

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202192Orig1s000

Trade Name: Jakafi Tablets

Generic Name: ruxolitinib

Sponsor: Incyte Corporation

Approval Date: November 16, 2011

Indications: Treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, postpolycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis

CENTER FOR DRUG EVALUATION AND RESEARCH

202192Orig1s000

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



NDA 202192

NDA APPROVAL

Incyte Corporation
Attention: Ronald C. Falcone, Ph.D.
Vice President, Regulatory Affairs
Rt 141 & Henry Clay Road, E336
Wilmington, DE 19880-0336

Dear Dr. Falcone:

Please refer to your New Drug Application (NDA) dated June 3, 2011, received June 3, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jakafi™ (ruxolitinib) Tablets.

We acknowledge receipt of your amendments dated June 10; July 8 and 12; August 1, 4, 5, 12, 18, 24, 29, and 30; September 12, 14, 27, 28, and 30; October 5, 12, 19, 20, 21, and 31; and November 2, 2011.

This new drug application provides for the use of Jakafi™ (ruxolitinib) Tablets for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

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 text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on October 20, 2011, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 202192.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

CHEMISTRY, CONTROLS AND MANUFACTURING

A 24-month expiration dating period is granted for the drug product (5 mg, 10 mg, 15 mg, 20 mg, and 25 mg) when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

ADVISORY COMMITTEE

Your application for Jakafi™ (ruxolitinib) Tablets was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of myelosuppression with longer-term exposure to Jakafi™ (ruxolitinib) Tablets therapy and to monitor safety findings occurring in the context of drug discontinuation to determine if specific cautions are necessary during drug discontinuation.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of myelosuppression with longterm exposure and safety findings in the context of drug discontinuation.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1838-1 Provide safety findings related to the interval of drug discontinuation in at least 75 patients previously entered on INCB-351 to determine if specific cautions are appropriate to describe discontinuation strategies.

The timetable you submitted on November 14, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	07/2009
Trial Completion:	08/2012
Final Report Submission:	10/2013

1838-2 Provide safety findings related to the interval of drug discontinuation in at least 75 patients previously entered on INCB-352 to determine if specific cautions are appropriate to describe discontinuation strategies.

The timetable you submitted on November 14, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2010
Trial Completion:	08/2012
Final Report Submission:	10/2013

1838-3 Collect and analyze safety information on myelosuppression for up to 144 weeks of therapy following randomization in the patients entered on INCB-351 who are continuing on therapy past 24 weeks.

The timetable you submitted on November 14, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	07/2009
Trial Completion:	03/2013
Final Report Submission:	12/2013

1838-4 Collect and analyze safety information on myelosuppression for up to 144 weeks of therapy following randomization in the patients entered on INCB-352 who are continuing on therapy past 48 weeks.

The timetable you submitted on November 14, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2010
Trial Completion:	03/2013
Final Report Submission:	12/2013

Submit the protocols to your IND 077456, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

1838-5 Provide longer-term efficacy and safety outcomes of current clinical trial INCB-351 to provide at least 3 year follow-up data.

The timetable you submitted on November 14, 2011, states that you will conduct

this trial according to the following schedule:

Final Protocol Submission:	07/2009
Trial Completion:	08/2013
Final Report Submission:	08/2014

1838-6 Provide longer-term efficacy and safety outcomes of current clinical trial INCB-352 to provide at least 3 year follow-up data.

The timetable you submitted on November 14, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	05/2010
Trial Completion:	08/2013
Final Report Submission:	08/2014

Submit clinical protocols to your IND 077456 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

PROMOTIONAL MATERIALS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more

information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Office Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
11/16/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202192Orig1s000

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

INDICATIONS AND USAGE

Jakafi is a kinase inhibitor indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. (1)

DOSAGE AND ADMINISTRATION

- The starting dose of Jakafi is 20 mg given orally twice daily for patients with a platelet count greater than $200 \times 10^9/L$, and 15 mg twice daily for patients with a platelet count between $100 \times 10^9/L$ and $200 \times 10^9/L$. (2.1)
- Perform a complete blood count before initiating therapy with Jakafi. Monitor complete blood counts every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. Modify dose for thrombocytopenia. (2.1) (2.2)
- Increase dose based on response and as recommended to a maximum of 25 mg twice daily. Discontinue after 6 months if no spleen reduction or symptom improvement (2.3)

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 can occur. Manage by dose reduction, or interruption or transfusion. (5.1)

- 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)

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- Strong CYP3A4 Inhibitors: Reduce Jakafi starting dose to 10 mg twice daily for patients with a platelet count greater than or equal to $100 \times 10^9/L$ and concurrent use of strong CYP3A4 inhibitors. Avoid in patients with platelet counts less than $100 \times 10^9/L$. (2.4) (7.1)

USE IN SPECIFIC POPULATIONS

- Renal Impairment: Reduce Jakafi starting dose to 10 mg twice daily for patients with moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min) and a platelet count between $100 \times 10^9/L$ and $150 \times 10^9/L$. Avoid in patients with end stage renal disease (CrCl less than 15 mL/min) not requiring dialysis and in patients with moderate or severe renal impairment and a platelet count less than $100 \times 10^9/L$. (2.5) (8.6)
- Hepatic Impairment: Reduce Jakafi starting dose to 10 mg twice daily for patients with any degree of hepatic impairment and a platelet count between $100 \times 10^9/L$ and $150 \times 10^9/L$. Avoid in patients with hepatic impairment with platelet counts less than $100 \times 10^9/L$. (2.5) (8.7)
- Nursing Mothers: Discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother. (8.3)

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

Revised: 11/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
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 - Dose Modification Based on Response
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 - Infections
 - Drug-drug Interactions
 - Dialysis
 - Compliance

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

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

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

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Starting Dose

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: Proposed Jakafi Starting Doses

Platelet Count	Starting Dose
Greater than $200 \times 10^9/L$	20 mg orally twice daily
$100 \times 10^9/L$ to $200 \times 10^9/L$	15 mg orally twice daily

2.2 Dose Modification Guidelines for Thrombocytopenia

Treatment Interruption

Interrupt treatment for platelet counts less than $50 \times 10^9/L$. After recovery of platelet counts above this level, dosing may be restarted or increased following recovery of platelet counts to acceptable levels. Table 2 illustrates the maximum allowable dose that may be used in restarting Jakafi after a previous interruption.

Table 2: Maximum Restarting Doses for Jakafi After Safety Interruption*

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

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: Dosing Recommendations for Thrombocytopenia

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

2.3 Dose Modification Based on Response

If efficacy is considered 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. Discontinue treatment after 6 months if there is no spleen size reduction or symptom improvement since initiation of therapy with Jakafi.

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.

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

- 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 CT or MRI;
- Platelet count greater than 125 X 10⁹/L at 4 weeks and platelet count never below 100 X 10⁹/L;
- ANC levels greater than 0.75 X 10⁹/L.

2.4 Dose Adjustment with Concomitant Strong CYP3A4 Inhibitors

On the basis of pharmacokinetic studies in healthy volunteers, when administering Jakafi with strong CYP3A4 inhibitors (such as but not limited to boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole), the recommended starting dose is 10 mg twice daily for patients with a platelet count greater than or equal to $100 \times 10^9/L$. Additional dose modifications should be made with careful monitoring of safety and efficacy.

Concurrent administration of Jakafi with strong CYP3A4 inhibitors should be avoided in patients with platelet counts less than $100 \times 10^9/L$ [see *Drug Interactions* (7.1)].

2.5 Organ Impairment

Renal Impairment

On the basis of pharmacokinetic studies in volunteers with renal impairment, the recommended starting dose is 10 mg twice daily for patients with a platelet count between $100 \times 10^9/L$ and $150 \times 10^9/L$ and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min). Additional dose modifications should be made with careful monitoring of safety and efficacy.

The recommended starting dose for patients with end stage renal disease on dialysis is 15 mg for patients with a platelet count between $100 \times 10^9/L$ and $200 \times 10^9/L$ or 20 mg for patients with a platelet count of greater than $200 \times 10^9/L$. Subsequent doses should be administered on dialysis days following each dialysis session. Additional dose modifications should be made with careful monitoring of safety and efficacy.

Jakafi should be avoided in patients with end stage renal disease (CrCl less than 15 mL/min) not requiring dialysis and in patients with moderate or severe renal impairment with platelet counts less than $100 \times 10^9/L$ [see *Use in Specific Populations* (8.6)].

Hepatic Impairment

On the basis of pharmacokinetic studies in volunteers with hepatic impairment, the recommended starting dose is 10 mg twice daily for patients with a platelet count between $100 \times 10^9/L$ and $150 \times 10^9/L$. Additional dose modifications should be made with careful monitoring of safety and efficacy.

Jakafi should be avoided in patients with hepatic impairment with platelet counts less than $100 \times 10^9/L$ [see *Use in Specific Populations* (8.7)].

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 hematologic adverse reactions, including thrombocytopenia, anemia and neutropenia. A complete blood count must be performed before initiating therapy with Jakafi [*see Dosage and Administration (2.1)*].

Patients with platelet counts of less than $200 \times 10^9/L$ at the start of therapy are more likely to develop thrombocytopenia during treatment.

Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily withholding Jakafi. If clinically indicated, platelet transfusions may be administered [*see Dosage and Administration (2.2), and Adverse Reactions (6.1)*].

Patients developing anemia may require blood transfusions. Dose modifications of Jakafi for patients developing anemia may also be considered.

Neutropenia (ANC less than $0.5 \times 10^9/L$) was generally reversible and was managed by temporarily withholding Jakafi [*see Adverse Reactions (6.1)*].

Complete blood counts should be monitored as clinically indicated and dosing adjusted as required [*see Dosage and Administration (2.2), and Adverse Reactions (6.1)*].

5.2 Infections

Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Active serious infections should have resolved before starting therapy with Jakafi. Physicians should carefully observe patients receiving Jakafi for signs and symptoms of infection and initiate appropriate treatment promptly.

Herpes Zoster

Physicians should inform patients about early signs and symptoms of herpes zoster and advise patients to seek treatment as early as possible [see *Adverse Reactions (6.1)*].

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

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 myelofibrosis 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 88.7% of patients treated for more than 6 months and 24.6% 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 a double-blind, randomized, placebo-controlled study of Jakafi, 155 patients were treated with Jakafi. The most frequent adverse drug reactions were thrombocytopenia and anemia [see *Table 5*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [see *Table 4*].

Discontinuation for adverse events, regardless of causality, was observed in 11.0% of patients treated with Jakafi and 10.6% of patients treated with placebo.

Following interruption or discontinuation of Jakafi, symptoms of myelofibrosis generally return to pretreatment levels over a period of approximately 1 week. There have been isolated cases of patients discontinuing Jakafi during acute intercurrent illnesses after which the patient's clinical course continued to worsen; however, it has not been established whether discontinuation of therapy contributed to the clinical course in these patients. When discontinuing therapy for reasons other than thrombocytopenia, gradual tapering of the dose of Jakafi may be considered [see *Dosage and Administration (2.6)*].

Table 4 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 4: Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

Adverse Reactions	Jakafi (N=155)			Placebo (N=151)		
	All Grades ^a (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Bruising ^b	23.2	0.6	0	14.6	0	0
Dizziness ^c	18.1	0.6	0	7.3	0	0
Headache	14.8	0	0	5.3	0	0
Urinary Tract Infections ^d	9.0	0	0	5.3	0.7	0.7
Weight Gain ^e	7.1	0.6	0	1.3	0.7	0
Flatulence	5.2	0	0	0.7	0	0
Herpes Zoster ^f	1.9	0	0	0.7	0	0

^a National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

^b includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura

^c includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis

^d includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present

^e includes weight increased, abnormal weight gain

^f includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Drug Reactions

Anemia

In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (0.3%) 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 $50 \times 10^9/L$ was 14 days. Platelet transfusions were administered to 4.7% of patients receiving Jakafi and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakafi and 0.9%

of patients receiving control regimens. Patients with a platelet count of $100 \times 10^9/L$ to $200 \times 10^9/L$ before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than $200 \times 10^9/L$ (16.5% versus 7.2%).

Neutropenia

In the two Phase 3 clinical studies, 1.0% of patients reduced or stopped Jakafi because of neutropenia.

Table 5 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 5: Worst Hematology Laboratory Abnormalities in the Placebo-controlled Study^a

Laboratory Parameter	Jakafi (N=155)			Placebo (N=151)		
	All Grades ^b (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Thrombocytopenia	69.7	9.0	3.9	30.5	1.3	0
Anemia	96.1	34.2	11.0	86.8	15.9	3.3
Neutropenia	18.7	5.2	1.9	4.0	0.7	1.3

^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

25.2% of patients treated with Jakafi and 7.3% 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 1.9% for Jakafi with 1.3% Grade 3 and no Grade 4 ALT elevations.

17.4% of patients treated with Jakafi and 6.0% 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 0.6% for Jakafi with no Grade 3 or 4 AST elevations.

16.8% of patients treated with Jakafi and 0.7% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was 0.6% for Jakafi with no Grade 3 or 4 cholesterol elevations.

7. DRUG INTERACTIONS

7.1 Drugs That Inhibit or Induce Cytochrome P450 Enzymes

Ruxolitinib is predominantly metabolized by CYP3A4.

Strong CYP3A4 inhibitors: The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively, with Jakafi administration (10 mg single dose) following ketoconazole 200 mg

twice daily for four days, compared to receiving Jakafi alone in healthy subjects. The half-life was also prolonged from 3.7 to 6.0 hours with concurrent use of ketoconazole. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding ruxolitinib AUC following concurrent administration with ketoconazole.

When administering Jakafi with strong CYP3A4 inhibitors a dose reduction is recommended [see *Dosage and Administration* (2.4)]. Patients should be closely monitored and the dose titrated based on safety and efficacy.

Mild or moderate CYP3A4 inhibitors: There was an 8% and 27% increase in the C_{max} and AUC of ruxolitinib, respectively, with Jakafi administration (10 mg single dose) following erythromycin, a moderate CYP3A4 inhibitor, at 500 mg twice daily for 4 days, compared to receiving Jakafi alone in healthy subjects. The change in the pharmacodynamic marker, pSTAT3 inhibition was consistent with the corresponding exposure information.

No dose adjustment is recommended when Jakafi is coadministered with mild or moderate CYP3A4 inhibitors (eg, erythromycin).

CYP3A4 inducers: The C_{max} and AUC of ruxolitinib decreased 32% and 61%, respectively, with Jakafi administration (50 mg single dose) following rifampin 600 mg once daily for 10 days, compared to receiving Jakafi alone in healthy subjects. In addition, the relative exposure to ruxolitinib's active metabolites increased approximately 100%. This increase may partially explain the reported disproportionate 10% reduction in the pharmacodynamic marker pSTAT3 inhibition.

No dose adjustment is recommended when Jakafi is coadministered with a CYP3A4 inducer. Patients should be closely monitored and the dose titrated based on safety and efficacy.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Jakafi in pregnant women. In embryofetal toxicity studies, treatment with ruxolitinib resulted in an increase in late resorptions and reduced fetal weights at maternally toxic doses. Jakafi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 was no evidence of teratogenicity. However, 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).

8.3 Nursing Mothers

It is not known whether ruxolitinib is excreted in human milk. Ruxolitinib and/or its metabolites were excreted in the milk of lactating rats with a concentration that was 13-fold the maternal plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Jakafi, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the total number of myelofibrosis patients in clinical studies with Jakafi, 51.9% were 65 years of age and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients.

8.6 Renal Impairment

The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects [CrCl 72-164 mL/min (N=8)] and in subjects with mild [CrCl 53-83 mL/min (N=8)], moderate [CrCl 38-57 mL/min (N=8)], or severe renal impairment [CrCl 15-51 mL/min (N=8)]. Eight (8) additional subjects with end stage renal disease requiring hemodialysis were also enrolled.

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

When administering Jakafi to patients with moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min) with a platelet count between $100 \times 10^9/L$ and $150 \times 10^9/L$ and patients with end stage renal disease on dialysis a dose reduction is recommended [*see Dosage and Administration (2.5)*].

8.7 Hepatic Impairment

The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects (N=8) and in subjects with mild [Child-Pugh A (N=8)], moderate [Child-Pugh B (N=8)], or severe hepatic impairment [Child-Pugh C (N=8)]. The mean AUC for ruxolitinib was

increased by 87%, 28% and 65%, respectively, in patients with mild, moderate and severe hepatic impairment compared to patients with normal hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in ruxolitinib exposure except in the severe (Child-Pugh C) hepatic impairment cohort where the pharmacodynamic activity was more prolonged in some subjects than expected based on plasma concentrations of ruxolitinib.

When administering Jakafi to patients with any degree of hepatic impairment and with a platelet count between $100 \times 10^9/L$ and $150 \times 10^9/L$, a dose reduction is recommended [*see Dosage and Administration (2.5)*].

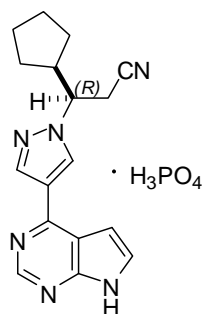
10. OVERDOSAGE

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 ruxolitinib.

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.

Myelofibrosis (MF) is a myeloproliferative neoplasm (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 (eg, TNF- α , IL-6).

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Absorption

In clinical studies, ruxolitinib is rapidly absorbed after oral Jakafi administration with maximal plasma concentration (C_{max}) achieved within 1 to 2 hours post-dose. Based on a mass balance study in humans, oral absorption of ruxolitinib was estimated to be at least 95%. Mean ruxolitinib C_{max} and total exposure (AUC) increased proportionally over a single dose range of 5 to 200 mg. There were no clinically relevant changes in the pharmacokinetics of ruxolitinib upon administration of Jakafi with a high-fat meal, with the mean C_{max} moderately decreased (24%) and the mean AUC nearly unchanged (4% increase).

Distribution

The apparent volume of distribution of ruxolitinib at steady-state is 53 to 65 L in myelofibrosis patients. Binding to plasma proteins *in vitro* is approximately 97%, mostly to albumin.

Metabolism

In vitro studies suggest that CYP3A4 is the major enzyme responsible for metabolism of ruxolitinib. Ruxolitinib is the predominant entity in humans representing approximately 60% of the drug-related material in circulation. Two major and active metabolites were identified in plasma of healthy subjects representing 25% and 11% of parent AUC. These two metabolites have one-fifth and one-half of ruxolitinib's pharmacological activity, respectively. The sum total of all active metabolites contributes 18% of the overall pharmacodynamics of ruxolitinib.

Elimination

Following a single oral dose of [¹⁴C]-labeled ruxolitinib in healthy adult subjects, 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. The mean elimination half-life of ruxolitinib is approximately 3 hours and the mean half-life of ruxolitinib + metabolites is approximately 5.8 hours.

Effects of Age, Gender, or Race

In healthy subjects, no significant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in myelofibrosis patients, no relationship was apparent between oral clearance and patient age or race, and in women, clearance was 17.7 L/h and in men, 22.1 L/h with 39% inter-subject variability.

Drug Interactions

In vitro, ruxolitinib and its M18 metabolite are not inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Ruxolitinib is not an inducer of CYP1A2, CYP2B6 or CYP3A4 at clinically relevant concentrations.

In vitro, ruxolitinib and its M18 metabolite are not inhibitors of 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.

12.4 Thorough QT Study

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

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Two randomized Phase 3 studies (Studies 1 and 2) were conducted in patients with myelofibrosis (either primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia-myelofibrosis). 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 10⁹/L were started on Jakafi 15 mg twice daily and patients with a platelet count greater than 200 X 10⁹/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 10⁹/L, of 10 mg twice daily for patients with platelet counts between 75 to less than or equal to 100 X 10⁹/L, and of 5 mg twice daily for patients with platelet counts between 50 to less than or equal to 75 X 10⁹/L.

