib 5-10 mg BID for acute GVHD failing steroid plus 2-6 other therapies. One achieved CR and 3 achieved PR (ORR 67%).

Zeiser et al. (2015) reported the results of a multicenter retrospective survey that identified 54 adults (age 21-75 years) treated with ruxolitinib 5-10 mg BID. The median number of prior therapies was 3 (range 1-7). All patients had Grade 3 or 4 GVHD. The CR rate was 46%, and the ORR rate was 82%. Median time to response was 1.5 weeks. Three (7%) has a recurrence of acute GVHD. OS at 6 months was 79%.

Maffini et al. (2016) reported on use of ruxolitinib 5 mg BID to treat one adult for acute GVHD failing steroids and MMF. They reported that the patient achieved a CR.

Khandelwal et al. (2017) conducted a single-institution retrospective review that identified 13

children age 1.6 - 16.4 years treated with ruxolitinib 2.5-10 mg BID for acute GVHD. The median number of prior therapies was 4 (range, 1-6). CR was achieved by 1 (8%) and ORR by 5 (38%) at 4 weeks.

Sarmiento Maldonado et al. (2017) reported on use of ruxolitinib 5 mg BID for treatment of acute GVHD failing steroids and ECP in 3 adults (age 28-56 years). Two patients achieved CR, and one had a PR.

Gonzalez Vicent et al. (2019) reported a single-institution case series that included 13 children (age 5 months - 18 years) treated with ruxolitinib 2.5 daily - 5 mg BID for acute GVHD. The median number of prior therapies was 3 (range 1-6). CR was achieved by 4 (31%) and ORR by 10 (77%).

Toama et al. (2019) conducted a single-institution retrospective review that identified 36 patients treated for at least 14 days with ruxolitinib 5-10 mg BID for acute GVHD. The median number of prior therapies was 2 (range, 0-5). They report an ORR of 58% and a CR rate of 25% lasting at least 21 days.

8.2 Integrated Review of Effectiveness

8.2.1 Assessment of Efficacy Across Trials

Methods

Clinical Development Program: The Applicant proposed the indication "for the treatment of patients with acute graft versus host disease (GVHD) who have had an inadequate response to corticosteroids." The clinical development program included one single-arm trial, Study 271, with efficacy data for patients with persistent or recurrent acute GVHD after treatment with steroids. FDA frequently requires multiple randomized trials to establish efficacy. However, in this case where the disease is life-threatening, there are no available therapies, the efficacy endpoint is objective, the activity of the drug is established in other diseases, and there is a substantial safety database, FDA indicated at the Type B meeting on 5/27/2018 that one single-arm trial might be sufficient to support the submission, but fileability would be a review issue.

Patient Population: Patients were eligible for Study 271 if acute GVHD progressed after 3 days of treatment with methylprednisolone 2 mg/kg/day equivalent, did not improve after 7 days of treatment with methylprednisolone 2 mg/kg/day equivalent, progressed to a new organ after treatment with methylprednisolone 1 mg/kg/day equivalent for skin and upper GI GVHD, or recurred during or after a steroid taper. FDA agreed that these criteria describe steroid-refractory acute GVHD if no treatment of acute GVHD other than corticosteroids was used. It should be noted, however, that Study 271 also accrued patients who prior to study therapy were not treated with an adequate dose of steroids as defined above or who received other

drugs for treatment of acute GVHD. Tables 13 and 14 in Section 8.1.1 and Tables 22 and 23 in Section 8.3.2 describe the baseline characteristics of the entire accrued population (n=71) and the subgroups used in the efficacy analysis, depending on whether they fulfilled the criteria for steroid-refractory acute GVHD listed above.

Primary Endpoint and Endpoint Assessment: The primary endpoint of Study 271 was Day-28 ORR (CR+VGPR+PR). The definition of this endpoint and its acceptance as a clinical benefit was discussed at the open public workshop on Clinical Trial Endpoints for Acute Graft-vs-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation held May 19, 2009, and co-sponsored by FDA, NHLBI, CIBMTR and ASBMT. Durability of the response is required in order to substantiate the benefit. In Study 271, response was to be assessed on Day 28 +/- 2 days, and durability was documented in follow-up visits weekly for 4 weeks and every 28 days thereafter, including days 100, 180 and 365, as well as at end-of-treatment should that occur outside the planned visits. This monitoring schedule was considered adequate to characterize the treatment effect.

Protocol Design: The SAP prespecified that for success, the results needed to exclude a 40% ORR rate; additionally, a 60% ORR rate was considered clinically meaningful. FDA found these assumptions to be acceptable for this trial. There was one planned futility analysis when 35 patients (50% of the accrual target) completed the Day-28 visit. The results of the futility analysis did not trigger the rule, and the study was continued. The final analysis was ORR was to be performed when enrollment was met and all patients completed the Day 28 response assessments or discontinued earlier. Additional follow-up was needed to establish durability of the responses.

Primary Endpoint

The results of the Applicant's analysis and FDA's analyses of ORR are shown in Table 21.

Table 21: Study 271 - Primary Endpoint Analyses

	Applicant's Analysis[a]	**FDA's Analyses[b]**	
Day-28 Response	**All Enrolled (n=71)**	**Failed Steroids Alone (n=49)**	**Failed Steroids +/- Other (n=58)**
ORR, n (%) (95% CI)	39 (54.9%) (42.7, 66.8)	28 (57.1%) (42.2, 71.2)	33 (56.9%) (43.2, 69.8)
CR, n (%)	19 (26.8%)	15 (30.6%)	16 (27.6%)
VGPR, n (%)	7 (9.9%)	2 (4.1%0	3 (5.2%)
PR, n (%)	13 (18.3%)	11 (22.4)	14 (24.1%)

Source: [a]Study 271 Clinical Study Report Table 13; [b]FDA analysis

As reported by the Applicant, the analysis performed on all enrolled patients showed a Day-28 ORR that excluded 40%, so the study was considered positive. Using FDA-adjudicated response

data, the results of FDA's analysis of ORR for the 49 patients who failed steroids alone also excluded 40%, thus supporting a conclusion that ruxolitinib is active for treatment of steroid-refractory acute GVHD. Since only the latter group represents the stated intended population, only the results for the 49 patients who failed steroids alone should be used in labeling.

For the patients who failed 2 or more therapies prior to study entry, the ORR was 55.6% (95% CI 21.2, 86.2). Although these results are consistent with the primary analysis in the intended population, the number of patients who failed 2 or more therapies is too small to draw conclusions about clinical meaningfulness. The results for this group in the published literature reviewed in Section 8.1.2 appear to be comparable, but none of the reports provides Day-28 ORR specifically, so they are not sufficient to be supportive. One might consider extrapolating efficacy from the primary analysis population to the group failing more treatments, but since the additional immunosuppressive drugs used in prior treatment may have altered the patients' immune status and the potential for response to ruxolitinib, the biology may not support such extrapolation. Hence, the available data are not sufficient to extend the indication to patients failing 2 or more therapies.

Durability of Response

The median follow-up for responders is 5.2 months (range, 1.1 - 14.4 months). For the 28 responders in the failed steroids alone group (n=49). For the 28 responders, the median DOR was 0.5 months (95% CI 0.3, 2.7). Although the median DOR is quite short, the definition of DOR does not take into account that GVHD may flare and resolve without additional treatment. An additional measure of the durability of response would be the time to treatment failure. For the 28 responders, the median time to either death or need for new therapy for acute GVHD (new GVHD drug or increase in steroids) was 5.7 months (95% CI 2.2, NE). By this measure, the durability of response is considered meaningful.

Subpopulations

The results in Table 17 demonstrate that responses were achieved independent of age, gender, race and various disease characteristics. Although pediatric patients were not included in the clinical trial, the biology of GVHD and the mechanism of action for ruxolitinib would not differ by age, so it would be appropriate to extrapolate efficacy to the pediatric population.

Of note, the ORR appeared to be greatest (100%) in patients with Grade 2 acute GVHD, but the response rate was still substantial in patients with a greater burden of disease or poorer prognosis as determined by Grade, ST2 level or MAGIC biomarker score (37.5-53.9%).

Secondary and Other Endpoints

Table 18 displays the results for NRM and OS. In the context of a single-arm trial, these time-to-

event endpoints are not interpretable and cannot be included in labeling.

Dose/Dose Response

Although treatment with ruxolitinib was to start at 5 mg BID and increase to 10 mg BID after 3 days, as described in Section 8.2.1, a substantial proportion of patients did not have an increased in ruxolitinib dose on time, or in some cases, at all. When looking at response by dose intensity through day 42, however, there was no substantial difference in ORR for the 23 patients with dose-intensity > 80% and the 26 patients with dose-intensity < 80% (52% vs 62%). This analysis supports the dose-schedule with the modifications as outlined in the protocol.

Additional Efficacy Considerations

Consistency of ORR and OS: As this is the first application for a treatment of acute GVHD using the efficacy endpoint of Day-28 ORR, an assessment of actual outcome by response would be of value to confirm whether Day-28 ORR as defined is associated with any long-term benefit. For the 49 patients who failed steroids alone, the 6-month OS was greater in those with Day-28 ORR than in those who did not respond (71% vs 24%). Although this responder analysis has no bearing on the analysis of the treatment effect itself, these results for ruxolitinib are consistent with the previously reported observations that Day-28 ORR is associated with reduced 6-month nonrelapse mortality in studies of other therapies for acute GVHD.

Chronic GVHD: Four patients were observed to have developed chronic GVHD (Section 8.1.1). However, the relatively short follow-up on this study precludes an accurate assessment of the incidence of chronic GVHD, so this outcome will not be reviewed further.

8.2.2 Integrated Assessment of Effectiveness

The ORR at Day 28 is 57.1% with 95% CI (42.2, 71.2) in the patients who failed steroids alone. Since the lower limit of the 95% CIs is greater than 40%, the predetermined criteria for a positive study outcome is met. It can be concluded that ruxolitinib is effective in treating patients with steroid-refractory aGVHD.

8.3 Review of Safety

8.3.1. Safety Review Approach

The safety profile of ruxolitinib has been established in review of prior approvals. The approved label carries warnings for cytopenias, infections, symptom exacerbation after discontinuation, nonmelanoma skin cancer and lipid elevations. The most common (> 20%) hematologic adverse reactions are thrombocytopenia and anemia, and the most common (> 10%) nonhematologic adverse reactions are bruising, dizziness and headache. An emerging class risk

is thromboembolism. On 2/25/2019, FDA issued a Safety Announcement regarding an increase in the incidence of "blood slots in the lungs and death" in patients with rheumatoid arthritis treated with tofacitinib.[3]

For the purposes of this review, the assessment of safety focused on the patients treated for acute GVHD in Study 271. The dose of ruxolitinib in Study 271 is the same as the dose proposed for labeling. The data files used for the analysis are from the safety update with a data cut-off of 4/2/2018.

8.3.2. Review of the Safety Database

Relevant Characteristics of the Safety Population

From 12/27/2016 through the data cut-off date of 4/2/2018, 84 patients were screened for Study 271, and 71 patients with acute GVHD were treated with ruxolitinib. Of these 71 patients, 49 had failed first-line steroids alone, 12 had failed steroids plus at least one other GVHD treatment, and 10 had failed steroid at a dose lower than required for eligibility. There were 3 patients (b) (6) whose first line steroid dose was low, but because they received a second-line treatment prior to study, they are included in the group of 12 patient who failed steroids plus at least one other GVHD treatment.

Table 22 shows the demographics and characteristics for all 71 patients treated.

Table 22: Study 271 - Demographics and Transplant Information

	Failed Steroids Alone (n=49)		Failed >= 2 Therapies (n=12)		Undertreated (n=10)		Total (n=71)	
Median age (range)	57 years (18 - 72 years)		61 years (22 - 73 years)		56.5 years (34 - 70 years)		58 years (18-73 years)	
Age Group								
<65 Years	43	88%	8	67%	7	70%	58	82%
>=65 Years	6	12%	4	33%	3	30%	13	18%
Sex								
Male	23	47%	5	42%	7	70%	35	49%
Female	26	53%	7	58%	3	30%	36	51%
Race								
White	45	92%	11	92%	10	100%	66	93%
Black/African American	2	4%	1	8%	0	0%	3	4%
Asian	2	4%	0	0%	0	0%	2	3%
Ethnicity								
Hispanic/Latino	7	14%	2	17%	0	0%	9	13%
Not Hispanic/Latino	41	84%	9	75%	10	100%	60	85%

[3] https://www.fda.gov/drugs/drug-safety-and-availability/safety-trial-finds-risk-blood-clots-lungs-and-death-higher-dose-tofacitinib-xeljanz-xeljanz-xr

Table 22: Study 271 - Demographics and Transplant Information

	Failed Steroids Alone (n=49)		Failed >= 2 Therapies (n=12)		Undertreated (n=10)		Total (n=71)	
Not Reported	1	2%	1	8%	0	0%	2	3%
Diagnosis								
Acute Leukemia/MDS	32	65%	9	75%	7	70%	48	68%
Lymphoma/CLL	7	14%	3	25%	2	20%	12	17%
Other	10	20%	0	0%	1	10%	11	15%
Donor								
Matched related	17	35%	3	25%	3	30%	23	32%
Matched unrelated	20	41%	7	58%	5	50%	32	45%
Mismatched unrelated	6	12%	1	8%	2	20%	9	13%
Haploidentical	5	10%	1	8%	0	0%	6	8%
Mismatched cord blood	1	2%	0	0%	0	0%	1	1%
Stem Cell Type								
HCTP-Apheresis	39	80%	11	92%	7	70%	57	80%
HCTP-Marrow	9	18%	1	8%	3	30%	13	18%
HCTP-Cord	1	2%	0	0%	0	0%	1	1%

Source: FDA analysis

Table 23 shows the baseline characteristics of acute GVHD for all 71 patients treated.

Table 23: Study 271 - Baseline Acute GVHD Characteristics

	Failed Steroids Alone (n=49)		Failed >= 2 Therapies (n=12)		Undertreated (n=10)		Total (n=71)	
Grade								
2	13	27%	3	25%	6	60%	22	31%
3	27	55%	4	33%	2	20%	33	46%
4	9	18%	5	42%	2	20%	16	23%
Visceral GVHD								
Yes	41	84%	9	75%	8	80%	58	82%
GVHD Onset before BMT Day 100								
Yes	34	69%	11	92%	7	70%	52	73%
MB risk group								
Low	8	17%	1	8%	3	30%	12	17%
High	39	83%	11	92%	7	70%	57	83%
Median MB score	0.47		0.51		0.38		0.46	
(range)	(0.10 - 0.92)		(0.26 - 0.96)		(0.14 - 0.77)		(0.10 - 0.96)	
Median log_{10}ST2 (ng/mL)	5.52		5.57		5.27		5.50	
(range)	4.74 -6.11		5.20 - 6.33		4.93 - 5.90		4.74 - 6.33	
Median Time from BMT to Ruxolitinib (range)	66 days (25 - 298 days)		72.5 days (29 - 214 days)		163.5 days (43 - 357 days)		74 days (25 - 357 days)	

Source: FDA Analysis

Overall Exposure

On Study 271, the patients were treated with ruxolitinib for a median of 46 days (range 4-382 days). Table 24 shows the breakdown of duration of treatment by prior therapy and for all enrolled patients. At the end of treatment, the dose was ruxolitinib was 10 mg BID for 20 (28%) patients, 5 mg BID for 20 (28%) patients, and 5 mg daily for 31 (44%) patients.

Table 24: Study 271 - Duration of Treatment with Ruxolitinib

Days	Failed Steroids Alone (n=49)		Failed >= 2 Therapies (n=12)		Undertreated (n=10)		Total (n=71)	
≤ 28	20	41%	5	42%	4	40%	29	41%
> 28-56	10	20%	4	33%	0	0%	14	20%
> 56-112	8	16%	0	0%	2	20%	10	14%
> 112-180	3	6%	1	8%	0	0%	4	6%
> 180	8	16%	2	17%	4	40%	14	20%

Source: FDA Analysis

All patients on Study 271 were allowed to continue treatment with corticosteroids and GVHD prophylaxis while on study. Due the problems with integrity of the data file as discussed in 8.1.1 above, descriptions of the concomitant medications and analyses of safety by concomitant medications would not be considered reliable and therefore were not performed.