Study 1

Study 1 was a double-blind, randomized, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. The median age was 68 years (range 40 to 91 years) with 61% of patients older than 65 years and 54% were male. Fifty percent (50%) of patients had primary myelofibrosis, 31% had post-polycythemia vera myelofibrosis and 18% had post-essential thrombocythemia myelofibrosis. 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 10⁹/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 cm³ (range 478 cm³ to 8881 cm³). (The upper limit of normal is approximately 300 cm³).

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

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

Study 2

Study 2 was an open-label, randomized study in 219 patients. Patients were randomized 2:1 to Jakafi versus best available therapy. Best available therapy was selected by the investigator on a patient-by-patient basis. In the best available therapy arm, the medications received by more than

10% of patients were hydroxyurea (47%) and glucocorticoids (16%). The median age was 66 years (range 35 to 85 years) with 52% of patients older than 65 years and 57% were male. Fifty-three percent (53%) of patients had primary myelofibrosis, 31% had post-polycythemia vera myelofibrosis and 16% had post-essential thrombocythemia myelofibrosis. 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 $236 \times 10^9/L$. 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

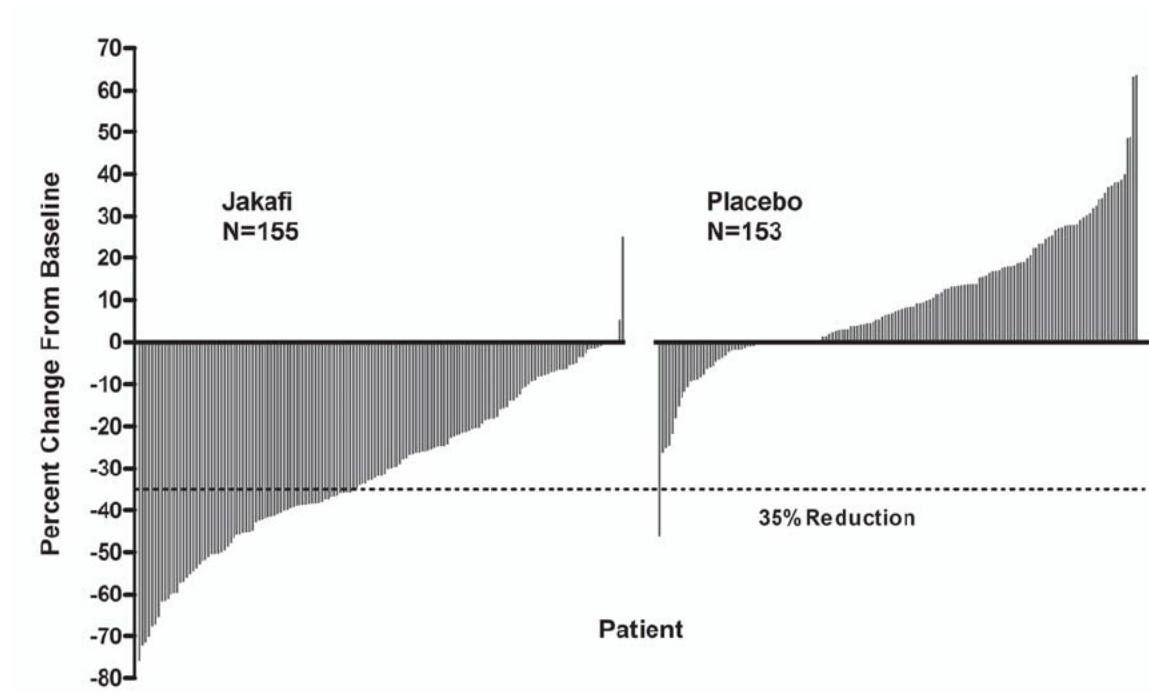
Efficacy analyses of the primary endpoint in Studies 1 and 2 are presented in Table 6 below. A significantly larger proportion of patients in the Jakafi group achieved a 35% or greater reduction in spleen volume from baseline in both studies compared to placebo in Study 1 and best available therapy in Study 2. A similar proportion of patients in the Jakafi group achieved a 50% or greater reduction in palpable spleen length.

Table 6: Percent of Patients with 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 (41.9)	1 (0.7)	41 (28.5)	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, myelofibrosis 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 myelofibrosis (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.

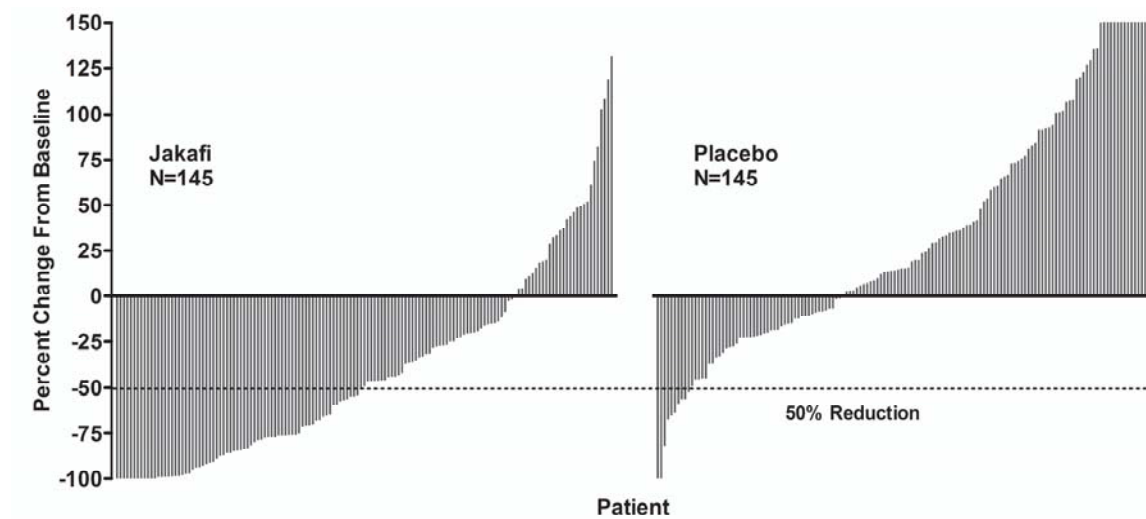
Table 7 presents assessments of Total Symptom Score from baseline to Week 24 in Study 1 including the proportion of patients with at least a 50% reduction (ie, improvement in symptoms). At baseline, the mean Total Symptom Score was 18.0 in the Jakafi group and 16.5 in the placebo group. A higher proportion 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 7: Improvement in Total Symptom Score

	Jakafi (N=148)	Placebo (N=152)
Number (%) of Patients with 50% or Greater Reduction in Total Symptom Score by Week 24	68 (45.9)	8 (5.3)
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.

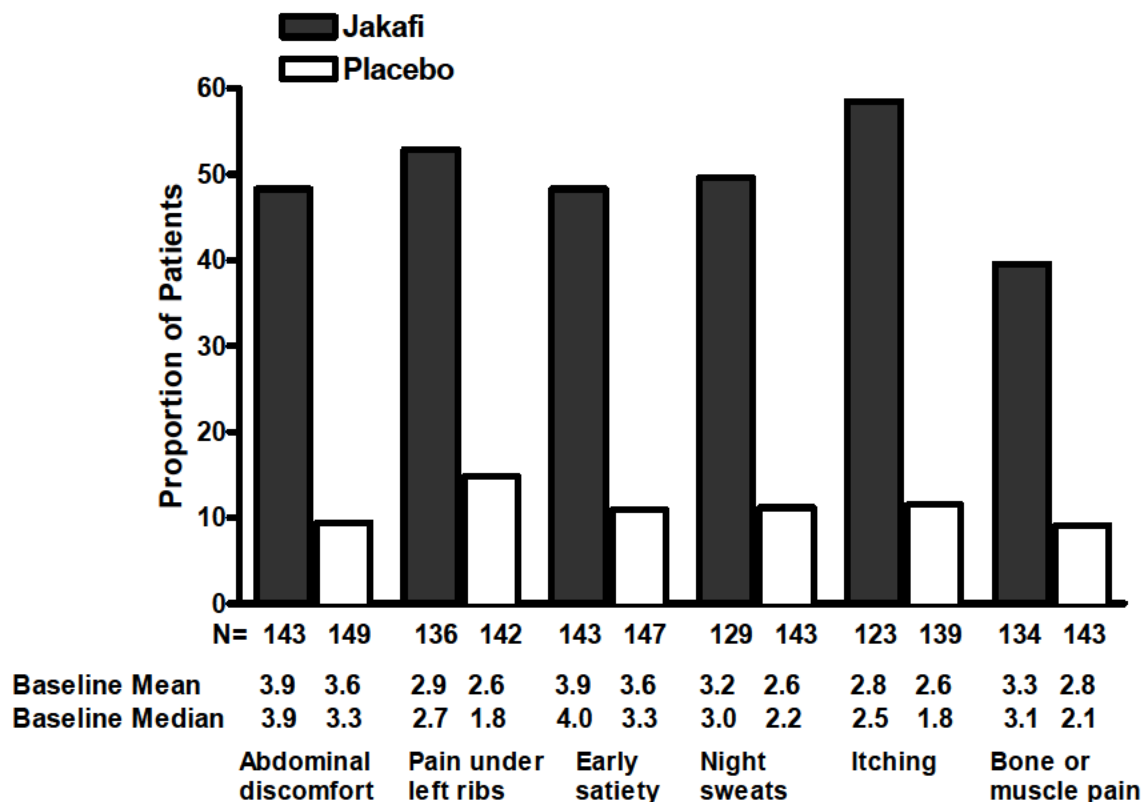
Figure 2: Percent Change from Baseline in Total Symptom Score at Week 24 or Last Observation for Each Patient (Study 1)



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 50% or Greater Reduction in Individual Symptom Scores at Week 24



Individual score range = 0 to 10

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).

Physicians and health care professionals are advised to discuss the following with patients prior to treatment with Jakafi:

17.1 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.

17.2 Infections

Patients should be informed of the signs and symptoms of infection and should report any such signs and symptoms promptly.

Patients should be informed of the early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible.

17.3 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.

17.4 Dialysis

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

17.5 Compliance

Patients should be advised 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, myelofibrosis signs and symptoms are expected to return.

Manufactured by:
DSM Pharmaceuticals, Inc.
Greenville, NC 27834

Manufactured for:
Incyte Corporation
Wilmington, DE 19880

Jakafi is a trademark of Incyte Corporation. All rights reserved.

U.S. Patent No. 7,598,257

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APPEARS THIS WAY ON ORIGINAL

Patient Information

Jakafi™ (JAK-ah-fye)

(ruxolitinib) Tablets

Read this Patient Information before you start taking Jakafi and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is Jakafi?

Jakafi is a prescription medicine used to treat people with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

It is not known if Jakafi is safe or effective in children.

What should I tell my healthcare provider before taking Jakafi?

Before taking Jakafi, tell your healthcare provider if you:

- have an infection.
- have or have had liver or kidney problems.
- are on dialysis. Jakafi should be taken after your dialysis.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if Jakafi will harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if Jakafi passes into your breast milk. You and your healthcare provider should decide if you will take Jakafi or breast-feed. You should not do both.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements. Taking Jakafi with certain other medicines may affect how Jakafi works.

Especially tell your healthcare provider if you take medicine for:

- Fungal infections
- Bacterial infections
- HIV-AIDS

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one listed above.

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.
- Do not drink grapefruit juice while taking Jakafi. Grapefruit juice can affect the amount of Jakafi in your blood.
- If you take too much Jakafi call your healthcare provider or go to the nearest hospital emergency room department right away. Take the bottle of Jakafi with you.
- If you miss a dose of Jakafi, take your next dose at your regular time. Do not take 2 doses at the same time.
- 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). 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 any of these symptoms:

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

Infection: You may be at risk for developing a serious infection while taking Jakafi. Tell your healthcare provider if you have:

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

The most common side effects of Jakafi include:

- dizziness
- headache

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of Jakafi. Ask your healthcare provider or pharmacist for more information.

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

How should I store Jakafi?

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

Keep this 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.

This Patient Information leaflet summarizes the most important information about Jakafi. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information that is written for healthcare professionals.

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

What are the ingredients in Jakafi?

Active ingredient: ruxolitinib.

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

This Patient Information has been approved by the U.S. Food and Drug Administration.

Jakafi is a trademark of Incyte Corporation. All rights reserved.

U.S. Patent No. 7,598,257

© 2011 Incyte Corporation. All rights reserved.

Issued: November 2011

LOT
EXP

Usual Dosage: See Prescribing Information.
Dispense in a tight container (See USP).
Store at room temperature 20°C - 25°C (68°F - 77°F);
excursions permitted between 15°C and 30°C
(59°F and 86°F) [See USP Controlled Room Temperature].
Protect from light.
Manufactured for: Incyte Corporation, Wilmington, DE 19880
Manufactured by: DSM Pharmaceuticals, Inc., Greenville, NC 27834

Rx only

NDC 50881-005-60

Jakafi™ (Ruxolitinib) Tablets

5 mg

60 tablets

Each tablet contains ruxolitinib phosphate equivalent
to 5 mg ruxolitinib free base.



Incyte Corporation
1-855-4-Jakafi
(452-5234)



008151

LOT
EXP

LOT
EXP

Usual Dosage: See Prescribing Information.
Dispense in a tight container (See USP).
Store at room temperature 20°C - 25°C (68°F - 77°F);
excursions permitted between 15°C and 30°C
(59°F and 86°F) [See USP Controlled Room Temperature].
Protect from light.
Manufactured for: Incyte Corporation, Wilmington, DE 19880
Manufactured by: DSM Pharmaceuticals, Inc., Greenville, NC 27834

Rx only

NDC 50881-010-60

Jakafi™ (Ruxolitinib) Tablets

10 mg

60 tablets

Each tablet contains ruxolitinib phosphate equivalent
to 10 mg ruxolitinib free base.



Incyte Corporation
1-855-4-Jakafi
(452-5234)



008152

LOT
EXP

LOT
EXP

Usual Dosage: See Prescribing Information.
Dispense in a tight container (See USP).
Store at room temperature 20°C - 25°C (68°F - 77°F);
excursions permitted between 15°C and 30°C
(59°F and 86°F) [See USP Controlled Room Temperature].
Protect from light.
Manufactured for: Incyte Corporation, Wilmington, DE 19880
Manufactured by: DSM Pharmaceuticals, Inc., Greenville, NC 27834

Rx only

NDC 50881-015-60

Jakafi™ (Ruxolitinib) Tablets

15 mg

60 tablets

Each tablet contains ruxolitinib phosphate equivalent
to 15 mg ruxolitinib free base.



Incyte Corporation
1-855-4-Jakafi
(452-5234)



008153

LOT
EXP

LOT
EXP

Usual Dosage: See Prescribing Information.
Dispense in a tight container (See USP).
Store at room temperature 20°C - 25°C (68°F - 77°F);
excursions permitted between 15°C and 30°C
(59°F and 86°F) [See USP Controlled Room Temperature].
Protect from light.
Manufactured for: Incyte Corporation, Wilmington, DE 19880
Manufactured by: DSM Pharmaceuticals, Inc., Greenville, NC 27834

Rx only

NDC 50881-020-60

Jakafi™

(Ruxolitinib) Tablets

20 mg

60 tablets

Each tablet contains ruxolitinib phosphate equivalent
to 20 mg ruxolitinib free base.



Incyte Corporation
1-855-4-Jakafi
(452-5234)



008154

LOT
EXP

LOT
EXP

Usual Dosage: See Prescribing Information.
Dispense in a tight container (See USP).
Store at room temperature 20°C - 25°C (68°F - 77°F);
excursions permitted between 15°C and 30°C
(59°F and 86°F) [See USP Controlled Room Temperature].
Protect from light.
Manufactured for: Incyte Corporation, Wilmington, DE 19880
Manufactured by: DSM Pharmaceuticals, Inc., Greenville, NC 27834

Rx only

NDC 50881-025-60

Jakafi™
(Ruxolitinib) Tablets

25 mg

60 tablets

Each tablet contains ruxolitinib phosphate equivalent
to 25 mg ruxolitinib free base.



Incyte Corporation
1-855-4-Jakafi
(452-5234)



008155

LOT
EXP

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

/s/

RICHARD PAZDUR
11/16/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202192Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Edvardas Kaminskas, M.D.
Subject	CDTL and Deputy Division Director Summary Review
NDA/BLA #	202192
Supplement #	
Applicant Name	Incyte Corporation
Date of Submission	June 3, 2011
PDUFA Goal Date	December 4, 2011
Proprietary Name / Established (USAN) Name	Jakafi™/ruxolitinib phosphate
Dosage Forms / Strength	5 mg, 10 mg , 15 mg, 20 mg, and 25 mg
Proposed Indications	
Action/Recommended Action for NME:	<i>Approval</i>

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Albert Deisseroth, M.D., Ph.D.
Statistical Review	Hong Lu, Ph.D., Mark Rothman, Ph.D., Rajeshwari Sridhara, Ph.D.
Pharmacology Toxicology Review	Wei Chen, Ph.D., Haleh Saber, Ph.D.
ONDQA – CMC and Biopharmaceutic Reviews	Tien Mien Chen, Ph.D., Sue-Ching Lin, Ph.D., Joyce Crich, Ph.D., Janice Brown, Ph.D., Richard T. Lostritto, Ph.D.
Microbiology Review	John Metcalfe, Ph.D.
Clinical Pharmacology Review	Joseph Grillo, Pharm.D., Jian Wang, Pharm.D., Julie Bullock, Pharm.D.
OPDP/DDTCP	Adora E. Nu, Pharm.D., James Dvorsky, Pharm.D.
OSI/DGCPC	Anothony Orenca, M.D., Lauren Iacono-Connors, Ph.D., Jean Mulinde, M.D.
OMPI/DMPP	Latonia Ford, BSN, MBA, LaShawn M. Griffiths, BSN, MSHS-PH
OSE/DMEPA	Lissa Owens, Pharm.D., Carlos Mena-Grillasca, RPh, Carol Holquist, RPh
IRT/QT	Qianyu Dang, Ph.D., Joanne Zhang, Ph.D., Jeffry Florian, Ph.D., Monica L. Fisman, M.D., Ph.D. Norman L. Stockbridge, M.D.

OND=Office of New Drugs

ONDQA=Office of New Drug Quality Assessment

OPDP/DDTCP=Office of Prescription Drug Promotion/Division of Direct-to-Consumer Promotion

OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance

OMPI/DMPP=Office of Medical Policy Initiatives/Division of Medical Policy Programs

OSE/DMEPA= Office of Surveillance and Epidemiology/ Division of Medication Error Prevention and Risk Management

Signatory Authority Review Template

1. Introduction

Jakafi™ (ruxolitinib) is a new molecular entity and the first of a new class of kinase inhibitors, that of JAK1 and JAK2 kinases, which act in signaling pathways involved in myeloid cell proliferation. It is the first therapeutic agent that decreases splenomegaly and ameliorates symptoms in primary or secondary myelofibrosis. This NDA is supported by results of trials that enrolled patients with myelofibrosis who needed treatment (intermediate-2 risk and high risk classifications). Clinical trials in other myeloproliferative disorders are in progress.

2. Background

Ruxolitinib was developed by the sponsor. Approximately 455 patients with myelofibrosis and 162 patients with other diseases (polycythemia vera, essential thrombocythemia, multiple myeloma, and prostate cancer) have been treated with the drug. Primary myelofibrosis is a chronic myeloproliferative disorder of unknown etiology characterized by progressive bone marrow fibrosis, extramedullary hematopoiesis, a leukoerythroblastic peripheral blood picture, splenomegaly, hepatomegaly and constitutional symptoms. The etiology of the disorder is unknown, but JAK2 mutations have been described in about 50% of patients. Constitutional symptoms are thought to be due to elevated levels of clonal cell-derived cytokines. Since myelofibrosis, whether primary or post-polycythemia vera or post-essential thrombocythemia, has a highly variable symptomatology and rate of disease progression, only high and intermediate-2 risk patients (by IWG-MRT criteria) need to be treated. The sponsor submitted the protocol of the pivotal trial for a SPA. Agreement with the Agency on the study protocol was reached on July 17, 2009. The NDA was submitted on June 3, 2011. It contained the results of two large, randomized trials with reduction of splenomegaly as the primary endpoint. A key secondary endpoint in the primary double-blinded trial was reduction of myelofibrosis-associated symptoms.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months when stored at USP controlled room temperature of 20-25°C (68-77°F); excursions are permitted to 15-30°C (59-86°F). I also concur with the conclusions reached by the biopharmaceutics reviewer regarding the biowaiver requests, the proposed dissolution acceptance criterion, and the *in vitro* study

evaluating the stability of ruxolitinib phosphate in oral solution after passing through NG tubes. There are no outstanding issues.

I concur with the conclusions reached by the microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

Pharmacology, safety pharmacology, pharmacokinetic/ADME (absorption, distribution, metabolism and excretion), and toxicology studies were conducted in *in vitro* systems and/or in animal species. Ruxolitinib was administered orally to animals in toxicology studies, consistent with the intended route of administration in patients. Drug-related toxicities were similar after single- or repeat-dose administration, therefore only repeat-dose general toxicology studies were reviewed for this NDA. Toxicities were mostly related to pharmacology of the drug, with lymphoid depletion, and reduced size of thymus and spleen being the primary adverse effects. When administered during the period of organogenesis, ruxolitinib was not teratogenic to rats or rabbits. Reduced fetal weight and/or increased post-implantation loss were seen in animals only at doses that resulted in maternal mortalities. In a designated fertility study, ruxolitinib did not impair male or female fertility but resulted in increased post-implantation loss. In a peri-post-natal study conducted in rats, there were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth, and development parameters at the doses evaluated. Reduced number of pups (F1) delivered compared to the control appears to be secondary to the post-implantation loss, as previously reported in the embryo-fetal developmental study.

Ruxolitinib was not genotoxic when tested *in vitro* or *in vivo* for mutagenic or clastogenic potential. When tested in a 6-month carcinogenicity study in Tg.rasH2 transgenic mouse, ruxolitinib was not carcinogenic. A 2-year carcinogenicity study in rat is ongoing. Considering the results of reproduction toxicology studies together with the negative results reported in the genetic toxicology studies, the Applicant's proposed Category C for pregnancy is acceptable.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology/Biopharmaceutics reviewer summarized the data on proposed starting dose and dose adjustment recommendations of ruxolitinib. Ruxolitinib is nearly completely absorbed following oral administration and reaches C_{max} at approximately 1-2 hours post-dose with a linear PK over a dose range of 5 mg to 200 mg. Food does not affect ruxolitinib exposure. Ruxolitinib is eliminated almost completely by oxidative metabolism (primarily by CYP3A4) with a terminal elimination half-life of approximately 3 hours (5.8 hours for ruxolitinib plus metabolites). Active metabolites contribute approximately 18% of the overall ruxolitinib activity. Ruxolitinib and its M18 metabolite are unlikely inhibitors of the major CYP and transporter pathways. Ruxolitinib is not a potent inducer of CYP isozymes

and an unlikely P-gp substrate. Ruxolitinib dose should be adjusted for thrombocytopenia, hepatic impairment and moderate or severe renal impairment.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

The results of two controlled trials support the efficacy of ruxolitinib in myelofibrosis (MF) (primary, post-polycythemia vera, and post-essential thrombocythemia). The pivotal trial (INCB-351), which was double-blind, prospectively randomized, placebo-controlled and carried out in the U.S., enrolled 309 patients with MF, who had failed available therapy and who needed treatment due to symptoms (IWG high-risk and intermediate-2 risk categories). Patients were randomized 1:1 to ruxolitinib or to placebo. The primary endpoint was a statistically significant difference between the two treatment arms in the percentage of patients with $\geq 35\%$ spleen volume reduction (SVR), as measured by MRI, by week 24 of treatment. The key secondary endpoint was a statistically significant difference between the two treatment arms in the percentage of patients who achieve $\geq 50\%$ reduction in Total Symptom Score as assessed by a validated patient reported outcome (PRO) instrument. Patients were balanced in the two arms with respect to gender, type of myelofibrosis (primary or secondary), years since diagnosis, median spleen volume (approximately 2,600 cm³, or about 8 times the upper limit of normal), ECOG PS status, prognostic category, and presence of V617F mutation. Ruxolitinib dosing was reduced, increased or interrupted according to dose recommendation guidelines using platelet counts. At the time of trial datalock, 87% of patients in the ruxolitinib arm and 53% of patients in the placebo arm remained on study. The results of the primary efficacy endpoint (SVR) and of the key secondary endpoint (TSS) are shown in Table 21 from the Clinical Review (shown below).

Table 21-Efficacy Results for INCB-351

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

*By Fisher's exact test; ** by Chi-square test; [&]NR=data not recorded or available.

[#] This patient died (105-002) from disease progression 4 days after this measurement. It was not determined if this patient had a splenic infarct which could have accounted for the rapid reduction in the splenic volume in this patient.

Interestingly, only about one-half (54%) of the patients who had SVR $\geq 35\%$ also had TSS reduction of TSS by $\geq 50\%$, and likewise only about one-half (51%) of patients who had TSS reduction by $\geq 50\%$ also had SVR $\geq 35\%$. Extensive analyses by baseline clinical characteristics

failed to elucidate this dichotomy. Of note, in TSS responders individual symptoms changed in concert; there were no symptom categories that were driving the response. The results of the secondary endpoints can be summarized as follows. Median duration of SVR $\geq 35\%$ could not be determined at the time of data lock, but were estimated by Kaplan-Meier plots to be about 45 weeks. Likewise, overall survival could not be determined because there had been very few deaths in the trial at the time of data lock. There were too few patients with data on bone marrow fibrosis, but there was no evident increase in the ruxolitinib arm. There was a slight (11%) reduction in the level of JAK2 V617F mutation in the ruxolitinib arm and a slight increase (4%) in the placebo arm. Changes in RBC transfusion dependency were approximately similar in both treatment arms. Ruxolitinib did not improve anemia and transfusion dependence in these patients. Subgroup analyses showed that female patients and patients treated with a higher starting dose had higher percentages of responses. Patients who had V617F mutations had higher percentages of responses than patients without these mutations (49% vs. 28%, $p=0.03$), but the CI's were overlapping for the two groups.

The supporting trial (INCB-352) enrolled a similar population of patients with MF, but was open-label. Patients were prospectively randomized 2:1 to ruxolitinib (N=146) or Best Available Therapy (N=73). The randomization was stratified for IWG risk category (high risk vs. intermediate-2). The primary endpoint was a statistically significant difference between the two treatment arms in the percentage of patients with $\geq 35\%$ spleen volume reduction (SVR), as measured by MRI or CT, by week 48 of treatment. Changes in MF-related symptoms were not assessed. Baseline demographic features were balanced between the two arms and were similar to those in INCB-351. The results of for the primary and the key secondary endpoint are shown in Reviewer's Table 44 below.

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

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

*Best available therapy.

The results of the primary and key secondary endpoints are consistent with the results in the pivotal trial. Data for PFS, LFS, and OS were not mature at the time of data lock. RBC transfusion dependency data was similar to that in the primary trial, as was change in the level of V617F mutation. Response rate in the V617F-positive group was higher than in the V617F-negative group (33% vs. 14%, $p=0.03$).

As noted above, responses occurred in both V617F-positive patients and V617F-negative patients; however, constitutive baseline activation of STAT3 pathway was observed in subjects regardless of the presence or absence of the V617F mutation. Thus, a V617F mutation testing kit does not have to be approved by CDRH. Other methods documenting STAT3 activation may emerge as predictive of response to ruxolitinib.

I concur with the conclusions reached by the clinical and statistical reviewers.

8. Safety

A total of 617 patients had been exposed to ruxolitinib; however, only patients with MF (509) were reviewed for safety. Patients with prostate cancer, multiple myeloma, polycythemia vera, and essential thrombocythemia were omitted from this analysis. The median duration of continuous therapy in patients initially started on ruxolitinib in the two Phase 3 trials and all Phase 2 trials was 14.8 months. In the pivotal Phase 3 trial, 87% of patients in the ruxolitinib arm and 52% in the placebo arm remained on treatment at the time of data lock. Thirteen percent of patients in the ruxolitinib arm and 48% in the placebo arm had discontinued treatment; 24% of patients in the placebo arm had crossed over to ruxolitinib treatment. In the supporting Phase 3 trial, 62% of patients in the ruxolitinib arm and 43% in the best available therapy (BAT) arm remained on treatment at the time of data lock. Thirty-eight percent of patients in the ruxolitinib arm and 58% in the BAT arm had discontinued treatment; 25% of patients in the placebo arm had crossed over to ruxolitinib treatment.

There were few deaths in both Phase 3 trials at the time of data lock. In the pivotal trial, 6% of patients in the ruxolitinib arm and 7% of patients in the placebo arm had died. In the supportive trial, 3% of patients in the ruxolitinib arm and 5% in the BAT arm had died. Deaths were mainly due to disease progression and infections. Approximately 30% of patients in both arms of each trial had non-fatal SAEs, most commonly bleeding, anemia, thrombocytopenia, and pneumonia. The most common adverse reactions in the ruxolitinib arms of both trials were thrombocytopenia and anemia (neutropenia was rare), and headache, dizziness, and confusion. The frequency of adverse reactions and of hematology laboratory abnormalities (from Clinical Review) is shown below.

Table 58-AEs $\geq$ 1% of Patients in the Phase III Trial in the ISS

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

Among adverse reactions, thrombocytopenia and anemia require close monitoring and treatment. The degree of thrombocytopenia was used to determine the starting dose and for dose adjustments. Platelet transfusions were administered to 4.7% of patients receiving

ruxolitinib and to 4.0% of patients receiving placebo. RBC transfusions were administered to 60% of patients treated with ruxolitinib and 38% receiving placebo. Neutropenia resulted in ruxolitinib discontinuation or dose reduction in 1.0% of patients. Headaches, dizziness and confusion were more common in ruxolitinib-treated patients.

Elevations of ALT, AST and cholesterol were more common in ruxolitinib-treated patients than in placebo controls. They were mostly Grade 1.

Labeling includes recommended starting dose, dose modification guidelines for thrombocytopenia, dose modification based on response, dose adjustment with concomitant strong CYP3A4 inhibitors, and cautions regarding use in patients with renal or hepatic impairment.

There are no considerations for REMS. PMRs and PMCs are stated in 13.

9. Advisory Committee Meeting

An Oncology Drugs Advisory Committee meeting is not planned for this submission, because the benefits of ruxolitinib in spleen volume reduction and symptom control are evident in the results of two adequate and well-controlled trials, while adverse reactions appear to be manageable.

10. Pediatrics

N/A. Jakafi™ (ruxolitinib phosphate) has been granted Orphan Drug Status for myelofibrosis.

11. Other Relevant Regulatory Issues

OSI/DGCPC conducted inspections at two of the eighty-nine clinical sites, in which the pivotal clinical trial was performed. The overall assessment was that the studies appear to have been conducted adequately, and the data generated appear acceptable in support of the application.

IRT/QT concluded that no significant QTc prolongation effect of ruxolitinib was detected in the TQT study.

There are no other unresolved relevant regulatory issues.

12. Labeling

OSE/DMEPA approved the proprietary name request.

OMPI/DMPP concluded that Patient Package Insert is acceptable with the recommended changes.

OSE/DMEPA made labeling recommendations to help prevent medication errors, and agreed with the revised label and labeling, including carton and container labels.

A Patient Counseling Information section and a Patient Information section are included in the labeling and were approved by OMPI/DMPP.

13. Decision/Action/Risk Benefit Assessment

- I recommend that ruxolitinib be granted Full Approval for patients with intermediate-2 and high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis with the labeling recommended by the review team.
- Risk Benefit Assessment

The following table is from the Clinical Review.

Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition: MF Clinical Manifestations Median Survival (all groups) Survival high risk Survival intermediate-2 Approved available therapy	Splenomegaly and symptoms which disrupt quality of life 57 months 27 months 48 months No approved therapy	MF is a serious, life-threatening condition in which death is due to evolution into AML (12%), bleeding (11%), portal hypertension (7%), and liver insufficiency (9%).
Unmet Medical Need: Therapy: Off label use of interferon-alpha, anagrelide, dexamethasone, hydroxyurea, erythropoietin, thalidomide, splenic radiation, and allografts.	Allograft is the only curative therapy (7-year survival is 60%). Only a fraction of patients with MF are eligible. All other therapies are palliative and have significant side effects.	For most patients, there is no curative therapy, and no effective treatment which reduces symptoms and splenomegaly for a long time. There is an unmet medical need in MF.
Clinical Benefit: 2 randomized, well controlled trials were conducted with reproducible results.	42% and 29% of ruxolitinib treated patients in the two trials displayed $\geq 35\%$ reduction of splenic volume. In the pivotal phase III trial, 46% of patients experienced $\geq 50\%$ reduction in total symptom score. Long term benefit and toxicity unknown.	Two large well controlled and well designed trials met efficacy endpoints when measured at 24 and 48 weeks of therapy. Uncertain is the how long benefits will last beyond the 24 and 48 weeks and what will be the toxicity of long-term treatment.
Risks: Early deaths (≤ 28 days) SAEs AEs ↓platelets (Grade 3) ↓platelets (no Grade 4) Bleeding	Ruxolitinib Arms Not increased Not increased Increased Not increased Not increased	Thrombocytopenia was successfully managed by a dose adjustment schedule. Anemia was managed by RBC transfusions. The risks of long term therapy have not been characterized.

Anemia (Grade 3) Anemia (Grade 4) Infections AEs leading to discontinuation AEs leading to dose reduction	Increased Increased Not increased Not increased Increased	
Risk Management: Need of studies for toxicity of long-term therapy.	Two phase III trials showed significant benefit and minimal risks for up to 48 weeks of treatment. Need PMC for longer term follow-up of response duration and toxicity.	PMR for follow-up (for 3 years after randomization) of phase III trial populations for myelosuppression PMC for post-marketing follow-up of efficacy and safety outcomes of current randomized trials and to report on discontinuation of at least 150 patients previously entered onto the randomized trials to determine if specific cautions are appropriate to describe discontinuation strategies.

Final Benefit-Risk Summary and Assessment: Two well designed, well controlled, randomized trials of ruxolitinib in patients with MF, who for the most part had no other available therapy, showed that clinically significant benefit was generated by ruxolitinib, and that the major side effect (thrombocytopenia) could be limited by dose adjustments which did not prevent the benefit otherwise generated by ruxolitinib.

- Recommendation for Postmarketing Risk Management Activities
None.
- Recommendation for other Postmarketing Study Commitments

On October 31, 2011 the sponsor committed to fulfill the 6 postmarketing commitments/requirements for safety and efficacy and provided proposed timelines.

1. Post-Marketing Study Commitment 1 (Post-Marketing Requirement Under 505(o): Provide safety findings related to the interval of drug discontinuation in at least 75 patients previously entered on INCB-351 to determine if specific cautions are appropriate to describe discontinuation strategies.

Final Protocol Submission	07/2009
Study/Trial Completion	08/2012
Final Report Submission	10/2013

2. Post-Marketing Study Commitment 2 (Post-Marketing Requirement Under 505(o): Provide safety findings related to the interval of drug discontinuation in at least 75 patients previously entered on INCB-352 to determine if specific cautions are appropriate to describe discontinuation strategies.

Final Protocol Submission	05/2010
Study/Trial Completion	08/2012
Final Report Submission	10/2013

3. Post-Marketing Study Commitment 3 (Post-Marketing Requirement Under 505(o): Collect and analyze safety information on myelosuppression for up to 144 weeks of therapy following randomization in the patients entered on INCB-351 who are continuing on therapy past 24 weeks.

Final Protocol Submission	07/2009
Study/Trial Completion	03/2013
Final Report Submission	12/2013

4. Post-Marketing Study Commitment 4 (Post-Marketing Requirement Under 505(o): Collect and analyze safety information on myelosuppression for up to 144 weeks of therapy following randomization in the patients entered on INCB-352 who are continuing on therapy past 48 weeks.

Final Protocol Submission	05/2010
Study/Trial Completion	03/2013
Final Report Submission	12/2013

5. Post-Marketing Study Commitment 5 (Subject to Reporting Requirements Under Section 506B): Provide longer-term efficacy and safety outcomes of current clinical trial INC-351 to provide at least 3-year follow-up data.

Final Protocol Submission	07/2009
Study/Trial Completion	08/2013
Final Report Submission	08/2014

6. Post-Marketing Study Commitment 6 (Subject to Reporting Requirements Under Section 506B): Provide longer-term efficacy and safety outcomes of current clinical trial INCB-352 to provide at least 3-year follow-up data.

Final Protocol Submission	05/2010
Study/Trial Completion	08/2013
Final Report Submission	08/2014

Rationale: PMCs #1 and #2 will provide safety data on drug discontinuation (i.e. whether the ruxolitinib dose needs to be decreased gradually or can be discontinued abruptly). PMCs #3 and #4 will provide information on longer-term effects of ruxolitinib on bone marrow functioning. PMCs #5 and #6 will provide data on duration of responses and overall survival in the two trials.

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/s/

EDVARDAS KAMINSKAS
11/15/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202192Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA #	202192
Supplement #	
Applicant Name	Incyte Corporation
Date of Submission	June 3, 2011
PDUFA Goal Date	December 4, 2011
Proprietary Name / Established (USAN) Name	Jakafi™/ruxolitinib phosphate
Dosage Forms / Strength	5 mg, 10 mg, 15 mg, 20 mg, and 25 mg
Proposed Indications	Jakafi is a kinase inhibitor indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Albert Deisseroth, M.D., Ph.D.
Statistical Review	Hong Lu, Ph.D., Mark Rothman, Ph.D., Rajeshwari Sridhara, Ph.D.
Pharmacology Toxicology Review	Wei Chen, Ph.D., Haleh Saber, Ph.D.
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OND=Office of New Drugs
 ONDQA=Office of New Drug Quality Assessment
 OPDP/DDTCP=Office of Prescription Drug Promotion/Division of Direct-to-Consumer Promotion
 OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance
 OMP/DMPP=Office of Medical Policy Initiatives/Division of Medical Policy Programs
 OSE/DMEPA= Office of Surveillance and Epidemiology/ Division of Medication Error Prevention and Risk Management
 IRT/QT=Interdisciplinary Review Team for QT Studies
 CDTL=Cross-Discipline Team Leader

1. Introduction

Jakafi™ (ruxolitinib) is the first of a new class of kinase inhibitors (JAK1 and JAK2 kinases) that signal pathways involved in myeloid cell proliferation. It is the first therapeutic agent that decreases splenomegaly and ameliorates symptoms in primary or secondary myelofibrosis. This NDA is supported by results of trials that enrolled patients with myelofibrosis who needed treatment (intermediate-2 risk and high risk classifications).

2. Background

Approximately 455 patients with myelofibrosis and 162 patients with other diseases (polycythemia vera, essential thrombocythemia, multiple myeloma, and prostate cancer) have been treated with ruxolitinib. Primary myelofibrosis is a chronic myeloproliferative disorder of unknown etiology characterized by progressive bone marrow fibrosis, extramedullary hematopoiesis, a leukoerythroblastic peripheral blood picture, splenomegaly, hepatomegaly and constitutional symptoms. JAK2 mutations have been described in about 50% of patients. This NDA, which was submitted on June 3, 2011, contains the results of two large, randomized trials with reduction of splenomegaly as the primary endpoint. A key secondary endpoint in the primary double-blinded trial was reduction of myelofibrosis-associated symptoms.