Adequacy of the Safety Database

The size of the safety database (n=71) will allow for detection of adverse reactions with at least a 4% true incidence. The small number of patients limits the ability to detect rare events, but it is considered adequate given that the safety profile established in other disease settings. The duration of treatment in the safety population is adequate to provide assessment of adverse reactions in the short term. There were no dose-ranging studies, so safety cannot be assessed by dose.

The demographics of the safety database is notable for the absence of pediatric patients. The additional relevant safety data in children is discussed in Section 8.3.8.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

See Section 8.1.1 for the discussion of data integrity and submission quality.

Categorization of Adverse Events

AEs were reported using the investigator's verbatim term and coded by the Applicant using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 terms. The events were graded using the NCI-CTCAE version 4.03. Treatment-emergent adverse (TEAE) events included all events occurring within 30 days after the last dose of ruxolitinib.

FDA compared verbatim terms to (MedDRA) terms for AEs, and no irregularities were identified. If GVHD was in the AE term or the lower level term, the event was not included in the analysis. In order to improve the accuracy of estimating the risk of adverse reactions, grouped terms were used by FDA for some analyses, as described in Table 25.

Table 25: Grouped Terms Used for FDA Analyses of Adverse Events

Grouped Term	Basis
Bacterial infection	HLGT Bacterial infectious disorders
Diarrhoea	HLT Diarrhoea (excl infective)
Dizziness	Vestibular disorders (SMQ)
Dyspnoea	HLT Breathing abnormalities
Fatigue	HLT Asthenic conditions
Fungal infection	HLGT Fungal infectious disorders
Gastrointestinal pain	HLT Gastrointestinal and abdominal pains (excl oral and throat)
Haemorrhage	Haemorrhage terms (excl laboratory terms) (SMQ)
Infections	HLGT Infections - pathogen unspecified
Jaundice	HLT Cholestasis and jaundice
Oedema	HLT Oedema NEC
Rash	HLT Rashes, eruptions and exanthems NEC
Renal injury	HLT Renal failure and impairment
Thrombosis	Embolic and thrombotic events (SMQ)
Viral infection	HLGT Viral infectious disorders

Routine Clinical Tests

The schedules of safety monitoring for Study 271 is described in section 8.1.1 above. The schedule of examinations and testing was adequate to assess the risks of safety events.

8.3.4. Safety Results

Deaths

There were 34 deaths reported, representing 48% of the population; 23 deaths (32%) occurred within 30 days of the last dose of ruxolitinib. FDA adjudicated the root cause of death as relapse for any patient who died after relapse on study, as GVHD for any patient who died with

active GVHD, and infection for any patient who died of infection without active GVHD. Table 26 shows the FDA-adjudicated root causes of death. There were no cases with ruxolitinib adverse reactions as the root cause of death.

Table 26: Study 271 - FDA-Adjudicated Root Cause of Death

Root Cause of Death	Deaths	Deaths with 30 Days of Last Dose of Ruxolitinib
GVHD	30 (42%)	21 (30%)
Infection	3 (4%)	2 (3%)
Relapse	1 (1%)	0

Source: FDA analysis

There were no TEAEs listed as Grade 5, but 22 (31%) patients had a TEAE with a fatal outcome. The TEAEs with a fatal outcome are listed in Table 27.

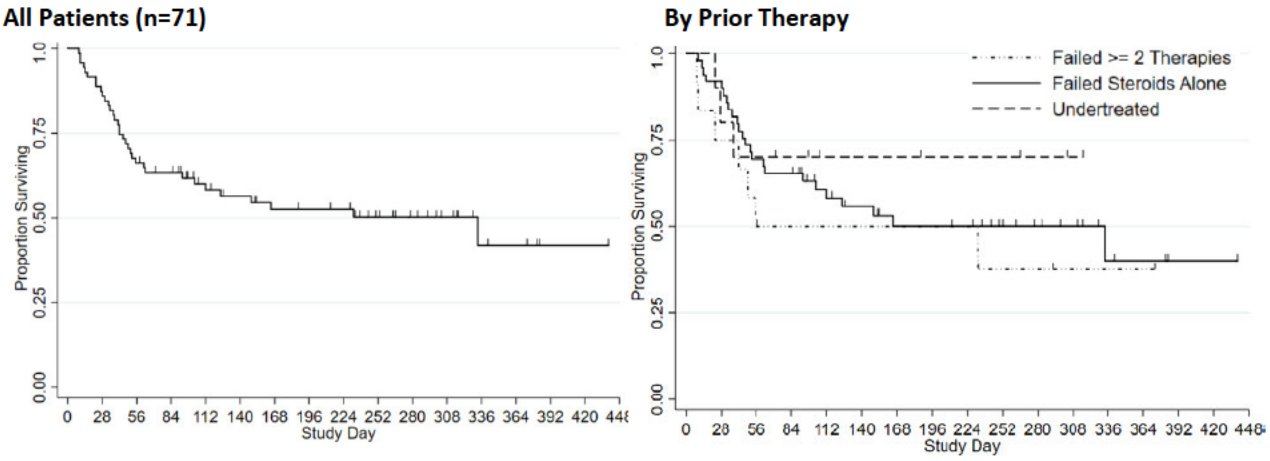
Table 27: Study 271 - TEAEs with Fatal Outcome

Term	N	(%)
Infection	8	11
Respiratory failure	6	8
Bacterial infection	3	4
Haemorrhage	3	4
Hepatic failure	2	3
Multiple organ dysfunction syndrome	2	3
Cardiac arrest	1	1
Fungal infection	1	1
Hypotension	1	1
Pulseless electrical activity	1	1
Renal injury	1	1
Sudden death	1	1
Thrombosis	1	1

Source: FDA analysis

Figure 12 shows the Kaplan-Meier survival curves for all 71 patients and by prior therapy. Although there are limitations in cross-study comparison, there do not appear to be late events that adversely impact long-term survival to an extent greater than that seen in this population in general.

Figure 12: Study 271 - Survival



Source: FDA analysis

Serious Adverse Events

An SAE was reported for 54 (76%) patients. The most common System Organ Class (SOC) for SAEs was Infections and infestations (48%). SAEs reported in more than 3% of patients are shown in Table 28.

Table 28: Study 271 - SAEs

Term	N	(%)
Infection	25	35
Bacterial infection	11	15
Hemorrhage	7	10
Pyrexia	7	10
Respiratory failure	7	10
Fungal infection	4	6
Pneumatosis intestinalis	4	6
Thrombosis	4	6
Diarrhea	3	4
Mental status changes	3	4
Viral infection	3	4

Source: FDA analysis

Dropouts and/or Discontinuations Due to Adverse Effects

There were 21 (31%) patients with a TEAE resulting in treatment discontinuation. The only TEAEs leading to treatment discontinuation that occurred in more than 1 patient were infection

(10%), renal injury (3%) and respiratory failure (3%).

There were 30 (42%) patients with a TEAE resulting in dose interruption, and 25 (35%) with a TEAE resulting in dose reduction. Table 29 shows the common (≥ 3%) TEAE leading to dose interruption or dose reductions.

Table 29: Study 271 - TEAEs with Dose Interruption or Reduction

Term	N	(%)
Term with Dose Interruption		
Infection	7	10
Platelet count decreased	7	10
Neutrophil count decreased	5	7
Alanine aminotransferase increased	3	4
Hypotension	3	4
Renal injury	3	4
White blood cell count decreased	3	4
Anaemia	2	3
Aspartate aminotransferase increased	2	3
Bacterial infection	2	3
Fungal infection	2	3
Haemorrhage	2	3
Thrombocytopenia	2	3
Term with Dose Reduction		
Neutrophil count decreased	7	10
Thrombocytopenia	7	10
Platelet count decreased	6	8
Anaemia	4	6
Neutropenia	4	6
Alanine aminotransferase increased	3	4
White blood cell count decreased	3	4
Mental status changes	2	3

Source: FDA analysis

Significant Adverse Events

Infections

An infection TEAE was reported in 78% of patients, the infection was Grades 3-5 in 62%, and the infection had a fatal outcome in 14%. The fatal infections included candida infection, device related infection, fungaemia, peritonitis, pneumonia, pneumonia legionella, sepsis septic shock, staphylococcal bacteraemia and staphylococcal sepsis. The most common

infections by HLT were sepsis (25%), cytomegaloviral infections (20%), lower respiratory tract infections (13%), urinary tract infections (11%) and staphylococcal infections (10%). Table 30 shows the range of infection TEAEs reported. All such infections are common in patients after allogeneic HSCT, and it is not clear that use of ruxolitinib was associated with an increased risk.

Table 30: Study 271 - Infection TEAEs

Infection Group	Term	N	(%)
Bacterial infection	Enterococcal infection	6	8%
	Staphylococcal infection	4	6%
	Klebsiella bacteraemia	2	3%
	Pseudomonas infection	2	3%
	Staphylococcal bacteraemia	2	3%
	Urinary tract infection bacterial	2	3%
	Cellulitis	1	1%
	Citrobacter infection	1	1%
	Clostridium difficile infection	1	1%
	Enterobacter bacteraemia	1	1%
	Escherichia urinary tract infection	1	1%
	Klebsiella infection	1	1%
	Otitis media bacterial	1	1%
	Pneumonia bacterial	1	1%
	Pneumonia legionella	1	1%
	Pseudomonal bacteraemia	1	1%
	Staphylococcal sepsis	1	1%
	Streptococcal bacteraemia	1	1%
	Streptococcal infection	1	1%
Protozoal infection	Cryptosporidiosis infection	1	1%
Fungal infection	Bronchopulmonary aspergillosis	3	4%
	Candida infection	2	3%
	Oral candidiasis	2	3%
	Hepatic infection fungal	1	1%
	Mycotic endophthalmitis	1	1%
	Oesophageal candidiasis	1	1%
	Oral fungal infection	1	1%
	Sinusitis fungal	1	1%
Infections Unspecified	Sepsis	8	11%
	Urinary tract infection	6	8%
	Bacteraemia	5	7%
	Pneumonia	5	7%
	Device related infection	4	6%
	Lung infection	4	6%
	Septic shock	4	6%
	Skin infection	3	4%
	Upper respiratory tract infection	3	4%
	Cystitis	1	1%
	Enterocolitis infectious	1	1%
	Fungaemia	1	1%
	Gastroenteritis	1	1%
	Kidney infection	1	1%

Table 30: Study 271 - Infection TEAEs

Infection Group	Term	N	(%)
	Peritonitis	1	1%
	Pharyngitis	1	1%
	Sialoadenitis	1	1%
	Sinusitis	1	1%
Viral infections	Cytomegalovirus infection	9	13%
	BK virus infection	5	7%
	Cytomegalovirus viraemia	4	6%
	Adenovirus infection	2	3%
	Corona virus infection	2	3%
	Respiratory syncytial virus infection	2	3%
	Cytomegalovirus chorioretinitis	1	1%
	Enterovirus infection	1	1%
	Human herpesvirus 6 infection	1	1%
	Influenza	1	1%
	Parainfluenzae virus infection	1	1%
	Rhinovirus infection	1	1%
	Urinary tract infection viral	1	1%

Source: FDA analysis

PTLD

There were no cases of EBV PTLD reported.

Graft Failure

One (1%) patient was reported as having secondary graft failure. This patient had only 17% donor chimerism at study baseline and hence was at risk for secondary graft failure prior to treatment with ruxolitinib. An associated between ruxolitinib and the event cannot be concluded.

Relapse

Only 2 (3%) patients had relapse of prior malignancy. There is no evidence that ruxolitinib is associated with an increased risk of relapse.

Hemorrhage

A hemorrhage TEAE was reported in 49% of patients, the TEAE was Grades 3-5 in 20%, and the TEAE had a fatal outcome in 4%. The fatal hemorrhages included 2 gastrointestinal hemorrhages and 1 pulmonary hemorrhage. The hemorrhage TEAE by High Level group Term (HLGT) are shown in Table 31.

Table 31: Study 271 - Hemorrhage TEAEs

HLGT	N	(%)
Gastrointestinal haemorrhages NEC	18	25%
Urinary tract signs and symptoms (e.g., hematuria)	11	15%
Upper respiratory tract disorders (e.g., epistaxis)	8	11%
Injuries NEC (e.g., bruising)	4	6%
Ocular haemorrhages and vascular disorders NEC	3	4%
Vascular haemorrhagic disorders	3	4%
Respiratory disorders NEC	2	3%
Skin vascular abnormalities	2	3%
Bladder and bladder neck disorders (excl calculi)	1	1%
Central nervous system vascular disorders	1	1%
Coagulopathies and bleeding diatheses (excl thrombocytopenic)	1	1%
Gastrointestinal vascular conditions	1	1%
Peritoneal and retroperitoneal conditions	1	1%
Procedural related injuries and complications NEC	1	1%
Vulvovaginal disorders (excl infections and inflammations)	1	1%

Source: FDA analysis

Thrombosis

A thrombosis TEAE was reported in 27% of patients, the TEAE was Grades 3-5 in 13%, and the TEAE had a fatal outcome in 1%. The fatal thrombosis TEAE was veno-occlusive disease, and it was considered unrelated to ruxolitinib. The types of thrombotic events reported are listed in Table 32.

Table 32: Study 271 - Thrombosis TEAEs

Term	N	(%)
Deep vein thrombosis	4	6%
Myocardial infarction	3	4%
Angina pectoris	2	3%
Thrombotic microangiopathy	2	3%
Troponin increased	2	3%
Acute myocardial infarction	1	1%
Disseminated intravascular coagulation	1	1%
Haemolytic uraemic syndrome	1	1%
Hepatic infarction	1	1%
Portal vein thrombosis	1	1%
Pulmonary embolism	1	1%
Splenic infarction	1	1%
Thrombosis in device	1	1%

Table 32: Study 271 - Thrombosis TEAEs

Term	N	(%)
Troponin I increased	1	1%
Vascular access site thrombosis	1	1%
Veno-occlusive liver disease	1	1%

Source: FDA analysis

Treatment Emergent Adverse Events and Adverse Reactions

At least one TEAE was reported in all (100%) patients. The numbers of patients with a TEAE are shown in Table 33 by SOC in decreasing order of incidence.

Table 33: Study 271 - TEAE by SOC

SOC	N	(%)
Metabolism and nutrition disorders	57	80
General disorders and administration site conditions	56	79
Infections and infestations	56	79
Gastrointestinal disorders	55	77
Investigations	50	70
Vascular disorders	49	69
Blood and lymphatic system disorders	48	68
Respiratory, thoracic and mediastinal disorders	47	66
Musculoskeletal and connective tissue disorders	44	62
Renal and urinary disorders	38	54
Nervous system disorders	36	51
Psychiatric disorders	34	48
Skin and subcutaneous tissue disorders	29	41
Cardiac disorders	27	38
Injury, poisoning and procedural complications	27	38
Eye disorders	18	25
Hepatobiliary disorders	17	24
Endocrine disorders	5	7
Reproductive system and breast disorders	5	7
Immune system disorders	4	6
Ear and labyrinth disorders	3	4
Neoplasms benign, malignant and unspecified	3	4
Surgical and medical procedures	1	1

Source: FDA analysis

The numbers of patients with the most common ($\geq$ 15%) TEAE are shown in Table 34 by PT in decreasing order of incidence.