3. CMC

The CMC review team recommends that this application be approved with acceptability of the manufacturing of the drug product and drug substance. Stability testing supports an expiry of 24 months when stored at USP controlled room temperature of 20-25°C (68-77°F); excursions are permitted to 15-30°C (59-86°F). Additionally, the microbiology reviewer has concluded that there are no outstanding microbiology or sterility issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

There are no pharmacology/toxicology issues that preclude the approval of ruxolitinib. Toxicities were mostly related to pharmacology of the drug, with lymphoid depletion, and reduced size of thymus and spleen being the primary adverse effects. When administered during the period of organogenesis, ruxolitinib was not teratogenic to rats or rabbits. Reduced fetal weight and/or increased post-implantation loss were seen in animals only at doses that resulted in maternal mortalities. In a designated fertility study, ruxolitinib did not impair male or female fertility but resulted in increased post-implantation loss.

Ruxolitinib was not genotoxic when tested *in vitro* or *in vivo* for mutagenic or clastogenic potential. When tested in a 6-month carcinogenicity study in Tg.rasH2 transgenic mouse, ruxolitinib was not carcinogenic. A 2-year carcinogenicity study in rat is ongoing. Considering the results of reproduction toxicology studies together with the negative results reported in the genetic toxicology studies, the Applicant's proposed Category C for pregnancy is acceptable.

5. Clinical Pharmacology

The Clinical Pharmacology team recommended approval, and there are no issues that would preclude approval from this discipline. Food does not affect ruxolitinib exposure. Ruxolitinib is eliminated almost completely by oxidative metabolism (primarily by CYP3A4) with a terminal elimination half-life of approximately 3 hours (5.8 hours for ruxolitinib plus metabolites). Active metabolites contribute approximately 18% of the overall ruxolitinib activity. Ruxolitinib and its M18 metabolite are unlikely inhibitors of the major CYP and transporter pathways.

Ruxolitinib is not a potent inducer of CYP isozymes and an unlikely P-gp substrate. Ruxolitinib dose should be adjusted for thrombocytopenia, hepatic impairment and moderate or severe renal impairment.

6. Clinical/Statistical-Efficacy

This NDA is supported by two randomized controlled trials in patients with intermediate or high risk myelofibrosis comparing ruxolitinib to placebo (Study 1) or to best available therapy (Study 2).

Study 1 was a double-blind, randomized, placebo-controlled study allocating 309 patients (1:1) to either ruxolitinib (15-20 mg orally twice daily) or placebo. Fifty percent of patients had primary myelofibrosis, 31% post-polycythemia vera myelofibrosis and 18% post-essential thrombocythemia myelofibrosis. Study 2 was an open-label trial allocating 219 patients (2:1) to either ruxolitinib (15-20 mg orally twice daily) or best available therapy. Fifty-three percent of patients had primary myelofibrosis, 31% post-polycythemia vera myelofibrosis, and 16% post-essential thrombocythemia myelofibrosis. The ruxolitinib starting dose in both trials was based on the entry platelet counts.

Ruxolitinib treatment in both trials continued as long as the patients continued to benefit or until unacceptable toxicity. The primary endpoint was a comparison of the proportion of patients in the two arms who achieved a $\geq 35\%$ reduction in spleen volume (by CAT scan or MRI) after 24 weeks (Study 1) or after 48 weeks of treatment (Study 2)

Both randomized trials achieved their pre-specified primary endpoints. In Study 1, 42% versus 1% of patients on the ruxolitinib and placebo arms, respectively, experienced a $\geq 35\%$ reduction of spleen volume at 24 weeks ($p < 0.0001$, Chi-square and Fisher's exact test). In Study 2, 29% versus 0% of patients on the ruxolitinib and best available therapy arms, respectively, experienced a $\geq 35\%$ reduction of spleen volume at 48 weeks ($p < 0.0001$, Cochran-Mantel-Haenszel test).

The key secondary endpoint for Study 1 was to determine the difference between the proportion of patients on ruxolitinib versus placebo who experienced $\geq 50\%$ reduction of a total symptom score. This symptom score evaluated abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain and early satiety at 24 weeks compared to baseline. The percentage of patients who achieved a $\geq 50\%$ reduction of the total symptom score at 24 weeks was 46% versus 5% on the ruxolitinib and placebo arms, respectively ($p < 0.0001$, Chi-square test).

The key secondary endpoint on Study 2 was to determine the difference between the two arms in the proportion of patients who achieved a $\geq 35\%$ reduction in spleen volume (by CAT scan or MRI) at 24 weeks of treatment. A $\geq 35\%$ reduction in spleen volume occurred in 32% of the patients on the ruxolitinib arm and 0% on the best available therapy arm ($p < 0.0001$, Chochran-Mantel-Haenszel test). At the time of approval, 75% of the patients on Study 1 and 67% on Study 2 who achieved a $\geq 35\%$ reduction in spleen volume maintained this reduction in spleen volume.

The results of Study 1 and Study 2 are shown in Tables 1 and 2 below.

Table 1-Efficacy Results for Study 1 (INCB-351)

Treatment Arm	Ruxolitinib	Placebo	P value
Patients Randomized	N=155	N=154	
Primary Endpoint	N=155	N=153	

% SVR $\geq$ 35% at week 24	41.9%	0.7%#	P<0.0001*
Key Secondary Endpoint	N=148&	N=154	
% $\downarrow$ TSS by $\geq$ 50% week 24	45.9%	5.3%	P<0.0001**

*By Fisher's exact test; ** by Chi-square test; &NR=data not recorded or available.

This patient died (105-002) from disease progression 4 days after this measurement. It was not determined if this patient had a splenic infarct which could have accounted for the rapid reduction in the splenic volume in this patient.

Table 2-Outcome of Primary and Key Secondary Endpoint for Study 2 (INCB-352)

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

*Best available therapy.

7. Safety

A total of 617 patients had been exposed to ruxolitinib; however, only patients with MF (509) were reviewed for safety. Patients with prostate cancer, multiple myeloma, polycythemia vera, and essential thrombocythemia were omitted from this analysis. The median duration of continuous therapy in patients initially started on ruxolitinib in the two Phase 3 trials and all Phase 2 trials was 14.8 months.

Among adverse reactions, thrombocytopenia and anemia require close monitoring and treatment. The degree of thrombocytopenia was used to determine the starting dose and for dose adjustments. Platelet transfusions were administered to 4.7% of patients receiving ruxolitinib and to 4.0% of patients receiving placebo. RBC transfusions were administered to 60% of patients treated with ruxolitinib and 38% receiving placebo. Neutropenia resulted in ruxolitinib discontinuation or dose reduction in 1.0% of patients. Headaches, dizziness and confusion were more common in ruxolitinib-treated patients.

Elevations of ALT, AST and cholesterol were more common in ruxolitinib-treated patients than in placebo controls. They were mostly Grade 1.

The most common adverse drug reactions observed in $\geq$ 1% of the patients treated with ruxolitinib included thrombocytopenia, anemia, bruising, dizziness and headache. Adverse drug reactions (grade 3 or greater) increased on the ruxolitinib arm compared to the placebo arm in Study 1 were thrombocytopenia (13% versus 1%) and anemia (45% versus 19%). Similar results were observed in Study 2.

8. Advisory Committee Meeting

An Oncology Drugs Advisory Committee did not occur because the benefits of ruxolitinib in spleen volume reduction and symptom control are evident in the results of two adequate and well-controlled trials, while adverse reactions appear to be manageable.

9. Pediatrics

Ruxolitinib has been granted Orphan Drug Status for myelofibrosis.

10. Other Relevant Regulatory Issues

OSI/DGCPD conducted inspections at two of the eighty-nine clinical sites, in which the pivotal clinical trial were performed. The overall assessment was that the studies appear to have been conducted adequately, and the data generated appear acceptable in support of the application.

IRT/QT concluded that no significant QTc prolongation effect of ruxolitinib was detected in the TQT study. There are no other unresolved relevant regulatory issues.

11. Labeling

OSE/DMEPA approved the proprietary name request. OSE/DMEPA made labeling (including to the Patient Package Insert) recommendations to help prevent medication errors, and agreed with the revised label and labeling, including carton and container labels.

OMPI/DMPP concluded that Patient Package Insert is acceptable with the recommended changes. A Patient Counseling Information section and a Patient Information section are included in the labeling and were approved by OMPI/DMPP.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Full Approval
- Risk Benefit Assessment

The following table is from the Clinical Review.

Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition: MF Clinical Manifestations Median Survival (all groups) Survival high risk Survival intermediate-2 Approved available therapy	Splenomegaly and symptoms which disrupt quality of life 57 months 27 months 48 months No approved therapy	MF is a serious, life-threatening condition in which death is due to evolution into AML (12%), bleeding (11%), portal hypertension (7%), and liver insufficiency (9%).
Unmet Medical Need: Therapy: Off label use of interferon-alpha, anagrelide, dexamethasone, hydroxyurea, erythropoietin, thalidomide, splenic radiation, and allografts.	Allograft is the only curative therapy (7-year survival is 60%). Only a fraction of patients with MF are eligible. All other therapies are palliative and have significant side effects.	For most patients, there is no curative therapy, and no effective treatment which reduces symptoms and splenomegaly for a long time. There is an unmet medical need in MF.
Clinical Benefit: 2 randomized, well controlled trials were conducted with reproducible results.	42% and 29% of ruxolitinib treated patients in the two trials displayed ≥35% reduction of splenic volume. In the pivotal phase III trial, 46% of patients experienced ≥50% reduction in total symptom score. Long term benefit and toxicity unknown.	Two large well controlled and well designed trials met efficacy endpoints when measured at 24 and 48 weeks of therapy. Uncertain is the how long benefits will last beyond the 24 and 48 weeks and what will be the toxicity of long-term treatment.

Risks: Early deaths (≤ 28 days) SAEs AEs ↓platelets (Grade 3) ↓platelets (no Grade 4) Bleeding Anemia (Grade 3) Anemia (Grade 4) Infections AEs leading to discontinuation AEs leading to dose reduction	Ruxolitinib Arms Not increased Not increased Increased Not increased Not increased Increased Increased Not increased Not increased Increased	Thrombocytopenia was successfully managed by a dose adjustment schedule. Anemia was managed by RBC transfusions. The risks of long term therapy have not been characterized.
Risk Management: Need of studies for toxicity of long-term therapy.	Two phase III trials showed significant benefit and minimal risks for up to 48 weeks of treatment. Need PMC for longer term follow-up of response duration and toxicity.	PMR for follow-up (for 3 years after randomization) of phase III trial populations for myelosuppression PMC for post-marketing follow-up of efficacy and safety outcomes of current randomized trials and to report on discontinuation of at least 150 patients previously entered onto the randomized trials to determine if specific cautions are appropriate to describe discontinuation strategies.

The benefits and risks of ruxolitinib were also discussed in the Division Director's Summary Review and Clinical Reviews. The review team found the risk-benefit assessment to be acceptable. This application is supported by the results of two well designed, well controlled, randomized trials of ruxolitinib in patients with MF demonstrating a clinically significant benefit with ruxolitinib. The major side effect of thrombocytopenia can be limited by dose adjustments. In conclusion, I concur with the review team's recommendation for approval.

- Recommendation for Postmarketing Risk Management Activities
None.

- Recommendation for other Postmarketing Study Commitments
See action letter for Postmarketing Requirements and Commitments.

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/s/

TAMY E KIM
11/16/2011

RICHARD PAZDUR
11/16/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202192Orig1s000

OFFICER/EMPLOYEE LIST

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Application: NDA 202192

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202192Orig1s000

MEDICAL REVIEW(S)

Clinical Review
Albert Deisseroth, MD, PhD
NDA 202192
Ruxolitinib

CLINICAL REVIEW

Application Type NDA
Application Number 202192
Priority or Standard Priority

Submit Date June 3, 2011
Received Date June 3, 2011
PDUFA Goal Date December 4, 2011

Reviewer Name Albert B Deisseroth, MD, PhD
Review Completion Date October 27, 2011

Established Name Ruxolitinib Phosphate
Proposed Trade Name JAKAFI™
Therapeutic Class JAK2 Inhibitor
Applicant Incyte Corporation

Formulation Tablets (5, 10, 15, 20, and 25 mg)
Dosing Regimen 15 mg po bid
Indication Treatment of Patients with
Myelofibrosis
Intended Populations Primary Myelofibrosis, Post-
polycythemia Vera Myelofibrosis,
and Post-essential
Thrombocythemia Myelofibrosis

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Table of Abbreviations

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

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

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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

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

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

I also recommend the following post-marketing commitments:

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

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

1.2 Risk Benefit Assessment

Benefit-Risk Summary and Assessment:

Conclusions Concerning Potential Benefits: Two prospectively randomized trials have been carried out in the treatment of patients with high risk or intermediate-2 risk MF (including PMF, PPVMF, and PETMF) in patients with anemia, splenomegaly and with symptoms that justified therapy. The first trial (INCB-351) that was the pivotal trial randomized patients with MF who were intolerant/refractory/ineligible for available therapy to receive continuous ruxolitinib therapy or to receive placebo (1:1 randomization). The second supporting trial (INCB-352) randomized patients with MF who had received prior therapy or no prior therapy, but who were not candidates for allogeneic stem cell transplantation, to continuous ruxolitinib or best available therapy (BAT), in a 2:1 randomization.

The primary endpoint in both trials was a statistically significant difference (as assessed by the Chi-square test in INCB-351 and by the Cochran-Mantel-Haenszel test stratified by prognostic category in INCB-352) between the two arms in the percentage of patients who (by 24 weeks on

INCB-351 and by 48 weeks on INCB-352) achieved a $\geq 35\%$ spleen volume reduction (SVR) as measured by MRI. The results for these primary endpoints in the two trials are presented below in Table 1.

Table 1-Primary Endpoint Results in Phase III Trials

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

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

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

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

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

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

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

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

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

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

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

[ISS, p. 56]

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

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

[ISS, pp. 78-81]

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

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

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

[ISS, pp. 60-66]

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

1. The on study deaths (≤ 28 days from last therapy) were lower in the ruxolitinib arm than in the other arm (placebo in INCB-351, and BAT in INCB-352);
2. There was no increase in SAEs on the ruxolitinib arms vs the comparison arms on INCB-351 or on INCB-352;
3. There was no increase in overall AEs on the ruxolitinib arms vs the comparison arms on INCB-351 or INCB-352.
3. The discontinuations due to adverse events on the ruxolitinib arms were equal to and no higher than those on the comparison arms in the two randomized trials;
4. Although the incidence of thrombocytopenia (including Grade 3 and Grade 4) was increased on the ruxolitinib arms of the two randomized trials vs the comparison arms, there was no increase in the incidence of bleeding on the ruxolitinib arms vs the comparison arms of INCB-351 and a minor increase in INCB-352. This was primarily the result of the dose adjustment schedule for thrombocytopenia (both prior to the commencement of therapy and during therapy). It is apparent that such dose adjustments to prevent severe thrombocytopenia did not prevent an impressive result in terms of efficacy.
5. The only adverse event (besides thrombocytopenia) for which there were clinically significant increases of Grade 3 and Grade 4 adverse events was anemia, for which significant increases occur on the ruxolitinib arms on INCB-351 (from 5 to 10% for Grade 3 and from 0 to 5% for Grade 4) and for which significant increases occur on the ruxolitinib arm on INCB-352 (3 to 11% for Grade 3, but no increase for Grade 4). Anemias were not seen to be a cause of discontinuations on the ruxolitinib arms of either INCB-351 or INCB-352 (see Table 54).
6. The other adverse events which were increased with ruxolitinib (diarrhea, nausea, confusion, headache, and dizziness) were grade 1-2 adverse events.

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

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

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

I also recommend the following post-marketing commitments:

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

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

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

Table 5-Benefit-Risk Assessment Framework

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

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

1.3 Recommendations for Postmarket Risk Management Activities: None

1.4 Recommendations for Postmarket Studies/Clinical Trials

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

2. Post-marketing commitments:

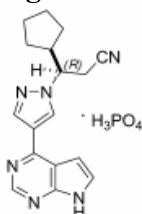
a. Commit to provide safety findings related to the interval of drug discontinuation in at least 150 patients previously entered onto INCB-351 and INCB-352 to determine if specific cautions are appropriate to describe discontinuation strategies.

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

2 Introduction and Regulatory Background

2.1 Product Information

Figure 1-Structure of Ruxolitinib



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

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

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

2.2 Tables of Currently Available Treatments for Proposed Indications

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

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

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

Table 6-Survival in IPSS Prognostic Categories

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

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

Table 7-Causes of Death in MF

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

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

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

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

2.3 Availability of Proposed Active Ingredient in the United States

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

Table 8-Drug Availability

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

2.4 Important Safety Issues With Consideration to Related Drugs

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

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The regulatory history of ruxolitinib is outlined in Table 9.

Table 9-Regulatory History

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

2.6 Other Relevant Background Information

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

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

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

Table 10-DSI Audit Sites for INCB-351

Site Number	Name of PI	Institution	Location	Number of Patients

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

3.2 Compliance with Good Clinical Practices

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

3.3 Financial Disclosures

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

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

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

4.2 Clinical Microbiology

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

4.3 Preclinical Pharmacology/Toxicology

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

[ISS, p. 193]

Testing did not reveal mutagenicity or clastogenic potential in human peripheral blood lymphocytes (see Module 2.4).

[ISS, p. 193]

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

[ISS, 187]

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

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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

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

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

STAT3 phosphorylation in response to stimulation of whole blood cells with thrombopoietin or IL-5 (IC₅₀ of 281 nM).

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

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

4.4.2 Pharmacodynamics

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

4.4.3 Pharmacokinetics

The analysis of the pharmacokinetics of ruxolitinib is outlined in the sections of the review that pertain to Clinical Pharmacology. The parent unchanged compound, ruxolitinib, has a plasma half life of 3.1 hours. The active metabolites have a plasma half-life of 5.8 hours. Only 1% of the parent compound is excreted unchanged. This drug is metabolized by CYP3A4. One of the issues discovered was that the response rate range was higher in women than in men in INCB-351 (non-overlapping ranges in the forest plot analysis which is presented in Figure 9 on page 49 of this report). The one remaining explanation is the well known antagonism of JAK2 by estrogens in women. This effect of estrogens could have made women with MF more sensitive to the effects of ruxolitinib.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

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

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

Table 11-Completed Clinical Trials

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

5.2 Review Strategy

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

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

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

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

5.3 Discussion of Individual Studies/Clinical Trials

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

Table 12-Patients Included in Integrated Safety Summary

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

Phase I/II Trials of MF

INCB-251: Phase I/II Single Arm Study of Ruxolitinib in PMF, PPVMF and PETMF.

The goal of this trial was to characterize the safety and tolerability of ruxolitinib in MF. The most common adverse events were anemia and thrombocytopenia. The most frequently reported SAE was pneumonia (7%).

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

Part 2: The goal was to study three schedules:

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

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

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

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

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

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

[CSR INCB-251, pp. 3-6]

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

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

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

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

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

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

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

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

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

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

Other secondary endpoints included: duration of maintenance of $\geq 35\%$ SVR, leukemia-free survival, overall survival, transfusion dependency, and a change in bone marrow histomorphology. There was no pre-specified order of analysis.

[CSR INCB-352, pp. 3-8]

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

Table 13-Design of Phase III Trials

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

6 Review of Efficacy

6.1 Indication for INCB-351 and INCB-352

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

6.1.1 Methods for INCB-351

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

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

Table 14-Eligibility for INCB-351

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

[Clin Protocol, July 21, 2009]

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

Table 15-Definition of Patients with MF Who Need Treatment

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

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

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

- a. The spleen length below the left costal margin had been reduced by $\leq 40\%$ by 4 weeks as compared to baseline;
 - b. The platelet count at Week 4 was $\geq 150,000/\text{microL}$ and the platelet count had never been $<150,000/\text{microL}$ from the time of baseline;
 - c. Absolute neutrophil counts (ANC) remained $\geq 1,000/\text{microL}$ since baseline.
- [CSR INCB-351, p. 39]

Dose Adjustments Due to Reductions in the Platelet or Neutrophil Count During

Treatment: During the 24 week treatment period, the CBC with differential count was done at weeks 1 and 2 and then every other week thereafter. The frequency of CBC determinations was increased to twice weekly if the platelet count falls less than $<50,000/\text{microL}$ or if the ANC is $<500/\text{microL}$.

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

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

Table 16 Guide for Dose Reductions

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

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

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

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

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

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

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

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

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

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

Table 18: Starting Dose of Ruxolitinib After Cross-Over

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

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

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

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

Additional secondary endpoints include:

- a. A comparison between the ruxolitinib and placebo arms for the percent change from baseline in the Week 24 TSS using the Wilcoxon Rank-Sum test and the analysis of covariance methods.
- b. Survival for each treatment group (estimated with 95% confidence intervals) using the log-rank test to test for an effect of treatment effect on survival.
- c. Another secondary endpoint was the duration of the reduction of the spleen volume by $\geq$ 35% using the Kaplan-Meier method. No comparative analysis was performed.

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

[CSR INCB-351, pp. 3-10]

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

[CSR INCB-351, p. 62]

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

6.1.2 Demographics for INCB-351

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

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

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

[CSR-351, pp. 70-72]

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

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

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

[CSR INCB-351, p. 74]

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

6.1.3 Subject Disposition for INCB-351

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

Table 20-Disposition on INCB-351

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

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

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

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

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

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

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

Table 21-Efficacy Results for INCB-351

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

*By Fisher's exact test; ** by Chi-square test; [&]NR=data not recorded or available.

[#] This patient died (105-002) from disease progression 4 days after this measurement. It was not determined if this patient had a splenic infarct which could have accounted for the rapid reduction in the splenic volume in this patient.

[CSR-351, pp. 87 and 103]

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

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

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

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

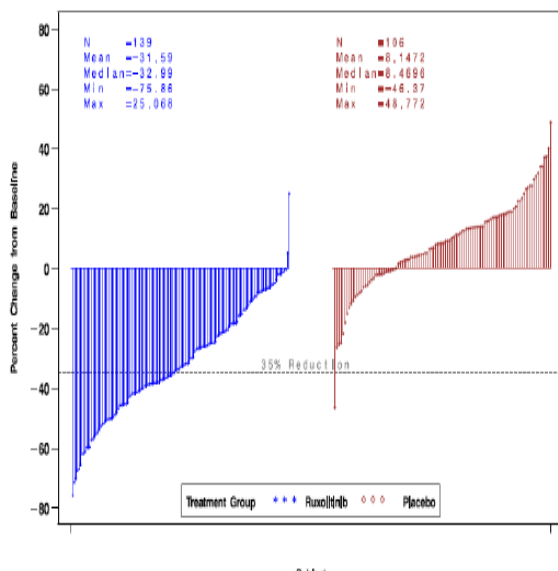


Figure 2A: SVR
 [CSR INCB-351, page 90]

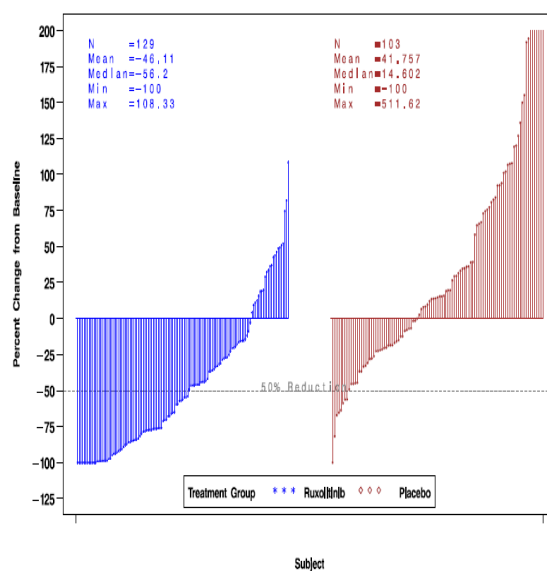


Figure 2B: TSS
 [CSR INCB-351, page 106]

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

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

Table 22-Number of Patients in Different Responder Subgroups

$\downarrow$ TSS without SVR	$\downarrow$ TSS and SVR both	SVR without $\downarrow$ TSS	SVR, no TSS data
33 patients	35 patients	27 patients	3 patients

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

Table 23: Efficacy Results in Different Responder Subgroups

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

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

- a. *$\downarrow$ TSS of $\geq 50\%$ and SVR of $\geq 35\%$ double positives*
- b. *$\downarrow$ TSS of $\geq 50\%$ without SVR of $\geq 35\%$*
- c. *SVR of 50% without $\downarrow$ TSS of $\geq 50\%$*

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

Table 24-Baseline Clinical Characteristics

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

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

Table 25-Individual Components of the TSS

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

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

Table 26-Responder Groups

<i>Group 1</i>	<i>↓TSS of ≥50% and SVR of ≥35% double positives</i>
<i>Group 2</i>	<i>↓TSS of ≥50% without SVR of ≥35%</i>
<i>Group 3</i>	<i>SVR of ≥35% without ↓TSS of ≥50%</i>

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

Table 27-Baseline Pre-treatment Splenic Volume

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

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

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

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

Table 28 Mean Percent Change in Individual Symptoms at Week 24

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

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

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

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

Table 29A-Prognostic Risk Category in the Responder Groups

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

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

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

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

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

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

Table 30-Percent of Cells Positive for V617F Mutation

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

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

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

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

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

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

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

Conclusions:

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

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

6.1.5.a. Durability of SVR by $\geq 35\%$

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

The definition of loss of response was: “the first day in patients who had reached a $\geq 35\%$ SVR on ruxolitinib that there was a $\geq 25\%$ increase from the nadir in spleen volume”. If a patient was discontinued from the study after achieving $\geq 35\%$ reduction of spleen volume on ruxolitinib, then the response was censored at that time. If the patient was still in remission at the time of data lock after achieving $\geq 35\%$ reduction of spleen volume on ruxolitinib, then the response was censored at that time.

[CSR INCB-351, Section 11.2.1.1.3 on p. 64]

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

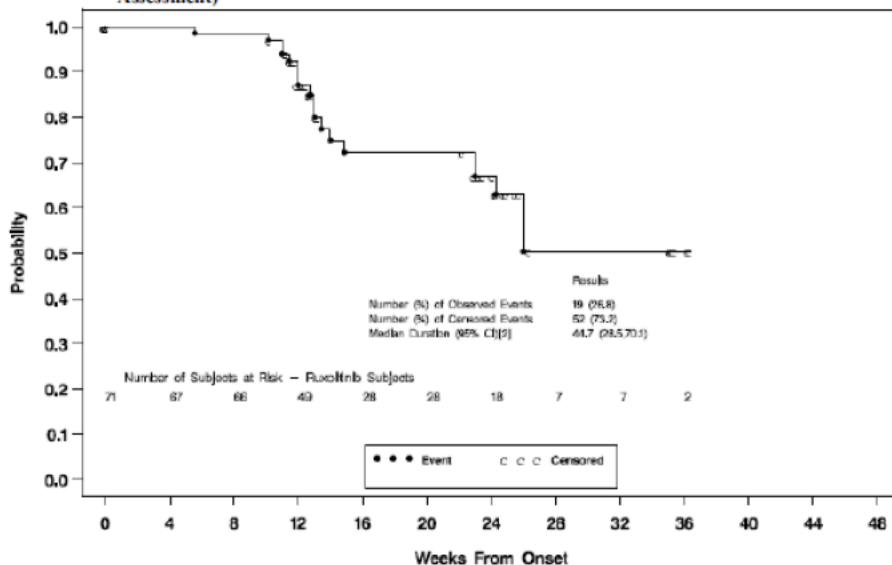
Table 33-Summary of Patients Who Lost SVR Response or Who Left INCB-351

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

[CSR INCB-351, p. 93]

Figure 3-Kaplan-Meier Analysis of Duration of SVR $\geq$ 35% on INCB-351

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



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

[CSR INCB-351, p. 96]

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

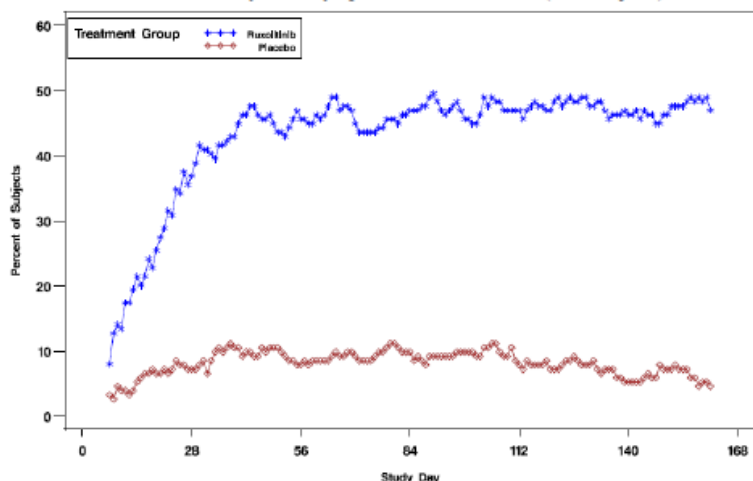
What is not clear from Table 33, is the time interval between the first date of establishing the pre-specified response threshold and the time at which the response was lost before the data lock of November 2, 2010 (for patients who lost their response within the period of observation), or the time interval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

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

6.1.5.b. Time to $\geq 50\%$ Reduction of TSS

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

Figure 4-Time to $\geq 50\%$ TSS on INCB-351
Figure 12: Daily Response Rate for Subjects Who Achieved $\geq 50\%$ Reduction From Baseline in Daily Total Symptom Score Over Time (ITT Subjects)



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[CSR INCB-351, page 109]

6.1.5.c Durability of $\geq 50\%$ Reduction of TSS responses

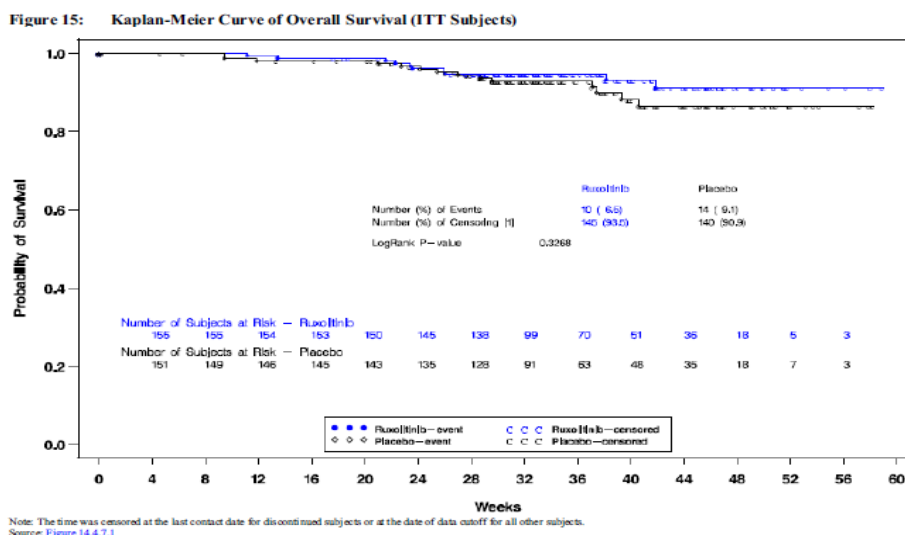
Although measurements of the TSS were made at the following time points: 4, 8, 12, 16, 20, and 24 weeks of treatment, no measurements of the TSS were made beyond 24 weeks on INCB-351.

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

6.1.5.d Analysis of Overall Survival on INCB-351

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

Figure 5: Analysis of OS in INCB-351



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[CSR INCB-351, p. 121]

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

6.1.5.e Bone Marrow Fibrosis

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

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

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

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

*one patient with Week 48 data had no Baseline data.

[CSR INCB-351, pp. 136-137]

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

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

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

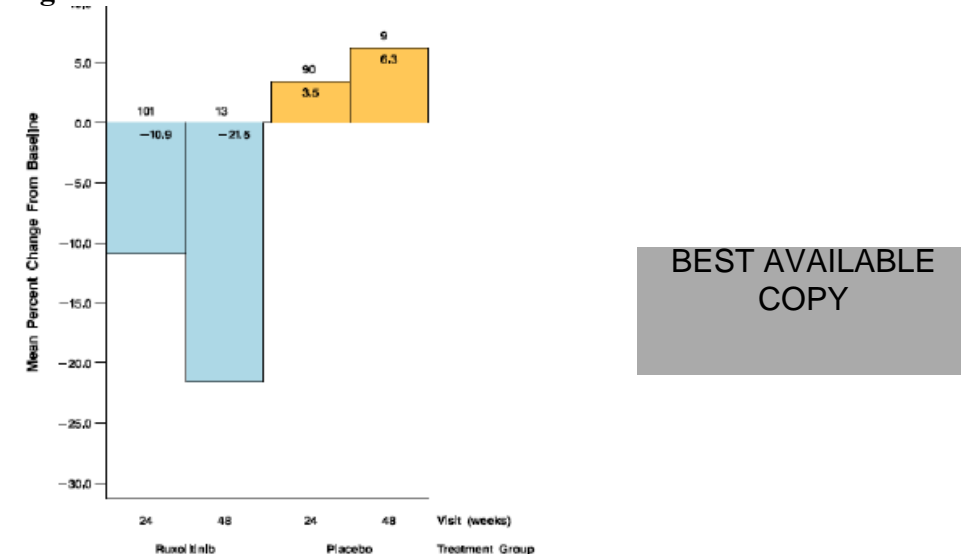
Table 35-Reduction of Level of V617F Mutation in INCB-351

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

*Rank sum test

[CSR INCB-351, pp. 136-137]

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



Source: Figure 14.4.23.1.1

[CSR INCB-351 pp 135-136]

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

6.1.5.g Transfusion Independency

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

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

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

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

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

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

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

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

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

[CSR INCB-351, p. 191]

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

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

[CSR INCB-351, p. 191]

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

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

[CSR INCB-351, p. 191]

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

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

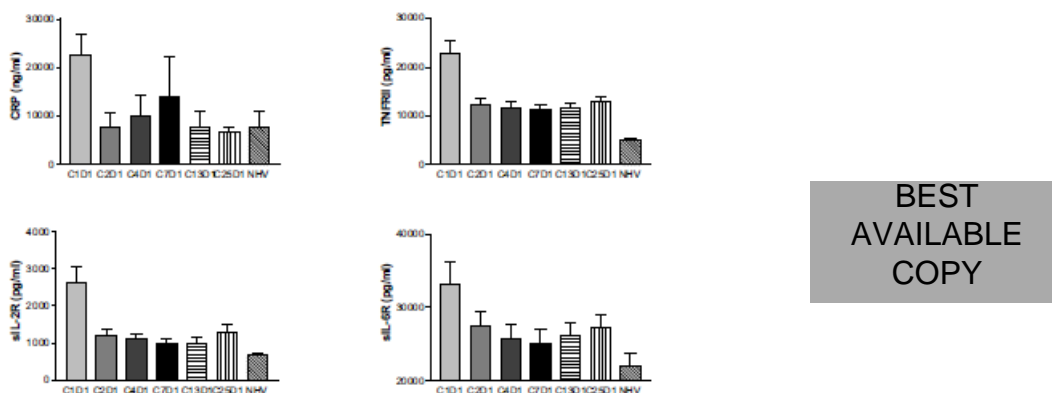
6.1.5.h. Reduction of Cytokine Release with Ruxolitinib

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

[CSR INCB-351, p. 81]

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

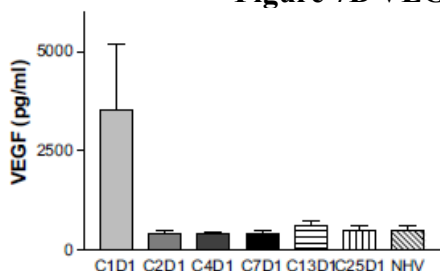
Figure 7A: Plasma Levels of Markers of Inflammation Following Ruxolitinib



[CSF INCB-251, page 312]

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

Figure 7B VEGF Levels Before and After Ruxolitinib



[CSR INCB-251, page 312]

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

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

6.1.6 Other Exploratory Endpoints for INCB-351

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

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

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

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

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

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

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

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

Reviewer Comment:

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

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

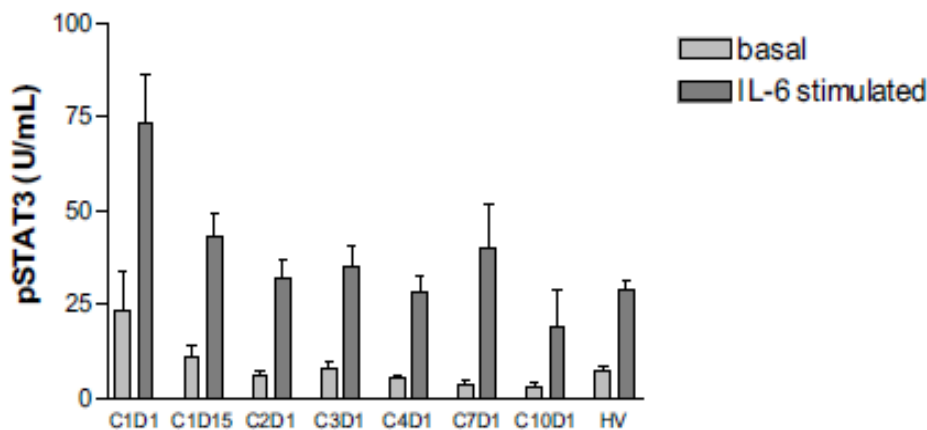
The Sponsor also provided data from INCB-251 that suggested that the inhibition of STAT3 activation by ruxolitinib in vivo is dependent on the dose of ruxolitinib, and that cells from patients exposed to ruxolitinib in vivo who are positive and negative for the V617F mutation in JAK2 are subject to inhibition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

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

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

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

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



HV = healthy volunteers

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

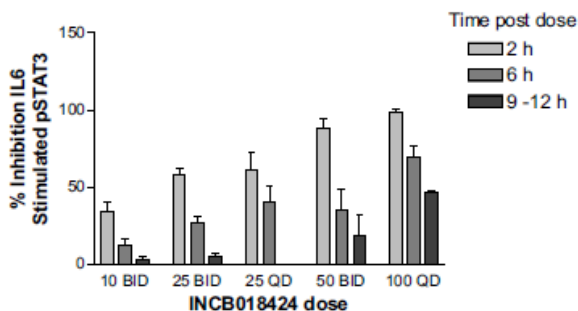
[INCYTE-IN-VITRO-10.06.2, page 275-see link on p. 83 of CSR INCB-351]