Table 34: Study 271 - TEAEs by PT

Term	N	(%)
Anaemia	43	61
Infection	39	55
Oedema	36	51
Haemorrhage	35	49
Hypokalaemia	34	48
Platelet count decreased	31	44
Fatigue	26	37
Neutrophil count decreased	26	37
Bacterial infection	23	32
Dyspnoea	23	32
Hypomagnesaemia	23	32
Renal injury	23	32
Hypocalcaemia	22	31
Muscular weakness	22	31
Viral infection	22	31
Hyperglycaemia	18	25
Nausea	18	25
Thrombosis	18	25
White blood cell count decreased	18	25
Alanine aminotransferase increased	17	24
Diarrhoea	17	24
Gastrointestinal pain	17	24
Hypophosphataemia	17	24
Aspartate aminotransferase increased	16	23
Rash	16	23
Headache	15	21
Hypotension	15	21
Vomiting	15	21
Back pain	14	20
Decreased appetite	14	20
Fall	14	20
Hypertension	14	20
Pyrexia	14	20
Sinus tachycardia	14	20
Thrombocytopenia	14	20
Hyponatraemia	13	18
Jaundice	13	18
Arthralgia	12	17

Table 34: Study 271 - TEAEs by PT

Term	N	(%)
Cough	12	17
Hypoalbuminaemia	12	17
Depression	11	15
Dizziness	11	15
Pain in extremity	11	15

Source: FDA analysis

A Grade ≥ 3 TEAE was reported in 67 (94%) patients. The numbers of patients with common (≥ 10%) grade ≥ 3 TEAEs are shown in Table 35 by PT in decreasing order of incidence.

Table 35: Study 271 - Grade ≥ 3 TEAEs by PT

Term	N	(%)
Anaemia	33	46
Infection	29	41
Platelet count decreased	27	38
Neutrophil count decreased	22	31
Bacterial infection	20	28
Haemorrhage	14	20
Hyperglycaemia	13	18
Hypokalaemia	13	18
Hypophosphataemia	11	15
White blood cell count decreased	11	15
Fatigue	10	14
Hypoalbuminaemia	10	14
Hyponatraemia	10	14
Respiratory failure	10	14
Thrombocytopenia	10	14
Viral infection	10	14
Hypertension	9	13
Hypotension	9	13
Oedema	9	13
Fungal infection	8	11
Hypocalcaemia	8	11
Jaundice	8	11
Thrombosis	8	11
Lymphocyte count decreased	7	10
Muscular weakness	7	10
Renal injury	7	10

Source: FDA analysis

A TEAE suspected to be related was reported in 52 (73%) patients. The numbers of patients with common (>5%) related TEAEs are shown in Table 36 by PT in decreasing order of incidence.

Table 36: Study 271 - Related TEAEs by PT

Term	N	(%)
Anaemia	23	32
Platelet count decreased	22	31
Neutrophil count decreased	18	25
White blood cell count decreased	13	18
Infection	12	17
Thrombocytopenia	11	15
Viral infection	9	13
Alanine aminotransferase increased	8	11
Lymphocyte count decreased	7	10
Bacterial infection	6	8
Haemorrhage	6	8
Oedema	6	8
Aspartate aminotransferase increased	4	6
Dizziness	4	6
Fatigue	4	6
Pneumatosis intestinalis	4	6
Pyrexia	4	6

Source: FDA analysis

Laboratory Findings

Table 37 shows the proportions of patients with shifts from Grades 0-1 to Grades 2-4 or Grades 3-4 in key laboratory parameters. Although chemistry abnormalities were modest, cytopenias occurred in the majority of patients.

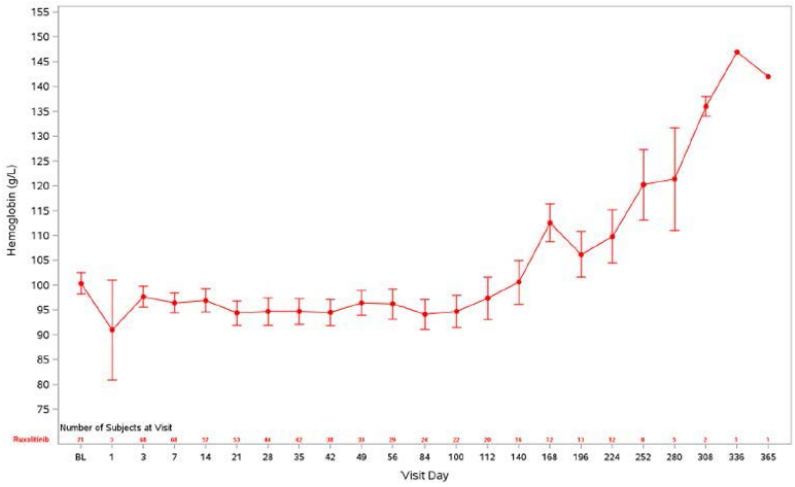
Table 37: Study 271 - Shift Table for Selected Laboratory Abnormalities

	Grade 0-1 Baseline	Grade 2-4 Max Post		Grade 3-4 Max Post	
Parameter	**(N)**	**N**	**%**	**N**	**%**
Hemoglobin	41	37	90	18	44
Platelets	35	30	86	21	60
Neutrophils	58	32	55	23	40
Bilirubin	52	15	29	2	4
Creatinine	69	17	25	3	4
Alanine aminotransferase	53	12	23	4	8
Aspartate aminotransferase	64	11	17	2	3

Source: FDA analysis

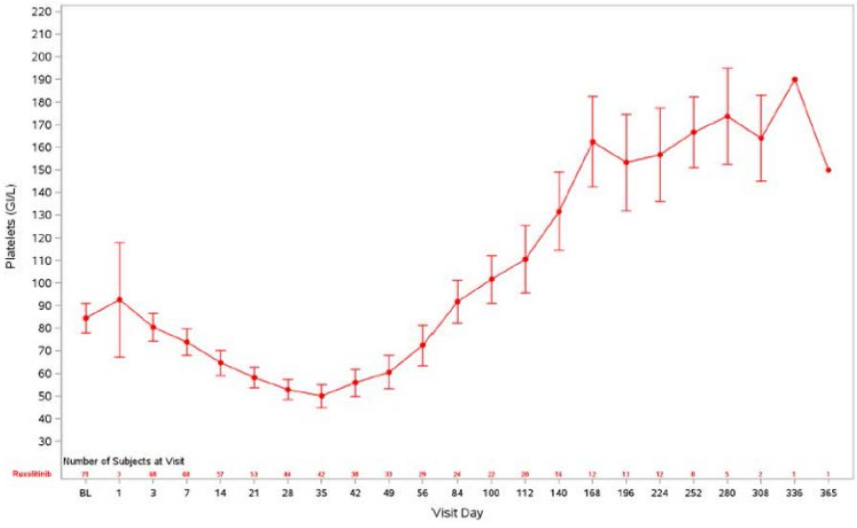
To further characterize the cytopenias during treatment with ruxolitinib, the Applicant provided a graphical analysis of hemoglobin, platelets and neutrophils over time (Figures 13-15). As shown, anemia and thrombocytopenia were frequent during the first 4-8 weeks, but blood count abnormalities appeared to resolve in patients on extended treatment.

Figure 13: Study 271 - Mean Hemoglobin Over Time



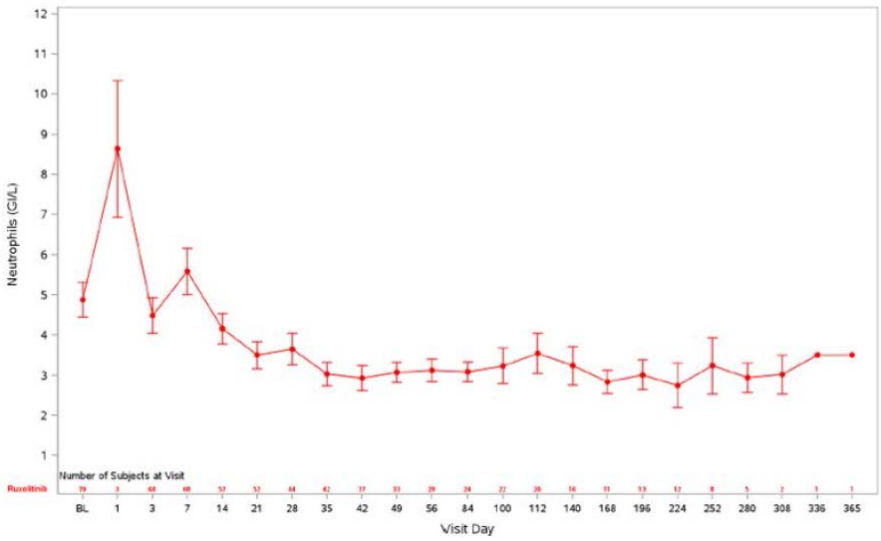
Source: Study 271 Clinical Study Report Figure 10

Figure 14: Study 271 - Mean Platelets Over Time



Source: Study 271 Clinical Study Report Figure 11

Figure 15: Study 271 - Mean Neutrophils Over Time



Source: Study 271 Clinical Study Report Figure 13

Vital Signs

The Applicant reported that there were no clinically relevant trends in vital signs in Study 271 (Study 271 Clinical Study Report Section 10.4.1). In view of the results in prior reviews confirming no expected effects on vital signs, no further analyses were undertaken.

QT/Electrocardiograms (ECGs)

Ruxolitinib has no effect on QT according to the IRT review (dated 9/6/2011) of the original application. There were four patients with abnormalities identified on ECG. The file eg.xpt, however, did not include actual ECG results, but the Applicant noted that the concurrent TEAE were supraventricular tachycardia, sinus tachycardia, myocardial infarction and increased pulse. The ECG data in this study provide no new safety issue except for the myocardial infarction as discussed in the section on thromboembolism above.

8.3.5 Analysis of Submission-Specific Safety Issues

There were no other submission-specific safety issues.

8.3.6 Safety Analyses by Subgroups

Table 38 shows the TEAE by age group in decreasing order of the difference in incidence between age groups. Only TEAE with a risk difference > 20% are shown. Older adult appeared to have more respiratory events, but the numbers of patients is too small for firm conclusions.

Table 38: Study 271 - TEAEs by Age Group

	< 65 years old (N = 58)		≥ 65 years old (N = 13)		Risk Difference (%)
Term	**N**	**%**	**N**	**%**	
Hypoxia	2	3	4	31	-27
Dyspnoea	16	28	7	54	-26
Oedema	27	47	9	69	-23
Hypotension	10	17	5	38	-21
Neutrophil count decreased	19	33	7	54	-21
Haemorrhage	32	55	3	23	32

Source: FDA analysis

Table 39 shows the TEAE by gender in decreasing order of the difference in incidence. Only TEAE with a risk difference > 20% are shown. Females appeared to have more gastrointestinal toxicities, and males had more muscle weakness.

Table 39: Study 271 - TEAEs by Gender

	Females (N = 36)		Males (N = 35)		Risk Difference (%)
Term	**N**	**%**	**N**	**%**	
Muscular weakness	7	19	15	43	-23
Anaemia	26	72	17	49	24
Hypomagnesaemia	16	44	7	20	24
Diarrhoea	13	36	4	11	25
Vomiting	12	33	3	9	25

Source: FDA analysis

There were too few patients who were not Caucasian to allow for a meaningful assessment of TEAEs by race.

Table 40 shows the TEAE by prior therapy in decreasing incidence in the subgroup failing steroids alone. In general, the incidence of TEAE was similar across the three subgroups.

Table 40: Study 271 - TEAEs by Prior Therapy

	Failed Steroids Alone (N = 49)		Failed >= 2 Therapies (N = 12)		Undertreated (N = 10)	
Term	**N**	**%**	**N**	**%**	**N**	**%**
Anaemia	33	67	5	42	5	50
Hypokalaemia	27	55	6	50	1	10
Infection	27	55	8	67	4	40
Haemorrhage	25	51	6	50	4	40

Oedema	24	49	8	67	4	40
Platelet count decreased	22	45	5	42	4	40
Hypocalcaemia	19	39	2	17	1	10
Neutrophil count decreased	19	39	4	33	3	30
Dyspnoea	18	37	3	25	2	20
Muscular weakness	17	35	3	25	2	20
Fatigue	17	35	4	33	5	50
Bacterial infection	16	33	4	33	3	30
Viral infection	16	33	3	25	3	30
Hyperglycaemia	15	31	1	8	2	20
Hypomagnesaemia	15	31	5	42	3	30
Renal injury	15	31	5	42	3	30
Gastrointestinal pain	14	29	3	25	0	0
White blood cell count decreased	14	29	2	17	2	20
Hypophosphataemia	13	27	3	25	1	10
Alanine aminotransferase increased	13	27	2	17	2	20
Nausea	13	27	3	25	2	20
Thrombosis	13	27	3	25	2	20
Pyrexia	12	24	1	8	1	10
Diarrhoea	12	24	3	25	2	20
Decreased appetite	11	22	2	17	1	10
Hyponatraemia	11	22	1	8	1	10
Sinus tachycardia	11	22	2	17	1	10
Thrombocytopenia	11	22	2	17	1	10
Rash	11	22	3	25	2	20
Aspartate aminotransferase increased	11	22	2	17	3	30
Headache	11	22	1	8	3	30
Hypertension	10	20	4	33	0	0
Cough	10	20	1	8	1	10
Fall	10	20	2	17	2	20

Source: FDA analysis

8.3.7 Clinical Outcomes Assessments Informing Tolerability/Safety

There were no patient-reported outcomes data submitted.

8.3.8 Specific Safety Studies/Clinical Trials

There were no specific clinical safety studies/trial submitted.

A literature review was performed as described in Section 8.1.2. There were no new safety issues identified in the literature review. Five publications identified 2 safety issues as follows:

- Cytopenias (Zeiser et al. 2015; Maffini et al. 2016; Maldonado et al. 2017; Gonzalez Vicent et al. 2018)
- Elevated liver enzymes (Khandelwal et al. 2017; Gonzalez Vicent et al. 2018)

8.3.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

There were 3 (4%) patients with a neoplasm reported in Study 271; 2 had recurrence of AML, and 1 had a urothelial transitional cell carcinoma.

Pediatrics and Assessment of Effects on Growth

The safety of ruxolitinib in the pediatric population was reviewed previously (see review of NDA 202192 Supplement 015), and the results are summarized in Section 8.4 of the US Prescribing Information. Gonzaelz Vicent et al (2017) and Khandelwal et al (2018) reported on safety of ruxolitinib in 22 and 13 children, respectively, during treatment for GVHD. The safety profile in the pediatric patients did not appear to differ from that described above for adults.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Exacerbation of symptoms is known to occur in patients with myelofibrosis and polycythemia vera after abrupt discontinuation of ruxolitinib. Study 271 provided instructions for tapering the dose of ruxolitinib, and there were no cases of such exacerbation reported in the patients treated. Given that many patients discontinued due to lack of efficacy, it may not have been possible to recognize an exacerbation of cytokine-mediated symptoms within the context of the progressive GVHD.

8.3.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

An Empirica Signal analysis of FAERS through 1Q2019 identified no new safety signals for ruxolitinib. There were 18 cases that included the term "acute graft-vs-host disease," but there was no unifying or unexpected ruxolitinib-related toxicity reported in these cases.

Expectations on Safety in the Postmarket Setting

Given the immunosuppressive nature of ruxolitinib, and the background risk of opportunistic infections in the intended population, there is concern that the rate of fatal or life-threatening infections, including PTLD, may be higher in the postmarket setting. This issue is addressed in part with the warning in labeling.

Additionally, as discussed in Section 8.3.9, there may be a risk for exacerbation of GVHD upon abrupt withdrawal. Labeling is clear about the need to taper the dose rather than to withdraw abruptly.

8.3.11 Integrated Assessment of Safety

In a single-arm, open-label study, 71 adults were treated with Jakafi for acute GVHD failing treatment with steroids with or without other immunosuppressive drugs. The median duration of treatment with ruxolitinib was 46 days (range, 4-382 days). A dose interruption was required for 42% and a dose reduction for 35%. By end of treatment, only 20 (28%) patients were on the full target dose of 10 mg BID.

There were no fatal adverse reactions attributed to Jakafi. A fatal infection occurred in 14% and a fatal hemorrhage in 4%. Although the cytopenias associated with ruxolitinib may be contributing factors in infection and hemorrhage, with the high background rate of these event in patients with GVHD and in the absence of a randomized control for comparison, it was not possible to clearly confirm a causal association. An adverse reaction resulted in treatment discontinuation occurred in 31%, the most common adverse reactions leading to treatment discontinuation was infection (10%).

Table 41 shows the adverse reactions other than laboratory abnormalities. Table 42 shows the laboratory abnormalities considered to be adverse reactions.