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

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

Figure 8-Dependency of Level of pSTAT3 on Ruxolitinib Dose

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



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

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

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

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

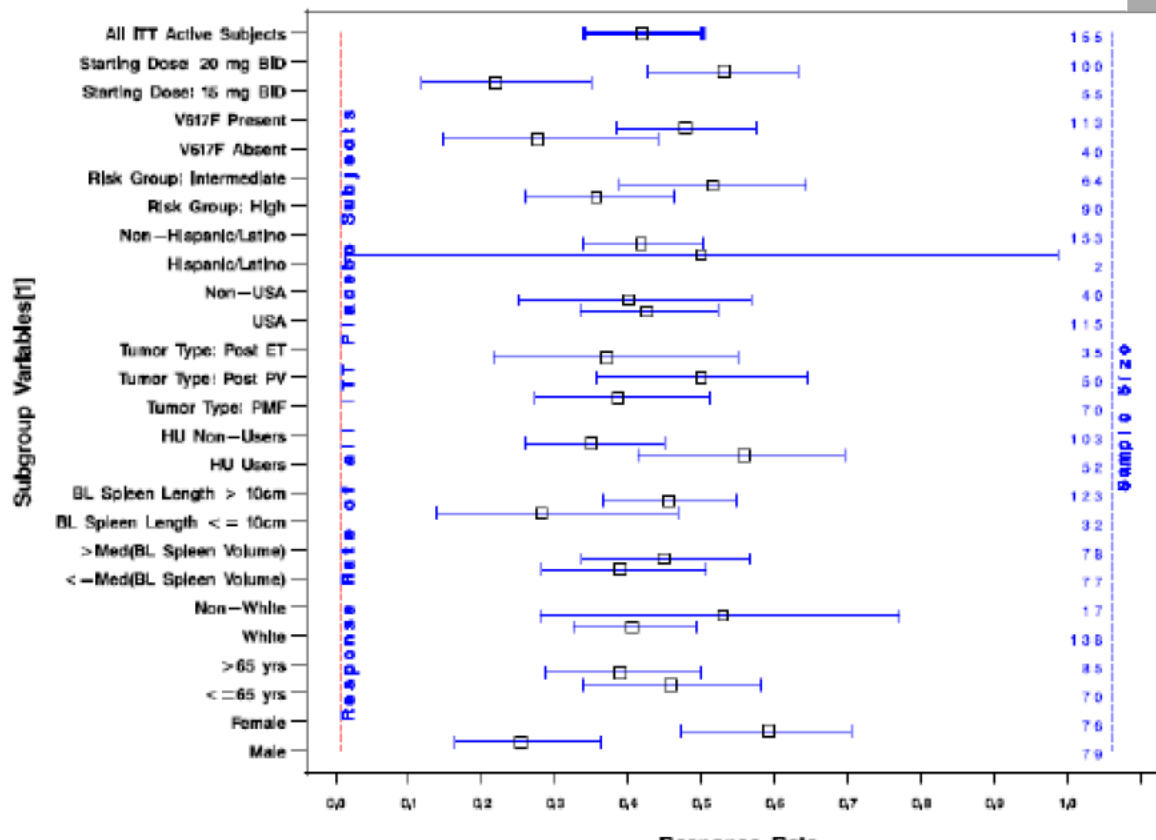
6.1.7 Subpopulations for INCB-351

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

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

Figure 9: Subgroup Analysis of Responders in INCB-351
Figure 23: Proportions of Subjects in Each Subgroup Who Achieved a $\geq 35\%$ Reduction From Baseline in Spleen Volume at Week 24 (Ruxolitinib-Treated ITT Subjects)

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[CSR INCB-351, p. 139]

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

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

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

6.1.9 Discussion of Persistence of Efficacy for INCB-351

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

6.1.10 Additional Efficacy Issues/Analyses for INCB-351

There are no issues for discussion.

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

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

Efficacy Summary for INCB-352

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

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

6.1.11 Methods for INCB-352

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

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

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

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

Table 41-Eligibility for INCB-352

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

[Clin Protocol, July 21, 2009]

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

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

- a. The spleen length below the left costal margin had been reduced by $\leq 40\%$ by 4 weeks as compared to baseline;
- b. The platelet count at Week 4 was $\geq 150,000/\text{microL}$ and the platelet count had never been $< 150,000/\text{microL}$ from the time of baseline;
- c. The absolute neutrophil counts (ANC) remained $\geq 1,000/\text{microL}$ since baseline.

[CSR INCB-351, page 39]

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

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

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

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

6.1.12 Demographics for INCB-352

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

Table 42-Demographic Features at Baseline for INCB-352

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

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

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

6.1.13 Subject Disposition for INCB-352

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

Table 43-Disposition of Patients in INCB-352

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

[CSR INCB-352, p.111]

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

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

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

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

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

[CSR INCB-352, p. 116]

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

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

6.1.15.a. Duration of SVR $\geq 35\%$

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

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

6.1.15.b. PFS, LFS, and OS

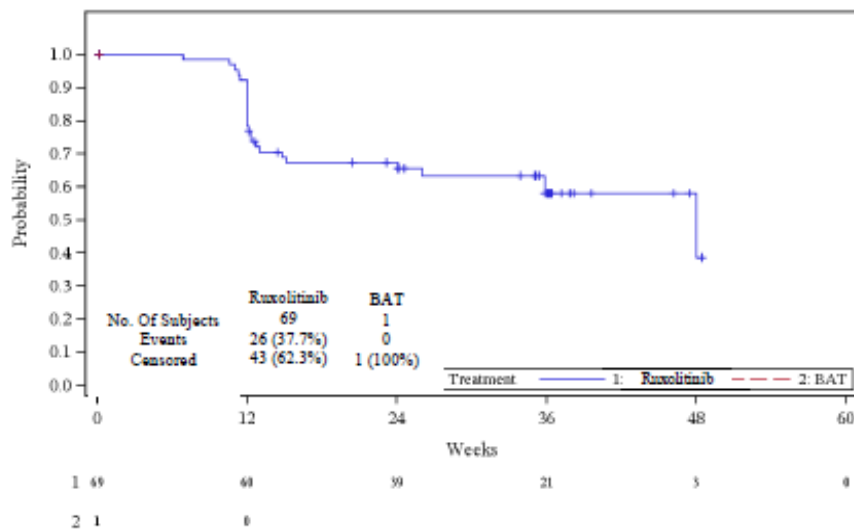
In Table 45 (see below) are presented the Kaplan-Meier estimates of the progression free survival (PFS), the leukemia free survival (LFS) and overall survival (OS). As shown by this analysis, there were no statistically significant differences in the secondary time to event endpoints analyzed in this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

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

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

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

Figure 10: Median Duration of SVR $\geq 35\%$ in INCB-352



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Subjects at risk: 1=ruxolitinib, 2=BAT

6.1.15.c Fibrosis Grade on INCB-352

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

6.1.15.d RBC Transfusion Dependency on INCB-352

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

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

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

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

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

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

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

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

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

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

6.1.17 Subpopulations for INCB-352

No comparisons.

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

No analysis.

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

See Section 6.1.15.a above.

6.1.20 Additional Efficacy Issues/Analyses for INCB-352

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

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

7 Review of Safety

Safety Summary

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

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

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

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

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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

Table 48-Population of Ruxolitinib Treated Patients for the ISS

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

[ISS, p. 26]

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

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

Table 49-Demographics in Phase III Trials of the ISS

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

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

[ISS, pp. 48 and 52]

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

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

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

^a Receiving treatment with ruxolitinib.

^b Notes the primary reason for withdrawal as noted on the eCRF. Because of differing CRF designs with regard to reasons for discontinuation across the studies, pooling of these data lead to difficulties in interpretation.

^c Includes only those subjects for whom death was reported as the primary reason for discontinuation of therapy and may exclude subjects who discontinued for a fatal AE.

^d This number is artificially low because there was no AE category on the INCB 18424-251 termination CRF.

[ISS, p. 46]

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

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

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

^bPatients whose date of death and withdrawal were the same were categorized as death.

^c8 subjects on each arm of INCB-351 were characterized as death in the CSR and as AEs in this table.

^dTwo patients who died in CSR for INCB-351 were captured as consent withdrawn in this table.

^eOne subject in the placebo group of INCB-351 was characterized as death in CSR and as disease progression in this table.

^fSubjects met criteria for progression remained on ruxolitinib in the extension.

[ISS, pp. 44 and 56]

7.1.2 Categorization of Adverse Events

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

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

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

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses in Target Populations

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

Table 52-Exposure to Ruxolitinib In Different Starting Dose Categories

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

[ISS, p. 37]

7.2.2 Explorations for Dose Response

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

7.2.3 Special Animal and/or In Vitro Testing

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

7.2.4 Routine Clinical Testing

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

7.2.5 Metabolic, Clearance, and Interaction Workup

An analysis of these issues will be found in the Clinical Pharmacology review. The parent unchanged compound, ruxolitinib, has a serum half life of 3.1 hours. The active metabolites have a serum half-life of 5.8 hours. Only 1% of the parent compound is excreted unchanged. This drug is metabolized by CYP3A4. One of the issues discovered was that the response rate range was higher in women than in men in INCB-351 (non-overlapping ranges in the forest plot analysis which is presented in Figure 9 on page 49 of the report and Figure 23 on page 139 of the CSR for INCB-351). The possibilities identified by Clinical Pharmacology analysis include: greater exposure of the tissues in women due to a higher dose in mg/kg or mg/body surface area,

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

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

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

7.3 Major Safety Results

7.3.1 Deaths

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

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

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

Table 53-Deaths on Study

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

^a Death occurred during treatment or within 28 days after last dose of study medication.

^b Death occurred during treatment with ruxolitinib or within 28 days after last dose of ruxolitinib.

^c Death occurred more than 28 days after last dose of study medication.

^d In the INCB018424-251 CSR, only 11 deaths are reported. The cut-off date for the CSR and ISS analysis is 31 December 2009. Subject 001-092 died in February 2010, but death date appears in the database as 10 February 2009. Therefore, 12 deaths are reported for this study in the ISS. PC=prostate cancer; MM=myeloma; MF=myelofibrosis; PV=polycythemia vera; ET=essential thrombocythemia.

[ISS, p. 73]

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

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

[ISS, p. 56]

Table 55: Specific Causes of Death on Phase III Trials

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

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

7.3.2 Nonfatal Serious Adverse Events

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

[ISS, pp. 78-81]

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

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

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

[ISS, pp. 78-81)

7.3.3 Dropouts and/or Discontinuations

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

[ISS, pp. 78-81]

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

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

[ISS, pp. 85-86]

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

7.3.4 Significant Adverse Events

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

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

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

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

[ISS, pp. 60-66]

7.3.5 Submission Specific Primary Safety Concerns

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

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

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

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

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

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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

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

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

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

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

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

[ISS, pages 70-71]

7.4.1.a. Dizziness, Confusion and Headache

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

[ISS, pp. 110-111]

7.4.1.b. Pneumonias

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

7.4.1.c. Urinary Tract Infections

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

7.4.1.d. Leukemic Transformation

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

7.4.1.e. Malignant Neoplasms

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

7.4.1.f. Cardiac Murmurs

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

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

7.4.1.g. Extremity Pain

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

7.4.1.h. Chills and Pyrexia

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

7.4.2 Laboratory Findings

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

7.4.2.a. Platelet Count

The platelet count declined over the first 4 weeks of therapy and then stabilized between 190 and 200 X 10⁹/L. New or worsening thrombocytopenia (Grade 3 and Grade 4) were reported by 12.9% of subjects in the ruxolitinib group and 1.3% of the placebo group in INCB-351. In INCB-352, 7.5% of patients in the ruxolitinib group and 5.8% in the BAT groups reported thrombocytopenia. The time to resolution of Grade 3 or 4 thrombocytopenia to Grade 2 or less was 14 days (median) in both studies. Platelet transfusions were given to 8 subjects in the ruxolitinib group and to 4 subjects in the placebo group in INCB-351, and to 6 subjects in the ruxolitinib group as compared to 4 subjects in the BAT group in INCB-352. One subject in the ruxolitinib group in each phase III study withdrew for thrombocytopenia (see Table 57 above).
[ISS, pp. 120-126]

7.4.2.b. Hemoglobin

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

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

7.4.2.c. White Blood Cell Count

The WBC was elevated in all patients prior to the onset of ruxolitinib therapy and tended to approach normal values during the therapy on both of the phase III studies. The baseline WBCs in the placebo and BAT arms on INCB-351 and INCB-352 respectively were 15.1 and 11.5 X 10⁹/L, whereas the WBCs on the ruxolitinib arms after the therapy periods were completed (24 and 48 weeks on INCB-351 and INCB-352) were: 11.9 and 9.4 X 10⁹/L.
[ISS, p. 141 and 141, and see Table 48 of this report which was taken from ISS pp. 48 and 52]

7.4.2.d. RBC Transfusions

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

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

7.4.2.e. Serum Transaminases

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

7.4.2.f. Serum Creatinine

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

7.4.2.g. Serum Cholesterol

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

7.4.2.h. Iron and Serum Ferritin Levels

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

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

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

[ISS, p. 169]

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

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

[ISS, p. 170]

7.4.3 Vital Signs

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

7.4.4 Electrocardiograms (ECGs)

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

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies.

7.4.6 Immunogenicity

There were no studies of immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

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

7.5.2 Time Dependency for Adverse Events

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

[ISS, pp. 120-131]

7.5.3 Drug-Demographic Interactions

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

[ISS, pp. 181, 185]

As mentioned above in Section 6.1.7, females had a greater probability of achieving a $\geq 35\%$ reduction in volume of the spleen while on ruxolitinib than did males.

[CSR INCB-351, p. 139]

7.5.4 Drug-Disease Interactions

The pharmacokinetics of ruxolitinib in patients with MF appeared to be similar to that seen in healthy subjects (see Module 2.7.2).

[ISS, p. 203]

There was no evidence of an interaction between ruxolitinib and drugs which are hepatotoxic.

[ISS, p. 204]

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

7.5.5 Drug-Drug Interactions

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

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

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

7.6 Additional Safety Evaluation

7.6.1 Human Carcinogenicity

No new cases of solid tumors or leukemias.

7.6.2 Human Reproduction and Pregnancy Data

No data.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

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

7.7 Additional Submissions

There were no additional submissions.

8 Postmarket Experience

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

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

This is under development.

9.3 Advisory Committee Meeting

No advisory committee meeting is planned.

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/s/

ALBERT B DEISSEROTH
10/27/2011

EDVARDAS KAMINSKAS
11/04/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202192

Applicant: Incyte

Stamp Date:

Drug Name: ruxolitinib

NDA/BLA Type: NME

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

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

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

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

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

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? X

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

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

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

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ALBERT B DEISSEROTH
07/01/2011

EDVARDAS KAMINSKAS
07/01/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202192Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo

NDA 202192, JAKAFI (ruxolitinib) Tablets 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg

Date: 21-OCT-2011

Introduction

JAKAFI (ruxolitinib) tablets are indicated for the treatment of myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

JAKAFI (ruxolitinib) Tablets may be administered with or without food. As necessary, JAKAFI tablets can be administered through a nasogastric tube. Doses are titrated based on safety and efficacy. The maximum dose is 25 mg twice daily.

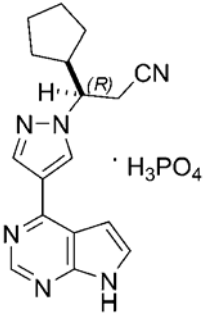
Administrative

Supported by IND 77,456 and five DMFs, this original 505(b)(1) NDA was received 03-JUN-2011 from Incyte Corporation of Wilmington, DE and was given Priority review status.

A total of 12 amendments received between 10-JUN-2011 and 19-OCT-2011 were also reviewed. This was a team review within ONDQA. An EES finding of "overall acceptable" is dated 11-OCT-2011. The ONDQA Biopharm review was entered into DARRTS on 20-OCT-2011.

ONDQA recommends approval from the CMC perspective.

Drug Substance: ruxolitinib phosphate

Chemical structure	
Molecular formula	C ₁₇ H ₂₁ N ₆ O ₄ P
Molecular weight	404.36 g/mole
United States Adopted Name (USAN)	ruxolitinib phosphate
Chemical name	(R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate
Chemical Abstracts Service (CAS) registry number	[941678-49-5]: free base; [1092939-17-7]: phosphate salt

Ruxolitinib phosphate is chemically synthesized as a *R*-isomer. (b) (4)

The submitted stability data support the proposed retest period of (b) (4) when packaged in the proposed container system and stored at controlled room temperature.

Drug Product: JAKAFI Tablets 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg.

JAKAFI Tablets are provided in 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg strengths. The tablets contain **ruxolitinib phosphate as the active pharmaceutical ingredient equivalent to 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base.**

The drug product also contains the following inactive ingredients: microcrystalline cellulose, lactose, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxylpropyl cellulose. (b) (4)

All the five strengths of ruxolitinib tablets (b) (4) (b) (4) Jakafi™ (ruxolitinib) Tablets are immediate release, non-coated tablets. They are white to off-white in color in different sizes and shapes (round for 5 mg and 10 mg strength, oval for 15 mg strength, capsule-shaped for 20 mg strength, and oval for 25 mg strength), with debossing on one side of tablets to reflect the strength with either “5”, or “10”, or “15”, or “20”, or “25” while other side remaining the same as “INCY”. JAKAFI Tablets are supplied in 75 mL HDPE bottles of 60 tablets.

CONVEY THE COMMENT BELOW TO APPLICANT IN ACTION LETTER:

Based on the provided stability data, a 24-month expiration dating period is granted for the drug product (5 mg, 10 mg, 15 mg, 20 mg, and 25 mg) when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

Thank you.

Rik Lostritto, Ph.D., Director, ONDQA Division I.

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/s/

RICHARD T LOSTRITTO
10/21/2011

NDA 202192

Jakafi™ (ruxolitinib) Tablets

Incyte Corporation

Drug Product Section of Team Review

Joyce Crich, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II**

**Chemistry, Manufacturing, and Controls (CMC)
For the Division of Hematology Products**

APPEARS THIS WAY ON ORIGINAL

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 202192
2. REVIEW #: 1
3. REVIEW DATE: 20-Oct-2011
4. REVIEWER: Joyce Crich, Ph.D
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
<u>Original IND 77,456 submission</u>	<u>30-Mar-2007</u>
<u>IND 77,456 CMC review of amendment (SDN# 93)</u>	<u>02-Oct-2009</u>
<u>IND 77,456 CMC review of amendment (SDN# 172)</u>	<u>04-Feb-2011</u>
<u>CMC end-of-phase-2 meeting (03-Dec-2008) minutes</u>	<u>02-Jan-2009</u>
<u>Type C CMC-only meeting (08-Jul-2009) minutes</u>	<u>02-Oct-2009</u>
<u>CMC only pre-NDA meeting (30-Nov-2010) minutes</u>	<u>20-Dec-2010</u>

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	03-Jun-2011	03-Jun-2011
Request for proprietary name (Jakafi) review	2	10-Jun-2011	10-Jun-2011
Response to FDA 29-Jun-2011 IR regarding dissolution data and nasogastric administration	3	08-Jul-2011	08-Jul-2011
Response to FDA 27-Jul-2011 IR regarding comparability protocols)	5	01Aug-2011	01Aug-2011
Background information for proprietary name)	6	04-Aug-2011	04-Aug-2011
Container and carton labeling	7	05-Aug-2011	05-Aug-2011
Container and carton labeling	9	18-Aug-2011	18-Aug-2011
Updated container and carton labeling	11	29-Aug-2011	29-Aug-2011
Stability update for drug substance and drub product	12	30-Aug-2011	30-Aug-2011
Withdrawal of two comparability protocols	13	12-Sep-2011	12-Sep-2011
Response to 16-Sep-2011 CMC IR	15	27-Sep-2011	27-Sep-2011
Response to 04-Oct-2011 CMC IR	19	12-Oct-2011	12-Oct-2011
Response to 18-Oct-2011 Telecon	20	19-Oct-2011	19-Oct-2011

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Incyte Corporation
Address: Route 141 & Henry Clay Road
Building 336
Wilmington, DE 19880
Representative: Ronald C Falcone, Ph.D., Vice President,
Regulatory Affairs
Telephone: 302-498-6846

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Jakafi™
b) Non-Proprietary Name: ruxolitinib tablets
c) Code Name/# (ONDQA only): INCB018424 (free base), INCB018424 phosphate (drug substance)
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 1 (new molecular entity)
 - Submission Priority: P (priority review)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: antineoplastic agent (a kinase inhibitor for Janus Associated Kinases (JAKs) JAK1 and JAK2)

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

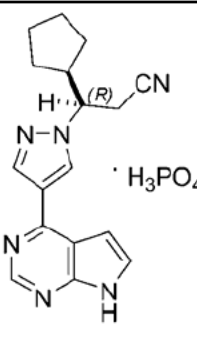
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CMC Review Data Sheet

Chemical structure	
Molecular formula	C ₁₇ H ₂₁ N ₆ O ₄ P
Molecular weight	404.36 g/mole
United States Adopted Name (USAN)	ruxolitinib phosphate
Chemical name	(R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate
Chemical Abstracts Service (CAS) registry number	[941678-49-5]: free base; [1092939-17-7]: phosphate salt

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4			See section 3.2.P.7
	III			4			See section 3.2.P.7
	III			4			See section 3.2.P.7
	III			4			See section 3.2.P.7
	III			3	Adequate	06-Dec-2008	Reviewed by Gene Holbert

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	77,456	INCB018424 (ruxolitinib phosphate)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	11-Oct-2011	D. Smith
Pharm/Tox	Impurity limits in drug substance are acceptable*	See DARRTS for review*	Wei Chen
Biopharm	Acceptable	20-Oct-2011	Tien-Mien Chen
LNC	N/A		
Methods Validation	Pending**		
DMEPA	The proposed proprietary name, Jakafi, is acceptable	16-Sep-2011	Lissa Owens
EA	Categorical exclusion (see review)	11-Oct-2011	Joyce Crich
Microbiology	Approval from microbiology product quality standpoint	23-Aug-2011	John W. Metcalfe

*Dr. Wei Chen, the pharm/tox reviewer for this NDA, informed the CMC reviewers in her 9/8/11 and 9/16/11 e-mails that the acceptance criteria for the impurities in the drug substance are qualified. None of the impurities are considered genotoxic, based on the submitted toxicology data. See Section III of the drug substance review for the e-mail correspondences.