Table 41: Nonhematological Adverse Reactions Occurring in ≥ 15% of Patients

Adverse Reactions	All Grades (%)	Grade ≥ 3 (%)
Infections	55	41
Edema	51	13
Hemorrhage	49	20
Fatigue	37	14
Bacterial infections	32	28
Dyspnea	32	7
Viral infections	31	14
Thrombosis	25	11
Diarrhea	24	7
Rash	23	3
Headache	21	4
Hypertension	20	13
Dizziness	16	0

Table 42: Laboratory Adverse Reactions

	Worst grade during treatment	
Laboratory Parameter	**All Grades[a] (%)**	**Grade 3-4 (%)**
Hematology		
Anemia	75	45
Thrombocytopenia	75	61
Neutropenia	58	40
Chemistry		
Elevated ALT	48	8
Elevated AST	48	6
Hypertriglyceridemia	11	1

The adverse reaction profile was based on TEAEs as reported excluding terms specifying GVHD and relapse; terms with no biologically-plausible association were also excluded. The analysis could be confounded if, for example, GI GVHD was coded as diarrhea rather than under the syndrome name of GVHD of the gastrointestinal tract, but it was not possible to identify such cases with the data files available. Established kinase inhibitor class effects (e.g., diarrhea, rash, edema, etc.) were included as adverse reactions.

There were no new safety signals that warranted a warning. The risk of infections noted warrants adding a recommendation for active surveillance and prophylactic antibiotics to the warning about infections.

SUMMARY AND CONCLUSIONS

8.4 Statistical Issues

During the review, two potential issues were identified. First, Study 271 was designed to be a single cohort study with no concurrent comparator arm (placebo or standard of care). The Applicant proposed to demonstrate the efficacious benefit of ruxolitinib by showing the lower limit of the 95% CI of the estimated ORR to be greater than or equal to a pre-specified threshold (historical control) of 40%. In general, a design without concurrent control may introduce bias to the study and undermine the interpretability of the study results, however, FDA has relied on single arm trials as evidence of efficacy. For this study, FDA indicated at the Type B meeting on 27 May 2018 that one single-arm trial might be sufficient to support the submission (refer to Methods section of Section 8.2.1).

Second issue was related to the reduced sample size from 71 patients to 49 patients (30%

reduction) for the primary efficacy analysis. The study was originally powered for 70 patients. However, during the review, FDA review team determined only patients who were steroid-refractory and failed steroids alone (n=49) were appropriate for the proposed indication by the Applicant, therefore, the results from this subpopulation were used for the labeling claim. A reduced sample size may decrease the study power because it gives a wider confidence interval and thus increase the probability of excluding the threshold of 40%. In this case, the lower limit of the 95% CI of the ORR with sample size of 49 patients still excluded 40%, hence, the issue was considered minor.

8.5 Conclusions and Recommendations

The result of Study 271 show that ruxolitinib is active in the treatment of steroid-refractory acute GVHD, and the risks are acceptable for the intended population with instructions in labeling to address the risks of infection and hemorrhage. Approval is recommended.

Lola Luo, PhD Primary Statistical Reviewer	Lei Nie, PhD Statistical Team Leader
Lea Cunningham, MD Primary Clinical Reviewer	Donna Przepiorka, MD, PhD Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

This application was not discussed by an advisory committee.

10 Pediatrics

Ruxolitinib has Orphan Designation for treatment of graft-versus-host disease and is therefore exempt from the requirement for pediatric studies under the Pediatric Research Equity Act (PREA). No pediatric data were submitted with this NDA. The intended population can be extended to adolescents (age 12 years and older) on the basis of extrapolation of efficacy and extant safety data in the pediatric population; the extended age range is limited to 12 years old by the formulation.

11 Labeling Recommendations

11.1 Prescribing Information

Summary of Significant Labeling Changes

Section	Approved Labeling
1.3 Indication and Usage	Revised indication to "for treatment of steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients 12 years and older."
2.3 Dosage and Administration	Added duration and instructions for tapering, added dose modifications for toxicity, and added dose modifications for organ impairment.
5.2 Warnings and Precautions	Added instructions for monitoring and prophylaxis for infections.
6.3 Adverse Reactions	Revised listing from adverse events to adverse reactions.
14.3 Clinical Studies	Limited displayed population to those refractory to steroids alone (n=49).

12 Risk Evaluation and Mitigation Strategies (REMS)

It was concluded that a REMS is not needed to ensure that the benefits of ruxolitinib outweigh its risks in the intended population. Healthcare providers who will prescribe and administer ruxolitinib are likely to be able to monitor for and manage the ruxolitinib-related adverse reactions without additional risk mitigation measures beyond labeling.

13 Postmarketing Requirements and Commitments

There are no postmarketing requirements or commitments.

14 Appendices

14.1 References

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D'Souza A, et al, (2018) Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides.

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Zeiser R, et al. (2015) Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Leukemia 29:2062-8.

14.2 Financial Disclosure

Covered Clinical Study: INCB 18424-271

Was a list of clinical investigators provided:	Yes X ☐	No ☐ (Request list from Applicant)
Total number of investigators identified: 473		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): NA No patients were enrolled at the clinical sites where these was an investigator with disclosable financial interests or arrangements		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No
Is a description of the steps taken to minimize potential bias provided:	Yes	No
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes	No

14.3 Nonclinical Pharmacology/Toxicology

None.

14.4 OCP Appendices

PHARMACOMETRIC REVIEW

1. Population PK analysis

1.1 Introduction

The objectives of this population pharmacokinetic (PK) analysis were:

• To describe the PK of ruxolitinib in patients with steroid-refractory acute graft versus host disease (SR-aGVHD).

• To evaluate the difference in PK between MF and SR-aGVHD patients.

• To identify predictors of exposure to the drug (demographics, laboratory values, disease status, concomitant medications, etc) and identify subpopulations with altered PK.

• To estimate the interpatient variability of ruxolitinib PK.

1.2 Model development

1.2.1 Data

The analyses were based on PK data from 3 studies. The study design, study population, and timing of blood samples varied among the 3 clinical studies. Brief descriptions of the studies included are presented in ***Table 43***.

The final NONMEM data file for analysis contained 646 PK observations from 71 subjects with SR-aGVHD and 2193 PK observations from 272 subjects with MF.

Table **44** provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 43. Summary of Studies with PK Sampling Included in Population PK Analysis

Protocol # & Study Design	**Dosage Regimen & Study Description**	**Number of Subjects in PopPK Analysis, Subject Type**	**Dose(s) [mg]**
INCB 18424-271 [REACH-1]: a single-cohort, Phase 2 Open-label study of ruxolitinib in combination with corticosteroids for	Ruxolitinib tablets were administered as oral doses in an outpatient setting.	71 patients with SR-aGVHD	Starting dose was 5 mg BID, and the dose of ruxolitinib did not exceed 10 mg BID.

the treatment of SR-aGVHD.			
INCB 18424-251: a phase 2 Open-label study in patients with MF	Ruxolitinib tablets were administered as oral doses in an outpatient setting.	154 subjects with PMF, post-PV/ET-MF	Part 1: 25 mg BID and 50 mg BID Part 2: 10 mg BID, 25 mg BID, 25 mg QD, 50 mg QD, and 100 mg QD Part 3: 10 mg BID, 15 mg BID, 25 mg BID, 50 mg QD, 100 mg QD, and 200 mg QD
INCB 18424-351 [COMFORT-1]): a phase 3 randomized, double-blind, placebo-controlled study in patients with MF	Ruxolitinib tablets were administered as oral doses in an outpatient setting.	Subjects with PMF, PPV-MF, or PET-MF (154 placebo, 155 active drug)	Subjects with baseline platelet count > 200,000/µL began dosing at 20 mg BID (four 5 mg tablets BID) Subjects with baseline platelet count of 100,000/µL to 200,000/µL (inclusive) began dosing at 15 mg BID (three 5 mg tablets BID). A standardized dosing paradigm was used to determine dose adjustments for safety and efficacy.

(Source: Applicant's Population PK report, Table 1)

Table 44. Summary of Baseline Demographic Covariates for Analysis

Participant Characteristics	Study 251 (N = 125)	Study 271 (N = 71)	Study 351 (N = 147)	Pooled (N = 343)
Age, year				
Mean (SD)	63.83 (8.26)	52.89 (14.18)	66.31 (8.65)	62.63 (11.13)
Median	65	58	66	64
Min, Max	39, 83	18, 73	43, 87	18, 87
Weight (kg)				
Mean (SD)	75.85 (18.05)	78.64 (21.65)	73.06 (15.95)	75.23 (18.09)
Median	74	75.9	72.3	73.6
Min, Max	45.3, 150.8	46, 139	45.1, 124.4	45.1, 150.8
Body mass index kg/m^2				
Mean (SD)	25.63 (4.8)	26.83 (6.24)	25.12 (4.86)	25.66 (5.18)
Median	25.69	25.47	24.4	24.9
Min, Max	16.6, 49.2	17.2, 46.59	16.3, 55.9	16.3, 55.9
Gender, n (%)				
Male	77 (61.6)	35 (49.3)	75 (51)	187 (54.5)
Female	48 (38.4)	36 (50.7)	72 (49)	156 (45.5)
Race, n (%)				
White	120 (96)	66 (93)	130 (88.4)	316 (92.1)
Black	1 (0.8)	3 (4.2)	6 (4.1)	10 (2.9)
Asian	2 (1.6)	2 (2.8)	5 (3.4)	9 (2.6)
Other	2 (1.6)		6 (4.1)	8 (2.3)
MDRD GFR ($mL/min/1.73\ m^2$)				
Mean(SD)	72.62 (21.2)	108 (50.85)	66.74 (19.6)	77.43 (33.28)
Median	71	96	66	71
Min, Max	35, 145	34, 259	27, 135	27, 259
Total bilirubin (µmol/L)				
Mean (SD)	13.42 (8.18)	38.01 (58.66)	15.89 (8.15)	19.57 (29.11)
Median	11.97	13.68	14	12
Min, Max	3.42, 49.59	3.42, 359.1	4, 50	3.42, 359.1
Creatinine, UMOL/L				
Mean (SD)	94.27 (26.87)	70.33 (29.88)	93.29 (26.3)	88.9 (28.81)
Median	88.4	63.648	88	88
Min, Max	44.2, 176.8	26.52, 178.57	44, 177	26.52, 178.57
Baseline platelet count, GI/L				
Mean (SD)	340.04 (216.55)	84.55 (55)	321.6 (201.06)	279.25 (211.83)
Median	268	74	264	222
Min, Max	101, 1195	10, 267	72, 984	10, 1195

Participant Characteristics	Study 251 (N = 125)	Study 271 (N = 71)	Study 351 (N = 147)	Pooled (N = 343)
Albumin (G/L)				
Mean (SD)	41.02 (3.84)	27.27 (6.75)	42.86 (3.74)	38.96 (7.56)
Median	42	27	43	41
Min, Max	31, 53	11, 42	27, 52	11, 53
Alkaline phosphatase (U/L)				
Mean (SD)	147.98 (110.09)	127.7 (116.82)	137.14 (85.06)	139.13 (101.65)
Median	114	77	117	108
Min, Max	42, 706	31, 622	42, 598	31, 706
Alanine aminotransferase (U/L)				
Mean (SD)	26.46 (18.01)	135.51 (201)	18.84 (10.37)	45.77 (102.73)
Median	21	53.5	17	21
Min, Max	8, 116	8, 1018	5, 65	5, 1018
Aspartate aminotransferase (U/L)				
Mean (SD)	38.64 (16.25)	53.58 (59.51)	27.78 (10.94)	37.08 (31.08)
Median	35	28	26	30
Min, Max	10, 90	6, 355	7, 58	6, 355
NCI hepatic impairment classification, n (%)				
Normal	63 (50.4)	39 (54.9)	116 (78.9)	218 (63.6)
Mild (B1)	32 (25.6)	9 (12.7)	6 (4.1)	47 (13.7)
Mild (B2)	19 (15.2)	4 (5.6)	19 (12.9)	42 (12.2)
Moderate	9 (7.2)	7 (9.9)	6 (4.1)	22 (6.4)
Severe		12 (16.9)		12 (3.5)
Unknown	2 (1.6)			2 (0.6)
Renal impairment category, n (%)				
Normal	14 (11.2)	43 (60.6)	17 (11.6)	74 (21.6)
Mild	71 (56.8)	18 (25.4)	75 (51)	164 (47.8)
Moderate	38 (30.4)	10 (14.1)	53 (36.1)	101 (29.4)
Severe			2 (1.4)	2 (0.6)
Unknown	2 (1.6)			2 (0.6)
Baseline skin involvement, n (%)				
Stage 0	125 (100)	35 (49.3)	147 (100)	307 (89.5)
Stage 1		4 (5.6)		4 (1.2)
Stage 2		7 (9.9)		7 (2)
Stage 3		22 (31)		22 (6.4)
Stage 4		3 (4.2)		3 (0.9)

Participant Characteristics	Study 251 (N = 125)	Study 271 (N = 71)	Study 351 (N = 147)	Pooled (N = 343)
Baseline upper GI involvement, n (%)				
Stage 0	125 (100)	49 (69)	147 (100)	321 (93.6)
Stage 1		22 (31)		22 (6.4)
Baseline lower GI involvement, n (%)				
Stage 0	125 (100)	21 (29.6)	147 (100)	293 (85.4)
Stage 1		11 (15.5)		11 (3.2)
Stage 2		9 (12.7)		9 (2.6)
Stage 3		19 (26.8)		19 (5.5)
Stage 4		11 (15.5)		11 (3.2)
Baseline liver involvement, n (%)				
Stage 0	125 (100)	56 (78.9)	147 (100)	328 (95.6)
Stage 1		2 (2.8)		2 (0.6)
Stage 2		4 (5.6)		4 (1.2)
Stage 3		8 (11.3)		8 (2.3)
Stage 4		1 (1.4)		1 (0.3)
MAGIC criteria grade at baseline, n (%)				
Grade 0	125 (100)		147 (100)	272 (79.3)
Grade 2		23 (32.4)		23 (6.7)
Grade 3		34 (47.9)		34 (9.9)
Grade 4		14 (19.7)		14 (4.1)

Concomitant Medication	Strength	Study 251 N = 125 (%)	Study 271 N = 71 (%)	Study 351 N = 147 (%)	Pooled N = 343 (%)
CYP3A4 inhibitor	Weak	16 (12.8)	24 (33.8)	14 (9.5)	54 (15.7)
	Moderate	5 (4)	12 (16.9)	14 (9.5)	31 (9)
	Potent		30 (42.3)	1 (0.7)	31 (9)
CYP3A4 inducer	Weak	7(5.6)	5 (7)	12 (8.2)	24 (7)
	Moderate	1 (0.8)		2 (1.4)	3 (0.9)
	Potent	1 (0.8)	1 (1.4)	2 (1.4)	4 (1.2)
CYP2C9 inhibitor	Weak	3 (2.4)	12 (16.9)	8 (5.4)	23 (6.7)
	Moderate		12 (16.9)		12 (3.5)
	Potent				
CYP2C9 inducer	Weak	1 (0.8)	1 (1.4)		2 (0.6)
	Moderate				
	Potent				
Dual CYP3A4 and CYP2C9 inhibitor		2 (1.6)	24 (33.8)	1 (0.7)	27 (7.9)
Dual CYP3A4 and CYP2C9 inducer		1 (0.8)	1 (1.4)		2 (0.6)
Use multiple CYP3A4 inhibitors		1 (0.8)	40 (56.3)	3 (2)	44 (12.8)

Abbreviations: N=Number of subjects, SD=Standard deviation
(Source: Applicant's Population PK report, Table 8, 9)

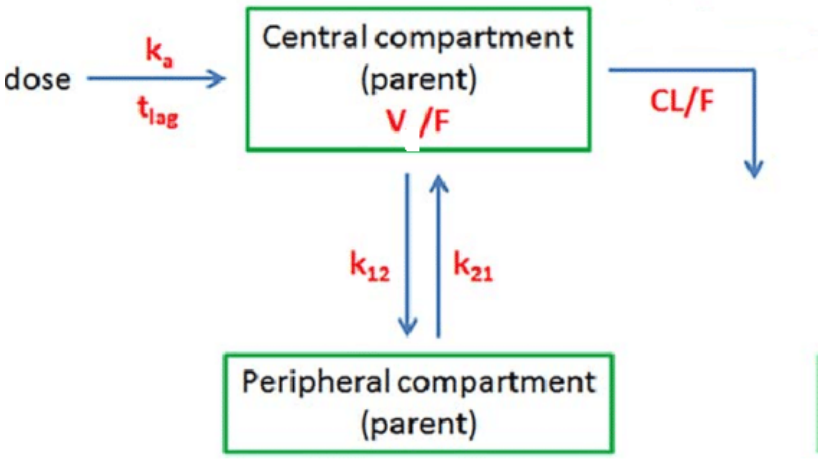
Base model

The final base model was a two-compartment PK model with lag time, first-order absorption, and first-order elimination from the central compartment. The effect of weight was included as

a fixed allometric exponent on Vc/F. (**Figure 16**)

Inter-individual variability (IIV) was modelled assuming a log-normal distribution for patient level random effects. Residual variability was tested with different error structures in order to determine the final model. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Figure 16. Scheme of Model Structure



Covariate analysis

The covariates that were examined included renal impairment, hepatic impairment, gender, race, age, body weight, study, patient population (MF vs SR-aGVHD), dose, BMI, AST, alanine aminotransferase (ALT), alkaline phosphatase (ALP), ALB, total bilirubin (TBIL), CLCr, survival status, baseline upper GI involvement, baseline lower GI involvement, baseline skin involvement, baseline liver involvement, baseline grade per MAGIC guidance, baseline platelet counts, and baseline MDRD. The time-depended disease status covariates tested included actual upper GI involvement, actual lower GI involvement, actual skin involvement, actual liver involvement, and actual grade per MAGIC guidance on each PK visit. The concomitant medications explored were CYP3A4 inhibitors/inducers; prednisone, CYP2C9 inhibitors, dual CYP3A4/CYP2C9 inhibitors, antifungal therapy, and anti-CMV therapy.