**Methods validation consult was sent to the FDA St. Louis Laboratory on 08-Sep-2011. See DARRTS for the consult request. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

Executive Summary Section

The CMC Review for NDA 202192

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, this NDA is recommended for approval. There are no outstanding CMC issues that impact approvability of this NDA.

Include the following language in the approval letter:

Based on the provided stability data, a 24-month expiration dating period is granted for the drug product (5 mg, 10 mg, 15 mg, 20 mg, and 25 mg) when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance is ruxolitinib phosphate, which is a new molecular entity. Detailed information regarding the drug substance is provided in the NDA.

Ruxolitinib phosphate is chemically synthesized as a *R*-isomer. (b) (4)

Detailed information regarding designation of the proposed starting materials for (b) (4) their commercial sources, acceptance criteria, and associated methods of analysis are provided in Section 3.2.S.2.3.1. The fate of starting materials and their impurities, data from purging studies, and change control

Executive Summary Section

strategies for the manufacturing changes for starting materials are provided in the 27-Sep-2011 amendment, in response to the FDA 16-Sep-2011 request. The results from purging studies demonstrate that the manufacturing process is capable of removing the impurities to the desired levels.

Ruxolitinib phosphate is a white to off-white to light pink powder. It has been classified as a BCS Class 1 compound (highly soluble and highly permeable material). It is non-hygroscopic. Polymorph screening has been carried out and only

(b) (4)

The submitted stability data support the proposed retest period of (b) (4) when packaged in the proposed container system and stored at controlled room temperature.

(2) Drug Product

Jakafi™ (ruxolitinib) Tablets are available in 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg dosage strengths. The tablets contain ruxolitinib phosphate as the active pharmaceutical ingredient equivalent to 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base together with microcrystalline cellulose, lactose, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxyl propyl cellulose. All the five strengths of ruxolitinib tablets

(b) (4)

(b) (4)

Jakafi™ (ruxolitinib) Tablets are immediate release, uncoated tablets, white to off-white in color in different sizes and shapes (round for 5 mg and 10 mg strength, oval for 15 mg strength, capsule-shaped for 20 mg strength, and oval for 25 mg strength), with debossing on one side of tablets to reflect the strength with either number “5”, or “10”, or “15”, or “20”, or “25” while other side remaining the same as “INCY”. Jakafi™ (ruxolitinib) Tablets are supplied in 75 ml HDPE bottles of 60 tablets.

Formulation development of ruxolitinib tablets was performed by Incyte through three sites; (b) (4) and DSM. The basic steps in the manufacturing process

(b) (4)

Standard release specifications for solid oral dosage forms have been proposed. DSM Pharmaceuticals, Inc. is the proposed commercial site for the drug product manufacturing, release testing, packaging, labeling and stability study.

The applicant submitted the stability data from three primary batches for the 5 mg strength and 25 mg strength tablets up to 18 months at 25°C/60% RH and up to 6

Executive Summary Section

months at 40°C/75% RH, and the additional stability data from eleven supportive batches across the five different strengths. Those stability data support the proposed 24 months shelf-life for the drug product in all five strengths packaged in HDPE bottles and stored at controlled room temperature. Additionally, the submitted photostability study results on the primary and supportive lots indicate that the drug product does not require protection from light.

The provided nasogastric (NG) tube study results confirm the compatibility between the drug product and NG tubes (≥ 8 French, three type tubes from Kendall) as well as the suspension stability of the tablets in water for up to 6 hours. The data demonstrate that it is suitable for administration of drug in aqueous suspension through a nasogastric tube to patients who have difficulty swallowing.

B. Description of How the Drug Product is Intended to be Used

Jakafi™ (ruxolitinib) Tablets are indicated for treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocy-themia myelofibrosis.

Jakafi™ (ruxolitinib) Tablets are dosed orally and can be administered with or without food. For patients unable to ingest tablets, Jakafi™ (ruxolitinib) Tablets can be administered through a nasogastric tube (≥ 8 French) as follows: (1) Suspend one tablet in approximately 40 mL of water with stirring for approximately 10 minutes; (2) 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 additional water.

The recommended starting dose of Jakafi™ (ruxolitinib) Tablets is 15 mg given orally twice daily for patients with a platelet count between $100 \times 10^9/L$ and $200 \times 10^9/L$ and 20 mg twice daily for patients with a platelet count of $> 200 \times 10^9/L$. There is limited information to recommend a starting dose for patients with platelet counts between $50 \times 10^9/L$ and $100 \times 10^9/L$. The recommended starting dose in these patients is 5 mg twice daily.

Doses may be titrated based on safety and efficacy. The maximum dose of Jakafi™ (ruxolitinib) Tablets is 25 mg twice daily.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Jakafi.

Executive Summary Section

Methods validation consult was sent to the FDA St. Louis Laboratory for the drug substance and drug product analysis. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. The revised container labels, as amended by the applicant on 12-Oct-2011 are acceptable from the CMC perspective.

The Office of Compliance has issued an overall “acceptable” recommendation dated 11-Oct-2011 for all facilities used for manufacturing and control of the drug substance and drug product.

III. Administrative

A. Reviewer’s Signature:

(See appended electronic signature page)

Joyce Crich, Ph.D, Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Janice Brown, Ph.D., CMC Lead, Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA)

Sarah Pope Miksinski, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DFS

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/s/

JOYCE Z CRICH
10/20/2011

JANICE T BROWN
10/20/2011
Janice Brown for Sarah Pope Miksinski, Ph.D.

NDA 202192

JakafiTM (ruxolitinib) Tablets

Incyte Corporation

Review of Drug Substance Sections

Sue-Ching Lin

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II**

**Chemistry, Manufacturing, and Controls (CMC)
Team Review of Original NDA
For the Division of Hematology Products**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 202192
2. REVIEW #: 1
3. REVIEW DATE: 20-Oct-2011
4. REVIEWER: Sue-Ching Lin, M.S., R.Ph. (Drug Substance Sections)
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 77,456 submission	30-Mar-2007
IND 77,456 CMC review of amendment (SDN# 93)	02-Oct-2009
IND 77,456 CMC review of amendment (SDN# 172)	04-Feb-2011
CMC end-of-phase-2 meeting (03-Dec-2008) minutes	02-Jan-2009
Type C CMC-only meeting (08-Jul-2009) minutes	02-Oct-2009
CMC only pre-NDA meeting (30-Nov-2010) minutes	20-Dec-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	03-Jun-2011	03-Jun-2011
Request for proprietary name (Jakafi) review	2	10-Jun-2011	10-Jun-2011
Response to FDA 29-Jun-2011 IR regarding dissolution data and nasogastric administration	3	08-Jul-2011	08-Jul-2011
Response to FDA 27-Jul-2011 IR regarding comparability protocols)	5	01Aug-2011	01Aug-2011
Background information for proprietary name)	6	04-Aug-2011	04-Aug-2011
Container and carton labeling	7	05-Aug-2011	05-Aug-2011
Container and carton labeling	9	18-Aug-2011	18-Aug-2011
Updated container and carton labeling	11	29-Aug-2011	29-Aug-2011
Stability update for drug substance and drub product	12	30-Aug-2011	30-Aug-2011
Withdrawal of two comparability protocols	13	12-Sep-2011	12-Sep-2011
Response to 16-Sep-2011 CMC IR	15	27-Sep-2011	27-Sep-2011
Response to 04-Oct-2011 CMC IR	19	12-Oct-2011	12-Oct-2011
Response to 18-Oct-2011 telecon	20	19-Oct-2011	19-Oct-2011

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Incyte Corporation
Address: Route 141 & Henry Clay Road
Building 336
Wilmington, DE 19880
Representative: Ronald C Falcone, Ph.D., Vice President,
Regulatory Affairs
Telephone: 302-498-6846

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Jakafi™
b) Non-Proprietary Name: ruxolitinib tablets
c) Code Name/# (ONDQA only): INCB018424 (free base), INCB018424 phosphate (drug substance)
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 1 (new molecular entity)
 - Submission Priority: P (priority review)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: antineoplastic

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

CMC Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical structure	
Molecular formula	C ₁₇ H ₂₁ N ₆ O ₄ P
Molecular weight	404.36 g/mole
United States Adopted Name (USAN)	ruxolitinib phosphate
Chemical name	(R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate
Chemical Abstracts Service (CAS) registry number	[941678-49-5]: free base; [1092939-17-7]: phosphate salt

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4			See section 3.2.P.7
	III			4			See section 3.2.P.7
	III			4			See section 3.2.P.7
	III			4			See section 3.2.P.7
	III			3	Adequate	06-Dec-2008	Reviewed by Gene Holbert

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

CMC Review Data Sheet

- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	77,456	INCB018424 (ruxolitinib phosphate)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	11-Oct-2011	D. Smith
Pharm/Tox	Impurity limits in drug substance are acceptable*	See DARRTS for review*	Wei Chen
Biopharm	Acceptable	20-Oct-2011	Tien-Mien Chen
LNC	N/A		
Methods Validation	Pending**		
DMEPA	The proposed proprietary name, Jakafi, is acceptable	06-Sep-2011	Lissa Owens
EA	Categorical exclusion	Date of this review	Sue-Ching Lin
Microbiology	Approval from microbiology product quality standpoint	23-Aug-2011	John W. Metcalfe

*Dr. Wei Chen, the pharm/tox reviewer for this NDA, informed the CMC reviewers in her 9/8/11 and 9/16/11 e-mails that the acceptance criteria for the impurities in the drug substance are qualified. None of the impurities are considered genotoxic, based on the submitted toxicology data. See Section III of the drug substance review for the e-mail correspondences.

**Methods validation consult was sent to the FDA St. Louis Laboratory on 08-Sep-2011. See DARRTS for the consult request. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

Executive Summary Section

The CMC Review for NDA 202192

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, this NDA is recommended for approval.

Include the following language in the approval letter:

Based on the provided stability data, a 24-month expiration dating period is granted for the drug product (5 mg, 10 mg, 15 mg, 20 mg, and 25 mg) when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance is ruxolitinib phosphate, which is a new molecular entity. Detailed information regarding the drug substance is provided in the NDA.

Ruxolitinib phosphate is chemically synthesized as a *R*-isomer (b) (4)

Detailed information regarding designation of the proposed starting materials for (b) (4) their commercial sources, acceptance criteria, and associated methods of analysis are provided in Section 3.2.S.2.3.1. The fate of starting materials and their impurities, data from purging studies, and change control strategies for the manufacturing changes for starting materials are provided in the

Executive Summary Section

27-Sep-2011 amendment, in response to the FDA 16-Sep-2011 request. The results from purging studies demonstrate that the manufacturing process is capable of removing the impurities to the desired levels.

Ruxolitinib phosphate is a white to off-white to light pink powder. It has been classified as a BCS Class 1 compound (highly soluble and highly permeable material). It is non-hygroscopic. Polymorph screening has been carried out and only

(b) (4)

The submitted stability data support the proposed retest period of (b) (4) when packaged in the proposed container system and stored at controlled room temperature.

(2) Drug Product

Jakafi™ (ruxolitinib) Tablets are available in 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg dosage strengths. The tablets contain ruxolitinib phosphate as the active pharmaceutical ingredient equivalent to 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base. The drug product also contains the following inactive ingredients: microcrystalline cellulose, lactose, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxypropyl cellulose. All the five strengths of ruxolitinib tablets are

(b) (4)

(b) (4)

Jakafi™ (ruxolitinib) Tablets are immediate release, uncoated tablets, white to off-white in color in different sizes and shapes (round for 5 mg and 10 mg strength, oval for 15 mg strength, capsule-shaped for 20 mg strength, and oval for 25 mg strength), with debossing on one side of tablets to reflect the strength with either number “5”, or “10”, or “15”, or “20”, or “25” while other side remaining the same as “INCY”. Jakafi™ (ruxolitinib) Tablets are supplied in 75 mL HDPE bottles of 60 tablets.

Formulation development of ruxolitinib tablets was performed by Incyte through three sites: (b) (4) DSM. The basic steps in the manufacturing process

(b) (4)

Standard release specifications for oral solid dosage forms have been proposed. DSM Pharmaceuticals, Inc. is the proposed commercial site for the drug product manufacturing, release testing, packaging, labeling and stability study.

The applicant submitted the stability data from three primary batches for the 5 mg strength and 25 mg strength tablets up to 18 months at 25°C/60% RH and up to 6 months at 40°C/75% RH, and the additional stability data from eleven supportive batches across the five different strengths. Those stability data support the proposed

Executive Summary Section

24 months shelf-life for the drug product in all five strengths packaged in HDPE bottles and stored at controlled room temperature. Additionally, the submitted photostability study results on the primary and supportive lots indicate that the drug product does not require protection from light.

The provided nasogastric (NG) tube study results confirm the compatibility between the drug product and NG tubes as well as the suspension stability of the tablets in water for up to 6 hours. The data demonstrate that it is suitable for administration of the drug in aqueous suspension through a nasogastric tube to patients with difficulty swallowing.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

Jakafi™ (ruxolitinib) Tablets are dosed orally and can be administered with or without food. For patients unable to ingest tablets, Jakafi™ (ruxolitinib) tablets can be administered through a nasogastric tube (≥ 8 French) as follows: (1) Suspend one tablet in approximately 40 mL of water with stirring for approximately 10 minutes; (2) 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 additional water.

The recommended starting dose of Jakafi™ (ruxolitinib) Tablets is 15 mg given orally twice daily for patients with a platelet count between $100 \times 10^9/L$ and $200 \times 10^9/L$ and 20 mg twice daily for patients with a platelet count of $> 200 \times 10^9/L$. There is limited information to recommend a starting dose for patients with platelet counts between $50 \times 10^9/L$ and $100 \times 10^9/L$. The recommended starting dose in these patients is 5 mg twice daily.

Doses may be titrated based on safety and efficacy. The maximum dose is 25 mg twice daily.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Jakafi.

Executive Summary Section

Methods validation consult was sent to the FDA St. Louis Laboratory for the drug substance and drug product analysis. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. The revised container labels, as amended by the applicant on 12-Oct-2011 are acceptable from the CMC perspective.

The Office of Compliance has issued an overall “acceptable” recommendation dated 11-Oct-2011 for all facilities used for manufacturing and control of the drug substance and drug product.

III. Administrative**A. Reviewer’s Signature:**

(See appended electronic signature page)

Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Janice Brown, CMC Lead, Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA)

Sarah Pope Miksinski, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

SUE CHING LIN
10/20/2011

JANICE T BROWN
10/20/2011
Janice Brown for Sarah Pope Miksinski, Ph.D.

**Initial Quality Assessment
Division of New Drug Quality Assessment I
Branch II**

OND Division: Division of Hematology Products
 NDA: 202192
 Applicant: Incyte Corporation
 Stamp Date: 03-Jun-2011
 PDUFA Date: 03-Dec-2011
 Proprietary (Brand) Name of Drug Product: Jakavi
 Established Name: Ruxolitinib phosphate tablets
 Dosage Form(s): Immediate release tablets
 Strength(s): 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg
 Route of Administration: Oral
 Proposed Indication(s): Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis
 CMC Lead: Janice Brown, Branch II/DNDQA1/ONDQA
 Chief, Branch II: Sarah Pope Miksinski, Ph.D., DNDQA1/ONDQA

Review team recommendation: Team review

	Yes	No
ONDQA Fileability:	X	☐
Comments for 74-Day Letter	X	☐ (see page 10)

CONSULTS/ CMC RELATED REVIEWS

Consult	Comment
Biopharm	Assigned to Karen Riviere, Ph.D. to evaluate both biowaiver requests
CDRH	Not Applicable
EA	Categorical Exclusion requested
EES	Inspection request was submitted on 09-Jun-2011
DMEPA	Labeling consult request will be sent as part of DHP request.
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.
Microbiology	Microbiology consult was requested on 06-Jun-2011
Pharm-Tox	Determined by primary reviewer

SUMMARY

Ruxolitinib tablets (INCB018424 and INC424) is a new molecular entity indicated for the treatment of patients with Primary Myelofibrosis (PMF), Post-Polycythemia Vera- Myelofibrosis (PPV-MF), or Post-Essential Thrombocythemia Myelofibrosis (PET-MF). Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. Dysregulation of the JAK-STAT pathway has been associated with several cancers and increased proliferation and survival of malignant cells.

Ruxolitinib is supplied as 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg tablets. The recommended starting dose of ruxolitinib is 15 mg given orally twice daily for patients with a platelet count between 100,000 and 200,000/ μ L and 20 mg twice daily for patients with an initial platelet count of > 200,000/ μ L. The highest human therapeutic dose is 25 mg bid orally.