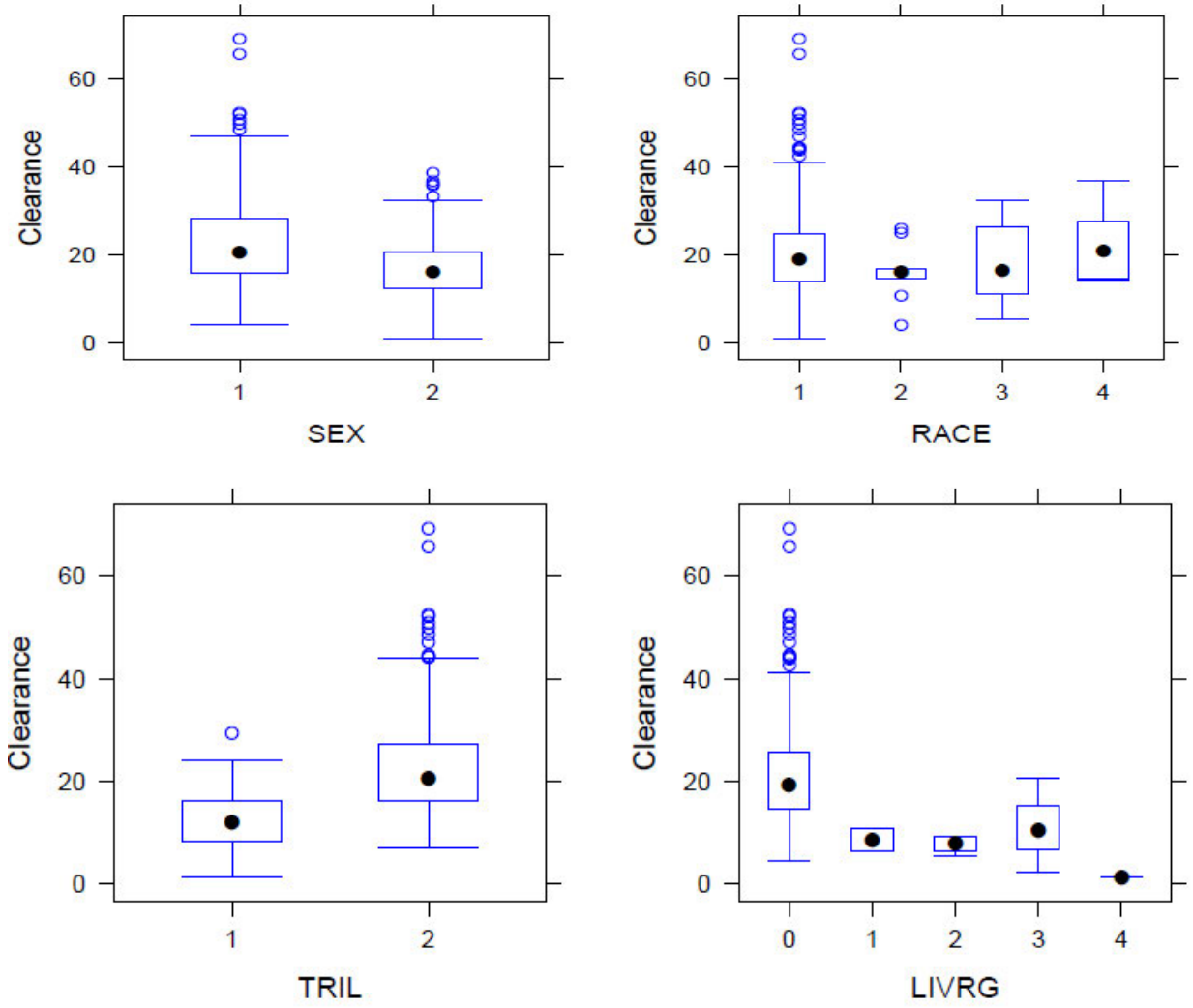
Through forward and backward selection, sex, patient population, actual MAGIC score, actual liver involvement and CYP3A4 inhibitor were selected as predictors for CL/F and actual MAGIC score for Ka.

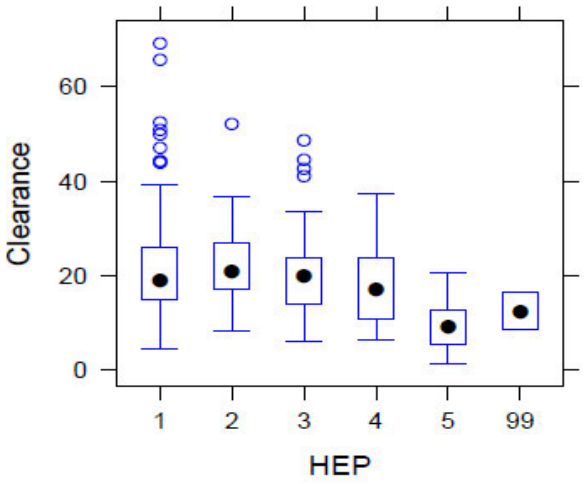
Furthermore, incorporation of anti-CMV therapy, acyclovir, ganciclovir, antifungal therapy, and prednisone on clearance did not improve the model, suggesting lack of effects of anti-CMV therapy, acyclovir, ganciclovir, antifungal therapy, and prednisone on clearance.

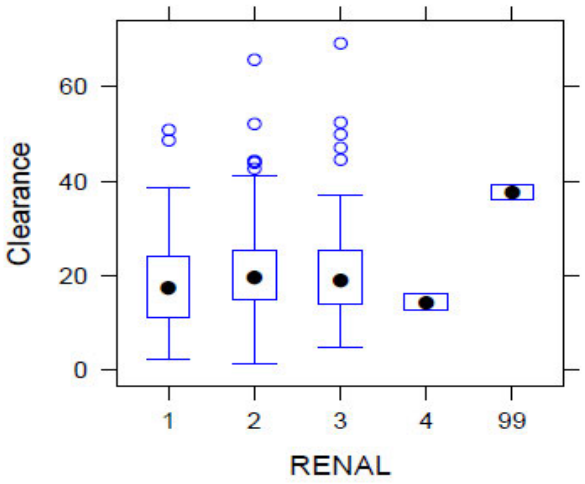
The reviewer's analysis of covariates effect on PK was similar to that of the applicant. The effects of sex, race, body weight, hepatic function, renal function, CYP3A4 inhibitor, actual liver

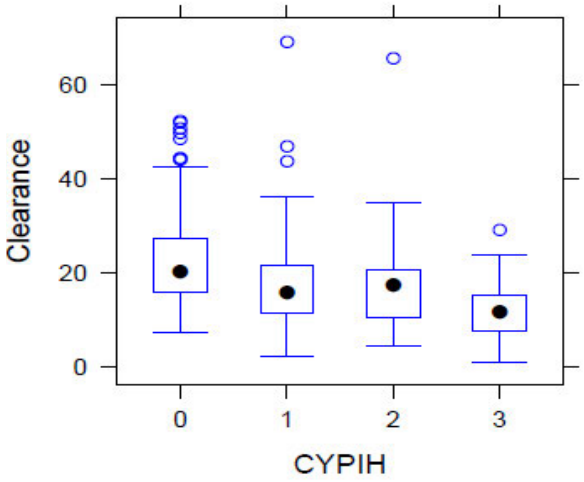
involvement, patient population and MAGIC score on clearance (CL/F) are explored in **Error! Reference source not found.**. The covariate effects on IIV for CL/F are illustrated in **Error! Reference source not found.**.

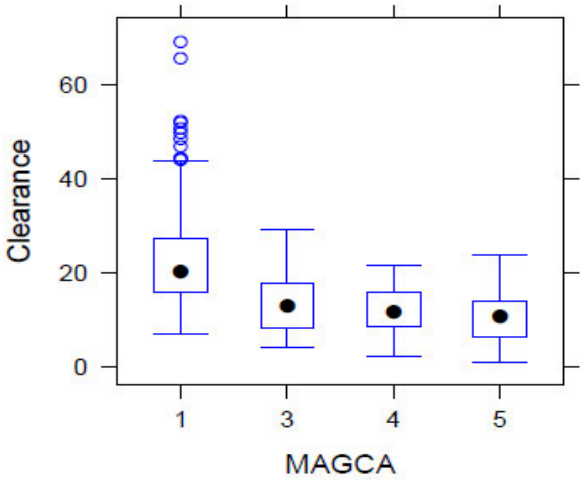
Figure 17. Covariate Effects on Apparent Clearance











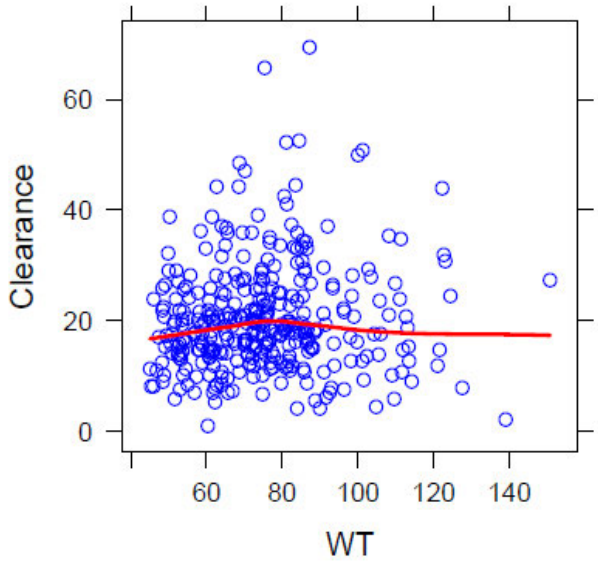
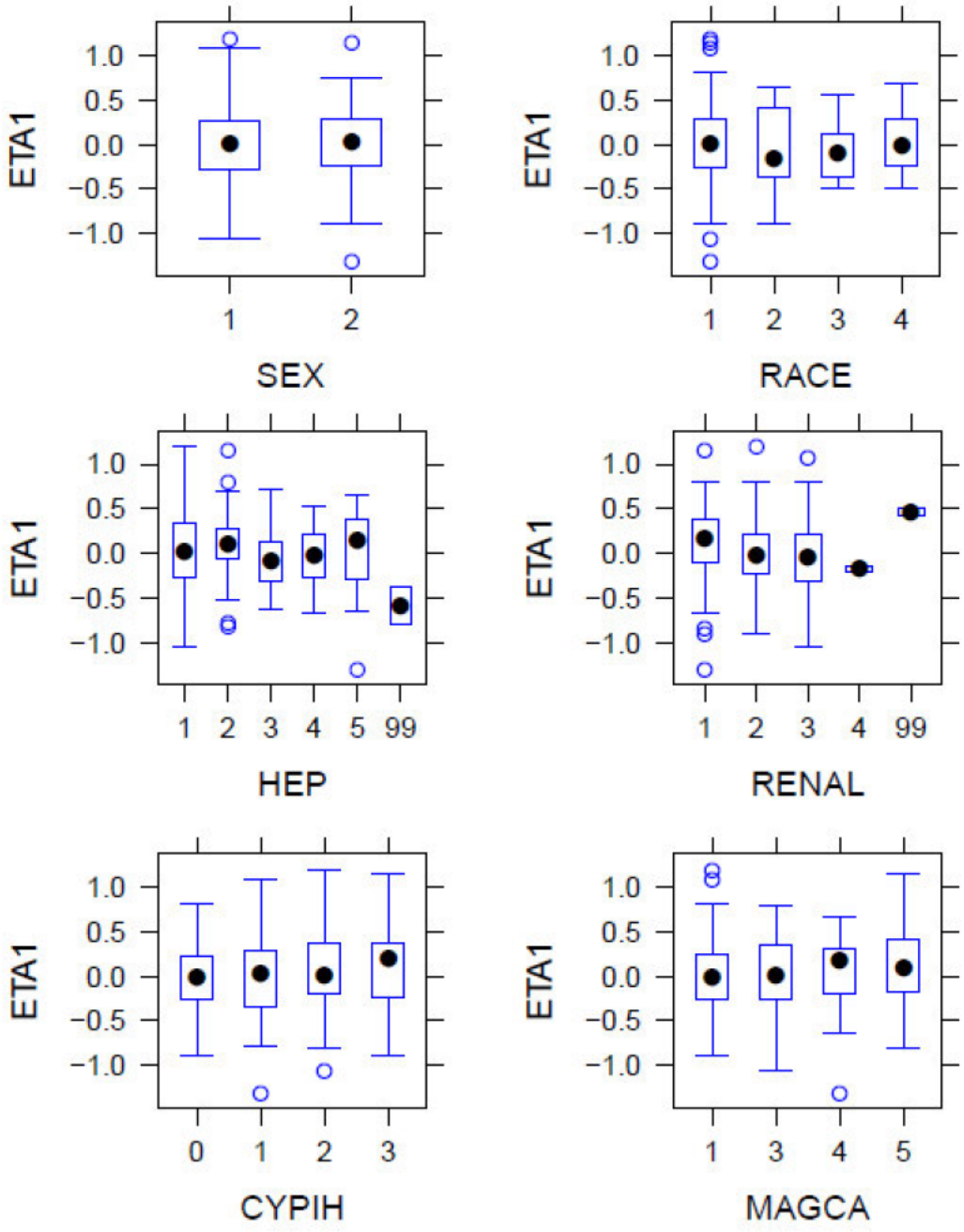
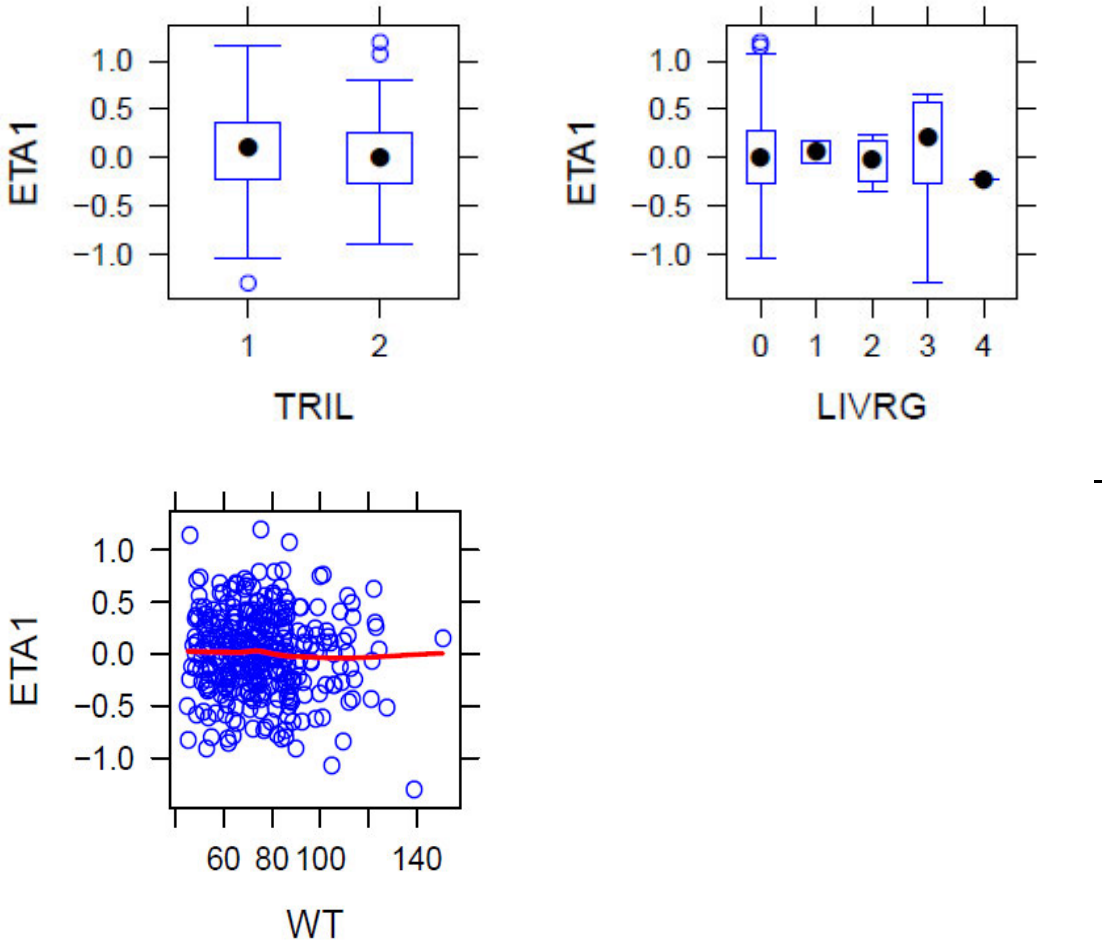


Figure 18. IIV by covariates





1.3 Results

The parameter estimates for the final covariate model are listed in ***Table 45***. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 17. The Visual Predictive Check (VPC) plot for the final covariate model with all data by dose is shown in Figure 18.

Table 45. Parameter Estimates (RSE) and Median (95% CI) for the Final Model without outliers

Parameter	Final Parameter Estimate			Magnitude of Inter-individual Variability (%CV)		
	Population Mean	%SEM	95% CI	Final Estimate	%SEM	95% CI
K_a (h^{-1})	4.06	13.3	3.08, 5.34	115	14.2	97.2, 131
$ALAG_1$ (h)	0.0753	4.25	0.068, 0.168	NE	NE	
CL/F (L/h) for male	23.5	3.45	22.0, 25.2	43.1[a]	9.68	38.5, 47.0
CL/F (L/h) for female	18.4	3.60	17.2, 19.7			
V_c/F[b] for subject with body weight of 72.9 kg (L)	59.3	2.63	55.7, 62.4	26.2	17.7	20.9, 31.2
V_p/F (L)	12.1	13.2	9.25, 17.0	88.2	44.5	50.0, 131
Q/F (L/h)	2.02	15.4	1.57, 2.91	NE	NE	
aGVHD on CL	-0.333	16.7	-0.43, -0.23			
Moderate and potent CYP3A4 inhibitor on CL	-0.154	41.3	-0.26, -0.023			
Actual grade per MAGIC guidance ($\leq$ I vs $>$ I) on K_a	-0.718	8.09	-0.81, -0.53			
Actual grade per MAGIC guidance ($<$ IV vs IV) on CL	-0.272	34.4	-0.45, -0.06			
Actual liver involvement Stages 1 to 3 on CL	-0.326	30.6	-0.51, -0.09			
Actual liver involvement Stage 4 on CL	-0.815	3.99	-0.86, 0.91[c]			
RV (SD)	0.193	8.08	0.163, 0.226	NA	NA	
Minimum value of the objective function -485.062						

ALAG1 = absorption lag time; CI = estimated 95% confidence interval by Bootstrap; CL/F = apparent oral clearance; K_a = first-order absorption rate constant; NE = not estimated; Q/F = apparent intercompartmental clearance; RV= residual variability; %SEM = percent standard error of the mean; V_c/F= apparent volume of distribution for the central compartment; V_p/F = apparent volume of distribution for the tissue (peripheral) compartment.

[a] Cov (IIV CL/F, IIV V_c/F) = 0.0864; r = 0.764

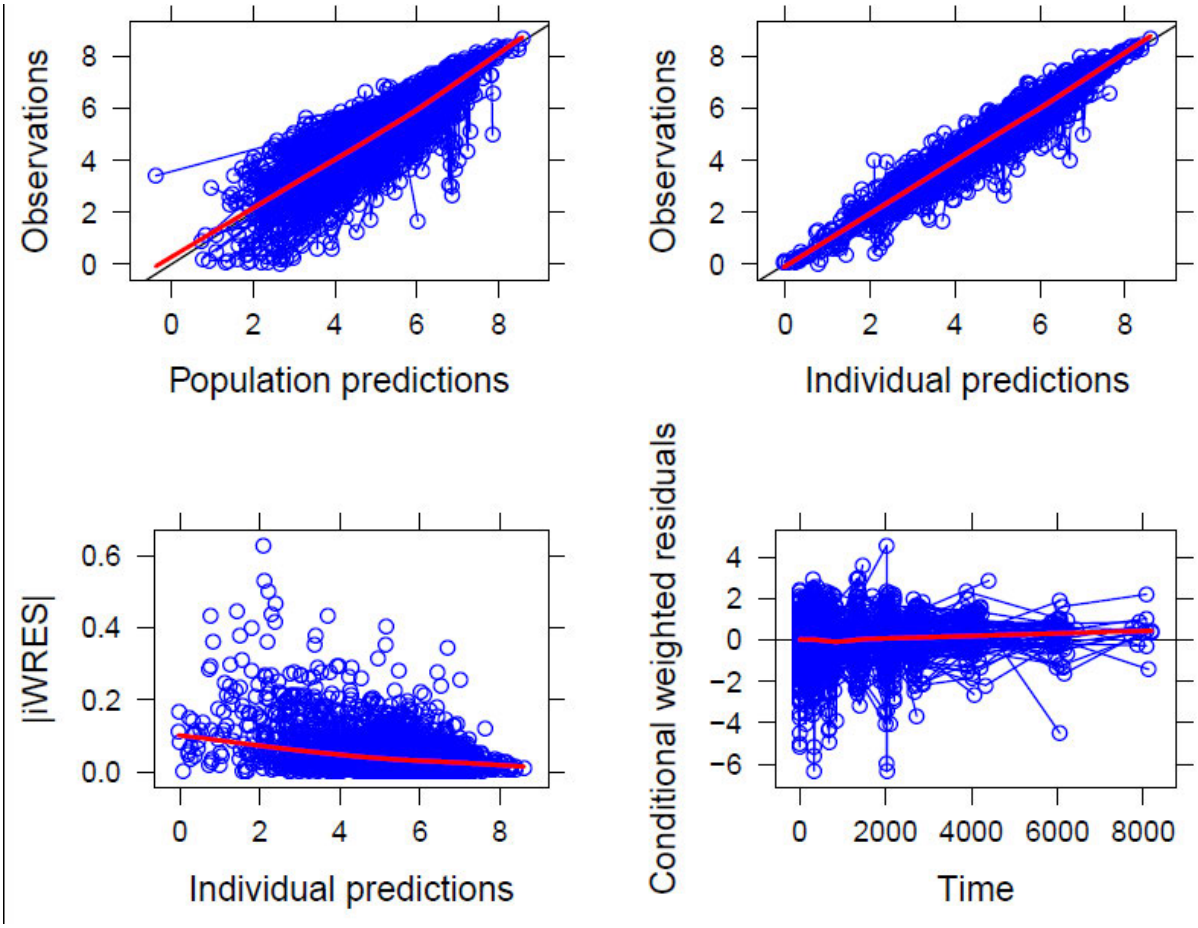
[b] $$V_c / F_j = 59.4 \times \left(\frac{WTKG_j}{72.9} \right)$$, where j represents the jth subject

[c] The 95% CI by the model is -0.879, -0.751.

* Correlations in omega are shown as the off-diagonal elements. SAME blocks are not shown.

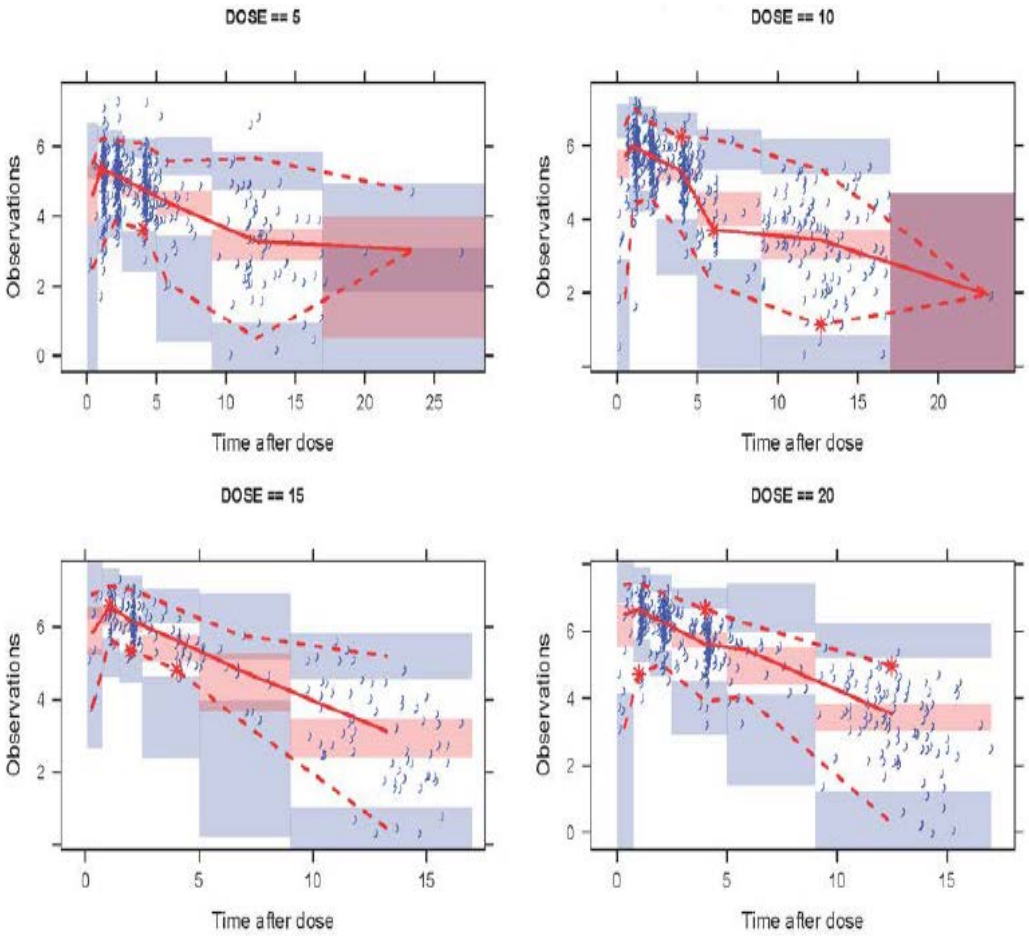
(Source: Applicant's Population PK report, Table 13)

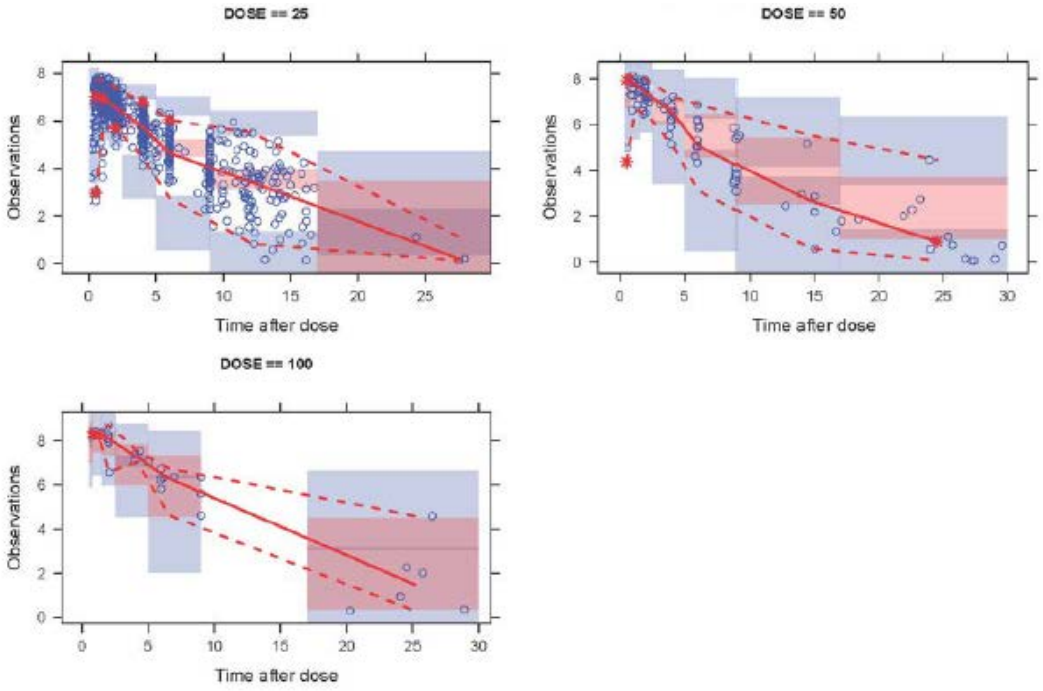
Figure 19. Goodness-of-fit plots for final covariate model



The black line in the DV vs PRED/IPRED plots represents the line of unity (y=x). The black line in the CWRES vs PRED/TIME plots represents the horizontal line (y=0). The red line represents a smooth regression line.

Figure 20. VPC plots for final covariate model





The closed blue circles represent the observed plasma concentrations. The solid red line represents the median observed plasma concentrations. The dashed red lines represent the 2.5% and 97.5% observed percentiles. The semitransparent red area represents a simulation based 95% confidence interval for the median. The semitransparent blue areas represent a simulation based 95% confidence interval for the 2.5% and 97.5% percentiles.
(Source: Applicant's Population PK report, Figure 12)

Reviewer's comments: *The applicant's population PK analysis appears acceptable. The goodness-of-fit plots and the visual predictive check indicate that the updated population PK model is adequate in characterizing the PK profile of ruxolitinib in subjects with GVHD. The inter-individual variability for CL/F and Vc/F are modest. Shrinkages for CL/F and Vc/F are reasonable, while for Vp/CL and Ka are > 30%. The applicant's analyses were verified by the reviewer, with no significant discordance identified.*

More specifically, the developed model was used to support the current submission as outlined in ***Table 46****.*

Table 46. Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support labeling statements about intrinsic and extrinsic	**Intrinsic factor**	(b) (4)	The statement is based on a previously conducted dedicated renal impairment study (\\cdsesub1\evsprod\nda202192\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\incb-18424-142\incb-18424-142-body.pdf) since only a small number of patients had moderate

factors		(b) (4)	RI and no patients had severe RI in the PopPK data. The reviewers recommend "Reduce the Jakafi dosage for patients with acute GVHD and moderate or severe renal impairment (CLcr 15 to 29 mL/min)."
			The statement for HI is supported by both the popPK analysis and a previously conducted dedicated liver impairment study (\\cdsesub1\evsprod\nda202192\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\incb-18424-137\incb-18424-137-body.pdf) Due to small number of patients with stages 3 or 4 liver GVHD in the dataset, the reviewers recommend "Monitor blood counts more frequently for toxicity and consider 5 mg once daily."
	Extrinsic factor		Based on the popPK analysis, co-administration of moderate or potent CYP3A4 inhibitors resulted in 15% decrease in CL/F, which suggest no dose adjustment is needed for the CYP3A4 inhibitors evaluated in the current analysis.

14.5 Additional Clinical Outcomes Assessment Analyses

None.

15 Division Director (OB)

Thomas E. Gwise, PhD
Deputy Division Director (OB)

APPEAS THIS WAY ON ORIGINAL

16 Division Director (DHP)

Summary Review of Supervisory Associate Division Director

(This section was derived in part from the review of Dr. Donna Przepiorka.)

On August 24, 2018, Incyte Corporation submitted S-017 of NDA 202192 which requested approval of ruxolitinib (Jakafi) for the following indication: the treatment of patients with acute graft versus host disease (aGVHD) who have had an inadequate response to corticosteroids.

Background: Ruxolitinib is already approved for the following indications: 1. the treatment of patients with intermediate or high-risk myelofibrosis (MF) including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF, and for 2. the treatment of patients with polycythemia vera (PV) who have had an inadequate response to or are intolerant of hydroxyurea.

This request relied on the results of study INCB 18424-271, a single cohort phase 2 study of ruxolitinib in combination with corticosteroids for the treatment of 49 patients with Grades 2-4 (MAGIC criteria) steroid-refractory aGVHD (REACH 1) (NCT)29536678. Patients received ruxolitinib 10 mg po BID after escalating from a starting dose of 5 mg po BID if hematological parameters remained stable. The statistical analysis plan prespecified that the results needed to exclude a 40% overall response rate (ORR). Corticosteroids are administered at a starting dose of 2.0 mg/kg per day on Day 1 and tapered through Day 56.

The primary objective (primary response endpoint) was ORR at Day 28 defined as the proportion of subjects demonstrating a complete response (CR), very good partial response (VGPR) or partial response (PR), as outlined by the Center for International Blood and Marrow Transplant Research. The secondary objectives included response duration and the incidence and severity of adverse events (AEs).

Eligible patients had Grades 2 to 4 steroid-refractory acute GVHD defined according to the MAGIC criteria (Harris et, 2016): progressive GVHD after 3 days of primary treatment with methylprednisolone ≥2 mg/kg/day; or GVHD that has not improved after 7 days of primary treatment with methylprednisolone with ≥2 mg/kg per day; or subject develops new GVHD in another organ system when methylprednisolone was started at <2mg/kg/day. The primary endpoint was ORR at Day 28. The key secondary endpoint was 3-month DOR, defined as the time from first response until GVHD progression or death when all subjects complete the 84th day visit.

Efficacy Results: The FDA-adjudicated Day-28 ORR was 57.1% (95% CI: 42.2, 71.2). Day-28 ORR was 100% for Grade 2 GVHD, 41.4% for Grade 3 GVHD, and 44.4% for Grade 4 GVHD. The

median follow-up for responders was 5.2 months (range 1.1-14.4 months). The median duration of response was 0.5 months (95% CI: 0.3, 2.7 months), calculated from the Day-28 response to progression, new salvage therapy for acute GVHD, or death from any cause (with progression being defined as worsening by one stage in any organ without improvement in other organs in comparison to prior response assessment). The median time from day-28 response to either death or need for new therapy for acute GVHD (additional salvage therapy or increase in steroids) was 5.7 months (95% CI: 2.2, NE).

Safety Results: Safety analysis was based on 71 individuals treated on Study 271 with at least one dose of ruxolitinib. The major toxicities of ruxolitinib are cytopenias and immunosuppression. Patients received a mean of 87 days of therapy with a median of 45 days and a range from 3 to 381 days. Death was listed as the reason for discontinuation on or before day 28 for 1 patient and as the primary reason for discontinuation on or before the data cutoff day of 04/2/18. None of the deaths were reported to be due to ruxolitinib. The reasons for deaths included: aGVHD, progression, infection, and malignancy relapse.

Eight patients experienced serious adverse events (SAEs). The grade 3-4 adverse reactions occurring in more than 20% of the safety population were: anemia (46%), platelet count decreased (38%), and neutrophil count decreased (32%).

Regulatory Recommendation of the Supervisory Associate Division Director: This reviewer agrees with the recommendation of the review divisions for regular approval for the following indication: for treatment of steroid-refractory acute graft-versus host disease in adult and pediatric patients 12 years and older.

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director (DHP)

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THOMAS E GWISE
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ALBERT B DEISSEROTH
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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 MEMORANDUM

Clinical Studies

NDA #:	202192
Supplement #:	017
Drug Name:	Jakafi® (ruxolitinib)
Indication(s):	Patients with acute graft versus host disease who have had an inadequate response to corticosteroids
Applicant:	Incyte Pharmaceuticals, Inc.
Receipt Date:	08/24/2018
Amendment Date:	02/01/2019
PDUFA Date:	05/24/2019
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Lola Luo
Concurring Reviewers:	Lei Nie, Team Leader Thomas E. Gwise, Deputy Division Director
Medical Division:	Division of Hematology Products
Clinical Team:	Lea Cunningham, Medical Reviewer Donna Przepiorka, Team Leader Ann T. Farrell, Division Director
Project Manager:	Suria Yesmin

Review is complete and has been added to the multidisciplinary review and evaluation document. My review is based on the information currently in the administrative record. If I must review information that is subsequently added to the administrative record, I will update my part of the multidisciplinary review and evaluation document accordingly.

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CDTL Review Memorandum

Application Number	**NDA 202192 S-017**
Applicant	Incyte
Date Received	8/24/2018
Trade Name	Jakafi
Established Name	Ruxolitinib
Dosage Form and Strength	Tablet (5 mg, 10 mg)
Route of Administration	Oral
Proposed Indication	For treatment of patients with acute graft versus host disease (GVHD) who have had an inadequate response to corticosteroids.
Proposed Dosing Regimen	5 mg orally twice daily
CDTL	Donna Przepiorka MD, PhD

The CDTL review is incorporated in the Multidisciplinary Review and Evaluation for this supplement.

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DONNA PRZEPIORKA
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Office of Clinical Pharmacology Memo	
NDA (Supplement)	202192 (17)
Link to EDR	\\CDSESUB1\evsprod\NDA202192\202192.enx
Submission Date(s)	August 24, 2018
Priority or Standard	Priority
PDUFA Goal Date	February 24, 2018
Generic Name	JAKAFI
Brand Name	Ruxolitinib
Dosage Form and Strength	Tablet, 5 mg, 10 mg, 15 mg, 20 mg or 25 mg
Route of Administration	Oral
Pharmacologic Class	Janus Associated Kinases (JAK) Inhibitor
Approved Indications	• Intermediate or high-risk myelofibrosis (MF), including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. • Polycythemia vera (PV) who have had an inadequate response to or are intolerant of hydroxyurea.
Applicant Proposed Indication(s)/Population(s)	Acute graft versus host disease (aGVHD) who have had an inadequate response to corticosteroids
Applicant	Incyte
Associated Applications	None
OCP Review Team	Sriram Subramaniam, Ph.D., Junshan Qiu, Ph.D., Lian Ma, Ph.D., and Ruby Leong, Pharm.D.
OCP Final Signatory	Ruby Leong, Pharm.D. Team Leader Office of Clinical Pharmacology

The Office of Clinical Pharmacology review is complete and has been added to the multidisciplinary review and evaluation document. My review is based on the information currently in the administrative record. If I must review information that is subsequently added to the administrative record, I will update my part of the multidisciplinary review and evaluation document accordingly.

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JUNSHAN QIU
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LIAN MA
01/15/2019 11:07:50 AM

RUBY LEONG
01/15/2019 11:12:07 AM

MEMORANDUM

Date: January 11, 2019

From: Ramadevi Gudi, PhD

Pharmacology/Toxicology Reviewer

Division of Hematology Oncology Toxicology for Division of Hematology Products

Through: Christopher Sheth, PhD

Supervisory Pharmacologist

Division of Hematology Oncology Toxicology for Division of Hematology Products

To: File for NDA 202192-017

JAKAFI® (ruxolitinib)

Re: Pharmacology and Toxicology

Incyte Corporation submitted NDA 202192-017 (supplement 17) for ruxolitinib, indicated for the treatment of patients with acute graft versus host disease (GVHD) who have had an inadequate response to corticosteroids. The nonclinical review is complete and has been added to the Multidisciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multidisciplinary Review and Evaluation for additional details. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of this application.

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RAMADEVI GUDI
01/11/2019 02:38:00 PM

CHRISTOPHER M SHETH
01/15/2019 07:54:58 AM

Memorandum

NDA	202192
Applicant	Incyte
Submission Type	Supplement
Brand Name	Jakafi
Generic Name	Ruxolitinib
Dosage Form and Strength	Tablet, 5 & 10 mg
Route of Administration	Oral
Proposed Indication	acute graft versus host disease (GVHD) who have had an inadequate response to corticosteroids
Proposed Dosing Regimen	(b) (4)
Clinical Review Team	Lea Cunningham, MD, Donna Przepiorka MD, PhD

Recommended indication: For treatment of patients with acute graft versus host disease (GVHD) who have had an inadequate response to corticosteroids

Please see the clinical review in the Multidisciplinary Review and Evaluation, which will be uploaded into DARRTS when it is finalized.

APPEARS THIS WAY ON ORIGINAL

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LEA C CUNNINGHAM
01/10/2019 12:28:29 PM

DONNA PRZEPIORKA
01/10/2019 12:30:33 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202192Orig1s017

OTHER REVIEW(S)

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

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

Memorandum

Date: May 14, 2019

To: Suria Yesmin, 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) tablets, for oral use

NDA: 202192/Supplement S-017

In response to DHP's consult request dated September 11, 2019, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for Jakafi. This supplement (S-017) pertains to a new proposed indication for the treatment of patients with acute graft versus host disease who have had an inadequate response to corticosteroids. On February 1, 2019, the Applicant submitted a major amendment to this application which extended the goal date by three months to provide time for a full review of the submission.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Suria Yesmin) on May 6, 2019 and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on May 9, 2019.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (b) (6) or Robert.Nguyen@fda.hhs.gov.

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ROBERT L NGUYEN
05/14/2019 12:20:34 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 9, 2019
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Robert Nguyen, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Amended Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	JAKAFI (ruxolitinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 202192
Supplement Number:	S-017
Applicant:	Incyte Corporation

1 INTRODUCTION

On August 24, 2018, Incyte Corporation submitted for the Agency's review a Prior Approval Supplement-Efficacy for New Drug Application (NDA) 202192/S-017 JAKAFI (ruxolitinib) tablets, for oral use. The Applicant propose revisions to the Patient Package Insert (PPI), to include a new indication for the treatment of patients with acute graft versus host disease (GVHD), who have had inadequate response to corticosteroids.

On February 1, 2019, the Applicant submitted a major amendment to this application which extended the goal date by three months to provide time for a full review of the submission.

This amended collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on May 4, 2019 for DMPP and OPDP to review the Applicant's revised Patient Package Insert (PPI) for JAKAFI (ruxolitinib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft JAKAFI (ruxolitinib) tablets PPI received on August 24, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 6, 2019.
- Draft JAKAFI (ruxolitinib) tablets Prescribing Information (PI) received on August 24, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on and May 6, 2019.
- JAKAFI (ruxolitinib) labeling approved October 26, 2018.
- DMPP and OPDP review of JAKAFI (ruxolitinib) PPI dated January 12, 2019

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
05/09/2019 01:02:45 PM

ROBERT L NGUYEN
05/09/2019 01:05:40 PM

BARBARA A FULLER
05/09/2019 01:09:36 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 12, 2019
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Robert Nguyen, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	JAKAFI (ruxolitinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 202192
Supplement Number:	S-017
Applicant:	Incyte Corporation

1 INTRODUCTION

On August 24, 2018, Incyte Corporation submitted for the Agency's review a Prior Approval Supplement-Efficacy for New Drug Application (NDA) 202192/S-017 JAKAFI (ruxolitinib) tablets, for oral use. The Applicant proposes revisions to the Patient Package Insert (PPI), to include a new indication for the treatment of patients with acute graft versus host disease (GVHD), who have had inadequate response to corticosteroids.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on August 24, 2018 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for JAKAFI (ruxolitinib) tablets, for oral use.

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To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

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4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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MARIA T NGUYEN
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ruxolitinib (JAKAFI) NDA 202192 S-017 DMPP-OPDP PPI FINAL JAN 2019

ROBERT L NGUYEN
01/11/2019 02:15:05 PM

BARBARA A FULLER
01/11/2019 02:32:38 PM

LASHAWN M GRIFFITHS
01/11/2019 03:10:28 PM

CLINICAL INSPECTION SUMMARY

Date	December 11, 2018
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Susan D. Thompson, M.D., GCPAB Team Leader, and Acting Branch Chief, for Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Lea Cunningham, M.D., Medical Officer Donna Przepiorka, M.D., Ph.D., Clinical Team Leader Ann Farrell, M.D., Director Rosa Lee-Alonzo, Pharm.D., Regulatory Project Manager Division of Hematology Products
NDA	202192 S-017
Applicant	Incyte Corporation
Drug	ruxolitinib (Jakafi®)
NME	No
Therapeutic Classification/Status	Tyrosine kinase inhibitor
Proposed Indication	Treatment of patients with acute graft versus host disease (GVHD) who have had an inadequate response to corticosteroid
Consultation Request Date	October 15, 2018 (Priority Review)
Summary Goal Date	January 17, 2019
Action Goal Date	February 8, 2019
PDUFA Date	February 24, 2019

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites (Drs. Haris Ali, Miguel-Angel Perales, and Mark Schroeder) were selected for inspection in support of NDA 202192 S-017. Incyte Corporation (study sponsor) was also inspected. The study data from these clinical sites, as reported by the sponsor to the NDA, are considered to be reliable in support of the requested indication.

The regulatory classification of Drs. Perales and Schroeder is No Action Indicated. The preliminary regulatory classification of Incyte Corporation is No Action Indicated. The preliminary regulatory classification of Dr. Ali is No Action Indicated.

2. BACKGROUND

Ruxolitinib (Jakafi®) is a *JAK2* family tyrosine kinase inhibitor indicated for treatment of patients with (a) intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis, and (b) polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea. There are currently no FDA-approved agents for the treatment of steroid-refractory acute graft versus host disease (SR-aGVHD). The applicant submits this supplemental NDA and proposes a drug label indication for the treatment of patients with acute graft versus host disease (GVHD) who have had an inadequate response to corticosteroids.

In review of this sNDA, the Division of Hematology Products (DHP) requested three clinical study site and sponsor inspections for Study INCB 18424-271. These clinical study sites are critical to CDER DHP's efficacy and safety review of the application.

Study INCB 18424-271 (REACH1)

Study INCB 18424-271 is a Phase 2 prospective, open-label, single-cohort, multicenter study of ruxolitinib in combination with corticosteroids for the treatment of steroid-refractory (SR) Grades II to IV acute graft versus host disease (aGVHD). Because there is no standard of care in this setting, a single-cohort noncomparative study was considered appropriate to demonstrate the efficacy of ruxolitinib in participants with SR-aGVHD. The primary study objective was to assess the efficacy of ruxolitinib in combination with corticosteroids in participants with Grades II to IV SR-aGVHD.

Seventy-one participants began treatment with ruxolitinib 5 mg twice daily; if hematologic parameters were stable and no treatment-related toxicity was observed after the first 3 days of treatment, the dose could be increased to 10 mg twice daily.

Overall response rate (ORR) at Day 28 was selected as the primary endpoint in this study based on evidence that Day 28 response was predictive of longer-term mortality. Overall response rate was defined as the proportion of participants demonstrating a complete response (CR), very good partial response (VGPR), or partial response (PR).

There were 71 subjects that were enrolled at 26 clinical study sites in the United States. The first patient enrolment occurred on December 27, 2016. The data cut-off for primary data analyses was on April 27, 2018. The study is ongoing.

3. RESULTS (by site):

Name of Clinical Investigator/Address	Protocol #/ Site #/ # Subjects Enrolled	Inspection Dates	Classification
Haris Ali, M.D. 1500 E. Duarte Road Duarte, CA 91010	Study 18424-271 Site #015 11 subjects	November 26 – 30, 2018	Preliminary NAI
Miguel-Angel Perales, M.D. 1275 York Ave New York, NY 10065	Study: 18424-271 Site #016 6 subjects	November 1 – 2, 2018	NAI
Mark Schroeder, M.D. 660 South Euclid Ave Campus Box 8100 St Louis MO 63110	Study 18424-271 Site #033 10 subjects	November 6 – 9, 2018	NAI
Sponsor: Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803	Study 18424-271 71 subjects	November 26 – 28, 2018	Preliminary NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
* Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator

1. Haris Ali, M.D.

A total of 13 subjects were screened and 11 subjects were enrolled. Four subjects received and completed study treatment; seven patients did not complete the treatment phase after enrollment (due to the following reasons: disease progression in three subjects, death in three subjects, and an an adverse event in one subject). The study is ongoing.

For this inspection, a complete review of all regulatory documentation at the study site was performed, including the source records for 11 subjects enrolled at the site prior to the database lock. A 100% review of informed consent forms was completed. The records reviewed included medical records, regulatory binder documents, source data worksheets, informed consent forms, monitoring follow-up reports, and pharmacy records.

Source documents for the 11 enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings for primary efficacy endpoints, adverse events, and serious adverse event reporting. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. There was no under-reporting of adverse events noted during this site audit. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. Miguel-Angel Perales, M.D.

A total of nine subjects were screened and six subjects were enrolled. Six subjects completed the treatment phase of this study. The study is ongoing.

The inspection evaluated the following documents: source records, screening and enrollment logs, physician clinical notes, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for six enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings for primary study endpoint assessment, adverse events, and serious adverse event reporting. A 100% review of the informed consent documentation was conducted for all enrolled study patients. Records review of these six subjects indicated that the eligibility criteria for enrollment were met. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 was not issued at the completion of the inspection

3. Mark Schroeder, M.D.

A total of 12 subjects were screened and 10 subjects were enrolled. One subject completed the treatment phase of the study; nine patients did not complete the study after enrollment (due to the following reasons: two study subjects developed adverse events, one subject discontinued due to disease progression, and six subjects died during the follow-up period). The study is ongoing.

The inspection evaluated the following documents: source records, screening and enrollment logs, physician clinical notes, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for 10 enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings for patient informed consent documentation, primary study endpoint assessment, adverse event and serious adverse event reporting. A comprehensive audit of the inclusion and exclusion criteria for patient enrollment was evaluated at this site inspection. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 was issued.

Sponsor

4. Incyte Corporation

Records reviewed included but were not limited to: organizational charts; vendor list; vendor oversight plans; transfer of obligations; investigator agreements; financial disclosures; monitoring plans; monitoring reports; monitor qualifications, safety reports; adverse events; protocol deviations; and standard operating procedures. Monitoring reports in Study 18424-271 were reviewed for three study sites (Site #15, Site #16, and Site #33). No underreporting of significant adverse events to the Agency was noted. At the end of the inspection, a Form FDA 483 was not issued. Data from this sponsor appear to be reliable.

{See appended electronic signature page}
Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Susan D. Thompson, M.D.
Team Leader, Good Clinical Practice Assessment Branch
Acting Branch Chief, for
Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
12/11/2018

SUSAN D THOMPSON
12/11/2018

LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 6, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 202192/S-017
Product Name and Strength:	Jakafi (ruxolitinib) tablets 5 mg, 10 mg, 15 mg, 20 mg, 25 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Incyte Corporation
FDA Received Date:	August 24, 2018 and November 7, 2018
OSE RCM #:	2018-1929
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1. REASON FOR REVIEW

Incyte Corporation submitted a Prior Approval Supplement (PAS) to NDA 202192/S-017 for a new indication for Agency review. The proposed indication is for the treatment of patients with acute graft versus host disease (GVHD) who have had an inadequate response to corticosteroids. The supplement proposes changes to the Prescribing Information (PI) based on efficacy and safety data from a Phase 2 study, and safety data in acute GVHD patients. The Division of Hematology Products (DHP) requested DMEPA evaluate the proposed PI for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND INFORMATION

Jakafi (ruxolitinib) was approved under NDA 202192 on November 16, 2011, for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis. In 2014, Jakafi received an additional indication for the treatment polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Incyte Corporation proposes changes to the PI based on efficacy and safety data from the pivotal, Phase 2 study, INCB 18424-271, and safety data in acute GVHD patients enrolled in expanded access programs with ruxolitinib.

We performed a risk assessment of the proposed PI to determine if it is acceptable from a medication error perspective.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations in Section 4.1 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Section 2 Dosage and Administration
   1. Section 2.3 Acute Graft Versus Host Disease
      a. The current information describing a dose increase to 10 mg twice daily states that the increase "(b) (4) " We recommend including more specific information regarding the hematologic parameters (e.g., lab tests and values) as presented for the other approved indications (see sections 2.1 and 2.2). We also recommend presenting this information in tabular format depending on the amount and complexity of the content.
      b. Section 2.3.1 Dose Modifications Guidelines for Patients with Acute Graft Versus Host Disease
         i. Dose modifications are presented in tabular format for the other approved indications (see subsections under 2.1 and 2.2). We recommend dose modification information be put in tabular format in this section as well to improve clarity.

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Jakafi received on September 7, 2018, from Incyte Corporation.

Table 2. Relevant Product Information for Jakafi	
Initial Approval Date	November 16, 2011
Active Ingredient	ruxolitinib
Indication	• 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 • *Proposed: acute graft versus host disease (GVHD) who have had an inadequate response to corticosteroids*
Route of Administration	Oral
Dosage Form	Tablets
Strength	5 mg, 10 mg, 15 mg, 20 mg, 25 mg
Dose and Frequency	Starting doses per indication: • Myelofibrosis o 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 o 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 o The starting dose of Jakafi is 10 mg given orally twice daily. • *Proposed: Acute Graft Versus Host Disease* o *The starting dose of Jakafi is 5 mg given orally twice daily.*
How Supplied	Bottles of 60 tablets
Storage	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)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 30, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, “ruxolitinib,” “Jakafi,” and “label”. Our search identified four previous labeling reviews, and we confirmed that our previous recommendations were implemented.

Reviewer	Document Title	Application	Date	RCM No.
Rahimi, L.	Label and Labeling Review Memo for Jakafi (ruxolitinib)	NDA 202192/S-015	2017 OCT 16	2017-1248
Vora, N.	Label and Labeling Review for Jakafi (ruxolitinib)	NDA 202192/S-008	2014 AUG 27	2014-1239
Owens, L.	Final Label and Labeling Review for Jakafi (ruxolitinib)	NDA 202192	2011 OCT 28	2011-2319
Owens, L.	Label and Labeling Review for Jakafi (ruxolitinib)	NDA 202192	2011 OCT 11	2011-2319

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On October 31, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR Long-Term Care Advise-ERR ISMP Canada Safety Bulletin Pennsylvania Patient Safety Advisory
Search Strategy and Terms	Match Any of the Words: Jakafi, ruxolitinib

D.2 Results

The search retrieved no relevant articles associated with label and labeling for Jakafi.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

On October 31, 2018, we searched FAERS using the criteria in the table below. We individually reviewed the cases and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[a] We narrowed the search results to reports that may be relevant to this review of the labeling, including incorrect dose administered (n=132), wrong technique in product usage process (n=9), and drug dispensing error (n=2).

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	10/15/2017 to 10/15/2018
Product Name:	N/A
Product Active Ingredient (PAI):	Ruxolitinib; ruxolitinib phosphate
Event:	SMQ *Medication errors* (Narrow)
Country (Derived):	USA

E.2 Results

Our review of the narrowed search results, which included 143 cases, determined that none of the reports described errors that were relevant for this review.

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-market safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[a] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with post-market medication error data, we reviewed the following Jakafi labels and labeling submitted by Incyte Corporation.

- Prescribing Information received on August 24, 2018.

G.2 Labeling – Prescribing Information

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APPEARS THIS WAS ON ORIGINAL

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEPHANIE L DEGRAW
12/06/2018

HINA S MEHTA
12/06/2018

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

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

Memorandum

Date: October 22, 2018

To: Suria Yesmin, 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) tablets, for oral use

NDA: 202192/Supplement S-017

In response to DHP's consult request dated September 11, 2018, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for Jakafi. This supplement (S-017) pertains to a new proposed indication for the treatment of patients with acute graft versus host disease who have had an inadequate response to corticosteroids.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Rosa Lee-Alonzo) on October 10, 2018 and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (b) (6) or Robert.Nguyen@fda.hhs.gov.

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

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROBERT L NGUYEN
10/22/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202192Orig1s017

Administrative/Correspondence Document(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077456

MEETING PRELIMINARY COMMENTS

Incyte Corporation
Attention: Adam Shilling, PhD
Executive Director, Regulatory Affairs
1801 Augustine Cut-Off
Wilmington, DE 19803

Dear Dr. Shilling:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Jakafi® (ruxolitinib).

We also refer to your April 13, 2018, correspondence, received April 13, 2018, requesting a meeting to discuss a proposed supplemental application for ruxolitinib tablets for the treatment of patients with acute GVHD who have had an inadequate response to corticosterioids.

Our preliminary responses to your meeting questions are enclosed.

You should provide a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 348-1725.

Sincerely,

{See appended electronic signature page}

Suria Yesmin, MS
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-sNDA
Meeting Date and Time:	Tuesday, June 5, 2018, 11am-12pm EST
Meeting Location:	Teleconference
Application Number:	077456
Product Name:	Jakafi® (ruxolitinib)
Indication:	Treatment of patients with acute GVHD who have had an inadequate response to corticosteroids
Sponsor/Applicant Name:	Incyte Corporation

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Tuesday, June 5, 2018, 11am – 12pm EST between Incyte Corporation and the Division of Hematology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Incyte Corporation submitted a Type B pre-sNDA meeting request to discuss a proposed supplemental application for ruxolitinib tablets for the treatment of patients with acute GVHD

who have had an inadequate response to corticosterioids. The meeting was granted on April 24, 2018.

2.0 DISCUSSION

Question 1: *Does the Division agree with the content and format of the planned sNDA to support the use of ruxolitinib in the treatment of patients with acute GVHD who have had an inadequate response to corticosteroids?*

FDA Response to Question 1:
No, you will need to include a summary of clinical efficacy (Module 2, Section 2.7.3), otherwise the overall outline of submission components appears to be consistent with FDA guidance. We will determine the completeness and acceptability of the data for filing and review at the time of the sNDA submission

Please include a custom data set (raw data) that includes the grade of acute GVHD for each patient and the parameters that determined that grade at baseline (entry into clinical trial) and at response assessments. Include laboratory values (bilirubin), skin findings (physical exam), and upper GI (intermittent or persistent nausea, vomiting and anorexia) and lower GI (stool output/day). Include the stage for each of the parameters (skin, liver, upper GI and lower GI) at baseline and at response assessments. Include a description of how this custom dataset was derived from the other datasets.

We note that after Day 56, the response assessment changes from weekly to every 28 days. In the efficacy analysis dataset include the actual date of progression or recurrence of GVHD after achieving CR, PR or VGPR.

Question 2:

a. *Does the Division agree with Incyte's proposal to summarize efficacy data from INCB 18424-271 for the planned sNDA in the Clinical Overview to support the proposed indication?*

FDA Response to Question 2a:
No, a summary of clinical efficacy (SCE) is still required for the proposed sNDA. The SCE should contain an executive high level overview summary and then summarize the analyses.

An integrated summary of efficacy (ISE) is a required component of the application. In this situation, however, it is acceptable to include a page with a cross-reference to the summary of clinical efficacy (SCE, Module 2, section 2.7.3) in the ISE. The summary of clinical efficacy can serve as the ISE provided that the data can be included within the space limitations of the SCE.

b. *Does the Division agree with Incyte's proposal that safety analyses will be described in text through the written Summary of Clinical Safety (SCS) provided in CTD Module 2 with no additional analyses planned for the ISS/SCS and with all supporting tables, figures, and datasets contained in the clinical study report for INCB 18424-271 and the interim report describing acute GVHD patients enrolled in the expanded access program (MED-18.01.1)?*

FDA Response to Question 2b:
An ISS is a required component of an application; however it is acceptable in this situation to include a page with a cross-reference to the SCS (Module 2, Section 2.7.4).

We agree no additional ISS analyses are necessary since the application will consist of a single pivotal study (INCB 18424-271) with supporting information from the expanded access program.

We also agree it is not appropriate to pool data from INCB 18424-271 with data from other ruxolitinib clinical trials conducted in patient populations outside of GVHD.

Question 3: *Does the Division agree with Incyte's plan to provide the Case Report Forms (CRFs) as required in 21 CFR 314.50 and to also include CRFs for subjects who had a serious adverse event while enrolled in INCB 18424-271?*

FDA Response to Question 3:
Yes.

Question 4: *Does the Division agree with Incyte's plan regarding financial disclosure?*

FDA Response to Question 4:
Yes, your proposal appears reasonable.

Question 5: *Does the Division agree with Incyte's proposal to file the sNDA when all the subjects in the pivotal study, INCB 18424 271, complete 3 months of follow-up, while committing to provide additional duration of response data with at least 6 months of follow-up for all subjects in a CSR addendum, along with the 4-month safety update?*

FDA Response to Question 5:
Based on the topline results you provided in the meeting package, your proposal to submit the sNDA when all the subjects in the pivotal study, INCB 18424 271, complete 3 months of follow-up appears reasonable.

The proposal to submit the additional duration of response data with at least 6 months of follow-up for all subjects in a CSR addendum, along with the 4-month safety is acceptable. Six-month duration of response data will be considered the key secondary endpoint your study. Include updated non-relapse mortality for all patients with at least 6 months of follow-up in the CSR addendum.

Your submission should include a custom data set that includes the date of acute GVHD onset, grade of acute GVHD at diagnosis for each patient and the parameters (laboratory and clinical) used to determine grade at baseline (entry into clinical trial). See response to Question 1.

The determination if the application is fileable will be made during the filing review process.

Question 6: *Does the Division agree with Incyte's plan for information to be included in the 4-month safety update?*

FDA Response to Question 6:
Clarify why your safety cut-off date for expanded access is different from the cut-off date from the pivotal study. We recommend that you include all available safety data from your expanded access program with the 02 APR 2018 data cutoff at the time of the sNDA submission. Updated safety data from this study with data cut-off date of 02 APR 2018 through 02 JUL 2018 may be submitted with the 4-month safety update.

Question 7: *Does the Division agree with Incyte's proposal to provide information on acute GVHD patients enrolled in the expanded access program by submitting an interim report?*

FDA Response to Question 7:
Yes; however see response above for cut-off date.

Question 8:

a. *Does the Division agree with the proposed population PK plan?*

FDA Response to Question 8a:
No, you should update your population PK model with the new PK data from your pivotal Study INCB 18424-271 in patients with aGVHD. You can include patient population as a covariate to evaluate the difference in PK between studies/patient population.

b. *Does the Division agree with the plan to describe the clinical pharmacology information for the sNDA in the Clinical Overview?*

FDA Response to Question 8b:
No, you should include a Summary of Clinical Pharmacology – which should include a summary of PK results from Study INCB 18424-271, comparison of PK results to historical PK results in other disease settings, and discussion of drug-drug interaction potential between ruxolitinib and corticosteroids.

Additional Comment

Clinical

- Clarify how many patients who achieved a CR or VGPR had tapering of the drugs (steroids, calcineurin inhibitors and ruxolitinib) and any adverse events that occurred in relationship to the taper.

3.0 OTHER MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product

development, please refer to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

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/s/

SURIA YESMIN
05/27/2018