STARTING MATERIALS

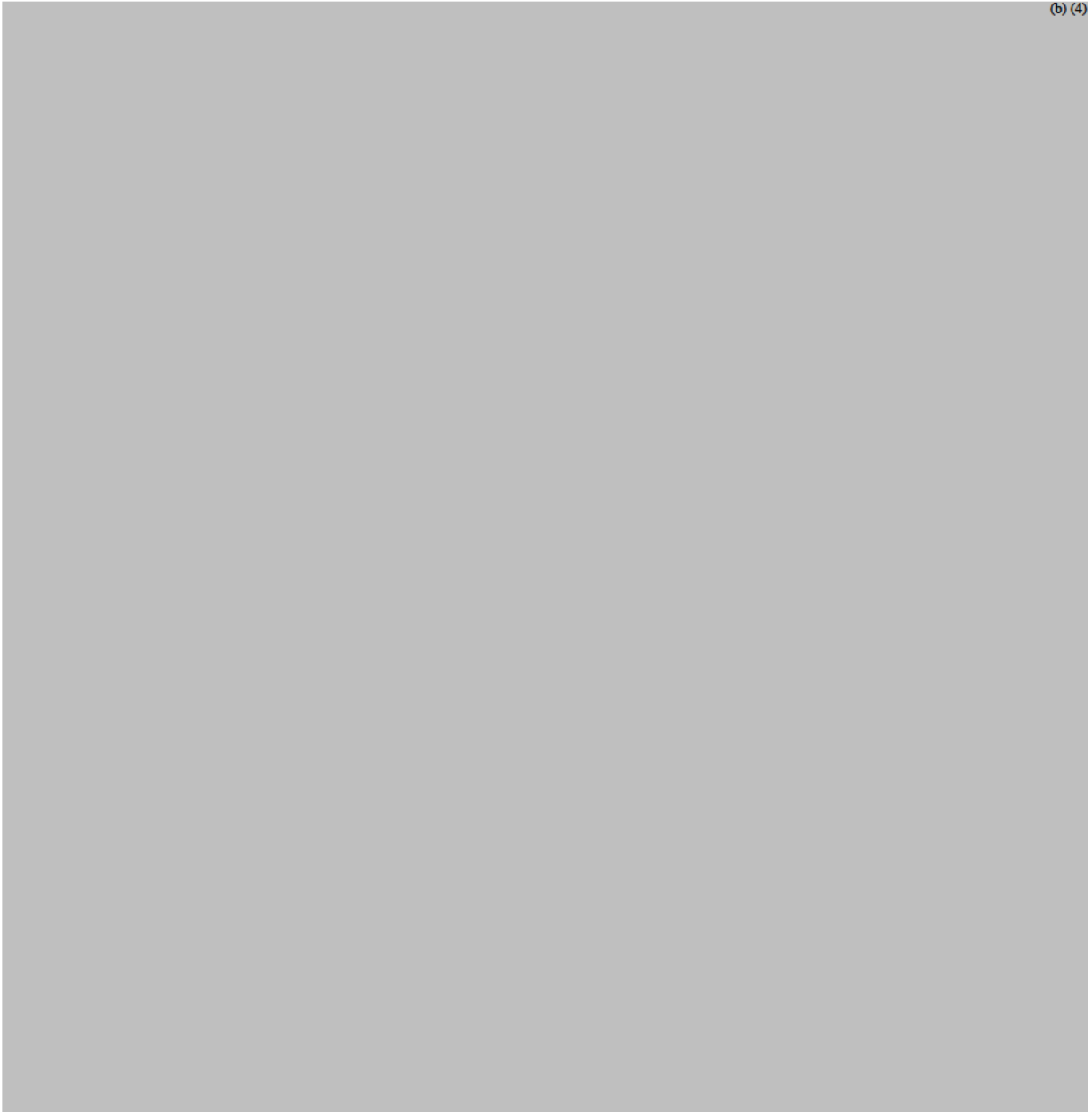
1. Agreement on the starting material classificatio (b) (4)
[REDACTED]
[REDACTED] was reached between the FDA and Incyte during a pre-NDA meeting held on 30-Nov-2010.

DRUG SUBSTANCE

2. Ruxolitinib phosphate is small molecule drug manufacture (b) (4)
[REDACTED]
3. A complete list of manufacturing facilities is appended as attachment 1.
4. Ruxolitinib phosphate has a chiral center at C-3. The asymmetric carbon possesses an (*R*) – configuration. The polymorph screening of ruxolitinib phosphate showed (b) (4)
[REDACTED] (b) (4) The chiral testing data showed that the major impurity, [REDACTED] (b) (4) remained unchanged throughout the stability studies.

5. IMPURITIES

5.1 The applicant has identified twelve product related impurities that may arise during the synthesis and purification of ruxolitinib phosphate. Reproduced in table 1 below is a summary of the impurities and the levels found in batches. Adequacy of the proposed limits will be determined by the reviewer.



5.2 **Genotoxicity** - *In silico* analysis was used to screen identified and potential impurities, starting materials and intermediates for mutagenicity. (b) (4)

None were found to be genotoxic. The remaining impurities that were analyzed by the program did not identify any structural alerts and were not tested any further.

5.3 Heavy Metals – The applicant includes the Heavy Metals by USP <231> limit test for heavy metals in the drug substance but does not identify the type of heavy metal that may be present in the drug substance. USP <231> is a qualitative test that demonstrates that the content of metallic impurities below a specified limit. Substances that typically respond to this test are lead, mercury, bismuth, arsenic, antimony, tin, cadmium, silver, copper, and molybdenum. All drug substance batches contained (b) (4) of Heavy Metals. The level of residual heavy metals is controlled in the drug substance specification with a limit of (b) (4)

5.4 Palladium (Pd) Content - (b) (4)

5.5 Residual Organic Solvents - (b) (4)

Limits for each residual organic solvent in the final drug substance were established based on ICH Q3C guidance. No batches exceed the established limit.

6.0 DRUG SUBSTANCE SPECIFICATION - The ruxolitinib phosphate drug substance specification is appended as attachment 4.

7.0 CONTAINER – CLOSURE - The primary container for the drug substance (b) (4)

8.0 STABILITY – The applicant submitted long-term and accelerated stability studies on ruxolitinib phosphate batches manufactured by (b) (4) (Lots 08-340-001R, 09-340-003 and 09-340-004) (b) (4) (Lots 08-340-002, 11-340-011 and 11-340-012). At the request of the Division (Information Request, dated December 22, 2010), two additional batches of drug substance manufactured (b) (4) and added to the stability studies.

8.1. Description, identification, assay, related substances, chirality and water content are monitored in the stability program.

8.2 The drug substance is surprisingly stable. Stability data showed that the drug substance primary stability batches have remained essentially unchanged; no degradation products are detected above the ICH reporting threshold of 0.05%.

8.3 The chiral testing data showed that the major impurity (b) (4) (b) (4) remained unchanged during storage at $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$ and $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$.

8.2 The applicant is requesting a re-test period of (b) (4) when stored at $25^\circ\text{C}/60\% \text{RH}$. As additional data becomes available, the retest date may be extended.

8.3 Photostability study results show that ruxolitinib phosphate drug substance manufactured by (b) (4) is not photosensitive.

DRUG PRODUCT

9.0 Ruxolitinib phosphate drug product is formulated as an immediate release tablet for oral administration. The ruxolitinib phosphate tablets 5 mg, 10 mg, 15 mg, 20 mg and 25 mg (b) (4)

10.0 The BCS committee reviewed the solubility, permeability, and dissolution information provided and concluded that INCB018424 phosphate is a BCS Class 1 compound (see correspondence dated 7/20/2009). The applicant requested a biowaiver for bioequivalence requirement for the 10 mg, 15 mg, 20 mg and 25 mg strength tablets. ONDQA Biopharmacology group will review the biowaiver request.

11.0. The tablet composition is summarized in table 2 below.

Table 2: Composition of Ruxolitinib Phosphate Tablets

Component	Quality Standard	Amount (mg/tablet)					Function
		5 mg	10 mg	15 mg	20 mg	25 mg	
Ruxolitinib Phosphate ^a	Incyte specification	(b) (4)					(b) (4)
Microcrystalline Cellulose	NF/EP/JP						
Lactose Monohydrate	NF/EP/JP						
Colloidal Silicon Dioxide	NF/EP						
Hydroxypropyl Cellulose	NF/EP						
Povidone	USP/EP						
Sodium Starch Glycolate	NF/EP						
Magnesium Stearate	NF/EP/JP						
(b) (4)	USP/EP						
Total Tablet Weight (mg)	-						

12. All excipients (microcrystalline cellulose, lactose monohydrate, colloidal silicon dioxide, hydroxypropyl cellulose, povidone, sodium starch glycolate, and magnesium stearate) used in the manufacturing of ruxolitinib phosphate tablets meet the current USP/NF specifications. Lactose monohydrate, NF in the tablet formulation is of animal origin. Verify that that

animal sourced lactose monohydrates complies with <http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi?TITLE=9&PART=94&SECTION=18&TYPE=TEXT> . The bovine milk derivatives used in the manufacture of the lactose originate from the U.S. Magnesium stearate, NF used in the tablet formulation is of vegetable origin.

13. The manufacturing flow diagram is reproduced in attachment 5. The drug product is manufactured using (b) (4)

14. The drug product specification for all strengths is listed in table 3.

Table 3: Drug Product Specification (all strengths)

Test		Acceptance Criteria	Method
Description	5 mg	White to off-white <u>round</u> tablets debossed with INCY on one side and 5 on the other side	IC/000000/030
	10 mg	White to off-white <u>round</u> tablets debossed with INCY on one side and 10 on the other side	
	15 mg	White to off-white <u>oval</u> tablets debossed with INCY on one side and 15 on the other side	
	20 mg	White to off-white <u>capsule shaped</u> tablets debossed with INCY on one side and 20 on the other side	
	25 mg	White to off-white <u>oval</u> tablets debossed with INCY on one side and 20 on the other side	
Identification HPLC Retention Time		The retention time of the principal peak in the sample chromatogram corresponds to that in the standard chromatogram.	IC/018424/011
UV Absorption		The UV absorption spectra of the test solution and the standard solution exhibit maxima and minima at the same wavelengths.	USP <197U>
Assay (w/w %)		(b) (4) of label claim	IC/018424/011
Degradation Products (Area %) Unspecified (Individual)		(b) (4)	IC/018424/011
Total		(b) (4)	
Content Uniformity		Conforms to USP <905> requirement for uncoated tablets	IC/018424/011
Dissolution		(b) (4) (Q) of the Label Claim dissolved in 30 min as defined in USP <711>	IC/018424/027
(b) (4)		(b) (4)	(b) (4)

- 14.1 Since the tablets of five strengths consistently meet compendial microbial limits, the applicant proposes to omit microbial limit testing in drug product release and stability testing. A microbiology consult was requested to evaluate appropriateness of removing routine microbial testing.
- 14.2 Ruxolitinib phosphate drug product exhibits rapid dissolution profiles (b) (4) dissolved in 15 min) in 0.1 N HCl, pH 4.5 and pH 6.8 buffers.
- 15.0 **Closure System** – All strengths of ruxolitinib phosphate drug product tablets are packaged in a 60-count presentation in 75 cc, HDPE bottles. The bottles are capped with (b) (4)
- 16.0 **Drug Product Stability Studies**
- 16.1 During a pre-NDA meeting, the agency requested that two additional batches of drug substance produced using (b) (4) to confirm the equivalency between the ruxolitinib phosphate batches obtained either from (b) (4). Two batches of 5 mg tablets and two batches of 25 mg tablets (one batch of each strength from Lots 11-340-011 and from 11-340-012) have been manufactured. The stability data (three-month accelerated and long term) of the two batches of 5 mg tablets (Lots A76072 and A76073) and two batches 25 mg tablets (Lots A76074 and A76075) will be submitted in a stability update during the NDA review cycle.
- 16.2 The applicant used a (b) (4)
- 16.3 The drug product quality attributes, description, identification, assay, degradation products, and (b) (4) were monitored in the stability program.
- 16.4 Stability results of 5 mg and 25 mg ruxolitinib phosphate tablets show that no degradation products are observed above the ICH reporting threshold (0.1%) during storage at long term conditions (25°C/60% RH) for at least 18 months and accelerated conditions (40°C/75% RH) for up to 6 months.
- 16.5 Chirality - Since release testing and stability study data of the 5 mg and 25 mg tablets demonstrate that no racemization is observed during drug product manufacture or storage, chiral stability will not be monitored on future drug product tablet stability batches. The chiral stability has been confirmed during long-term and accelerated storage conditions on both drug substance and drug product tablets.

- 16.6 The applicant is requesting a shelf life of 24 months for ruxolitinib phosphate tablets of the five strengths under the long term storage conditions at $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$.
- 16.7 Based on the results of the photostability study, ruxolitinib phosphate tablets are not light sensitive.
- 16.8 Nasogastric (NG) Tube Study Procedure – For patients that can't swallow tablets, the applicant evaluated the stability of the crushed tablet suspended in sterile purified water and held for 6 hours at room temperature. They followed the same bracketing strategy where they used 5 mg and 25 mg tablets along with three types of NG tubes. Samples were analyzed for assay and degradation products. Little to no degradation was observed in NG Tube Compatibility samples as compared to control samples.

The applicant requested a biowaiver to establish the in vivo bioequivalence between the disperse solution/suspension product and the intact tablets of 5 mg, 10 mg, 15 mg, 20 mg and 25 mg. The biowaiver will be reviewed by ONDQA Biopharm group.

17. COMPARABILITY PROTOCOL – Two comparability protocols were included the submission.

17.1 Additional Drug Product Manufacturer - Incyte intends to qualify additional drug product manufacturers for the manufacture, release testing, packaging, labeling and stability study for ruxolitinib phosphate tablets of 5 mg, 10 mg, 15 mg, 20 mg and 25 mg strengths; however, the manufacturing site has not been determined. As noted in the 2003 Draft Guidance for Comparability Protocol, the new manufacturing site must have a satisfactory CGMP inspection. There are a number of issues that have been identified and sent to the applicant (see comments to the applicant in 74 day letter).

17.2 Additional Drug Substance Manufacturer - Incyte plans to qualify alternate suppliers for ruxolitinib phosphate for future commercial production (b) (4)
(b) (4) As with the alternate drug product manufacturer, Incyte has not determined the new drug substance manufacturer. See comments in 74-day letter.

18. DMF - The following DMFs were referenced. Review recommendations are included in the comments column.

Supporting DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	<u>No chemistry review is needed</u> The item referenced was found adequate for tablets on 06-Dec-04. This review was located using http://fdaeseach.fda.gov/
	III			<u>No chemistry review is needed</u> The HDPE bottle referenced was found adequate for tablets on 15-Sep-2000. This review was located using http://fdaeseach.fda.gov/
	III			<u>A review is needed</u>
	III			<u>No chemistry review is needed</u> The item referenced was found adequate for solid oral dosage packaging on 06-Dec-2004. This review was located using http://fdaeseach.fda.gov/
	III			<u>A chemistry review is needed</u>

17. Adventitious Agents – As noted in #12, lactose monohydrate, NF in the tablet formulation is of animal origin. Verify that the animal sourced lactose monohydrate complies with <http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi?TITLE=9&PART=94&SECTION=18&TYPE=TEXT> .
18. Environmental Assessment: The applicant has submitted a claim for categorical exclusion under 25.31(b) which states that use of this product will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment.
19. Establishment Evaluation: A full list of facilities involved in the manufacture, packaging and testing of ruxolitinib phosphate tablets is reproduced in attachment 1.

CRITICAL ISSUES FOR REVIEW

1. Overall, this NDA is well written and the conclusions are supported by actual data.

2. Based on the batch data, the applicant is requesting removal of microbial limits and chirality testing in the drug product stability protocol. Microbiology will review removal of the microbial testing. Removal of chiral testing should be assessed by the CMC reviewer.
3. Generally particle size distribution is a critical to dissolution properties. Batch data indicate that the particle size distribution is relatively consistent. In this case due to the high aqueous solubility, the particle size distribution of ruxolitinib phosphate is not likely to have a significant impact on drug product dissolution.
4. See comments for Comparability Protocol in 74-day letter.

Comments for 74-Day Letter: Yes.

1. Your submission includes two proposed comparability protocols for an alternate drug substance and drug product manufacturer. Identify the proposed alternate drug substance and drug product manufacturer.
2. Your CP for an alternate drug substance manufacturer states “There will be no major manufacturing process modifications; no changes in acceptance criteria and no major changes to analytical methods for starting materials, intermediates, reagents and solvents involved. The scale of the drug substance manufacture will be comparable with the approved commercial scale. Equipment changes will be limited to those needed to accommodate the site change.” A similar statement is included in your drug product CP. Revise your CP to fully describe all CMC changes for both manufacturers.
3. In your CP for the alternate drug substance manufacturer, specify the manufacturing process that will be used at the alternate manufacturing site. Your submission states that “Incyte may elect to file for an alternate site to manufacture the ruxolitinib phosphate drug substance [REDACTED] (b) (4) initially. In this case, the request to qualify the site for [REDACTED] (b) (4) will follow at a later date.”
4. Revise your drug substance CP to include drug substance characterization analysis.
5. Your request for a proposed reporting category of a CBE-0 is not acceptable.
6. Each proposed CP is a stand alone submission. Revise your CP’s to include all changes and acceptance criteria for each specified test to demonstrate equivalence between pre- and post-change material.

11 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JANICE T BROWN
07/11/2011

SARAH P MIKSINSKI
07/12/2011

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number:	Supplement Number and Type:	Established/Proper Name:
202192	Original NDA	Ruxolitinib phosphate
Applicant:	Letter Date:	Stamp Date:
Incyte Corporation	03-Jun-2011	03-Jun-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	PARAMETER	YES	NO	COMMENT
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

B. FACILITIES*				
	PARAMETER	YES	NO	COMMENT
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	
E. drug product (dp)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Expiry will be determined by primary reviewers in ONDQA/OBP
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

I. Labeling				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N.A.
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		See attached

Comments for 74-Day Letter:

1. Your submission includes two proposed comparability protocols for an alternate drug substance and drug product manufacturer. Identify the proposed alternate drug substance and drug product manufacturer.
2. Your CP for an alternate drug substance manufacturer states “There will be no major manufacturing process modifications; no changes in acceptance criteria and no major changes to analytical methods for starting materials, intermediates, reagents and solvents involved. The scale of the drug substance manufacture will be comparable with the approved commercial scale. Equipment changes will be limited to those needed to accommodate the site change.” A similar statement is included in your drug product CP. Revise your CP to fully describe all CMC changes for both manufacturers.
3. In your CP for the alternate drug substance manufacturer, specify the manufacturing process that will be used at the alternate manufacturing site. Your submission states that “Incyte may elect to file for an alternate site to manufacture the ruxolitinib phosphate drug substance using only [REDACTED]^{(b) (4)} initially. In this case, the request to qualify the site for [REDACTED]^{(b) (4)} will follow at a later date.”
4. Revise your drug substance CP to include drug substance characterization analysis.
5. Your request for a proposed reporting category of a CBE-0 is not acceptable.
6. Each proposed CP is a stand alone submission. Revise your CP’s to include all changes and acceptance criteria for each specified test to demonstrate equivalence between pre- and post-change material.

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

APPEARS THIS WAY ON ORIGINAL

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

{See appended electronic signature page}

Janice Brown
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Date: 22-Jun-2011

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch 2
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Date: 22-Jun-2011

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

/s/

JANICE T BROWN
07/11/2011

SARAH P MIKSINSKI
07/12/2011

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 202192/000	Sponsor:	INCYTE
Code:	161		RT 141 & HENRY CLAY RD BLDG 336
Priority:	1		WILMINGTON, DE 19880
Stamp Date:	03-JUN-2011	Brand Name:	RUXOLITINIB PHOSPHATE
PDUFA Date:	03-DEC-2011	Estab. Name:	
Action Goal:		Generic Name:	RUXOLITINIB PHOSPHATE
District Goal:		Product Number; Dosage Form; Ingredient; Strengths	

002; TABLET; RUXOLITINIB PHOSPHATE; 10MG
 003; TABLET; RUXOLITINIB PHOSPHATE; 15MG
 004; TABLET; RUXOLITINIB PHOSPHATE; 20MG
 005; TABLET; RUXOLITINIB PHOSPHATE; 25MG
 001; TABLET; RUXOLITINIB PHOSPHATE; 5MG

FDA Contacts:	T. LAMBERT	Project Manager	301-796-4246
	S. LIN	Review Chemist	301-796-1403
	J. BROWN	Team Leader	301-796-1652

Overall Recommendation: ACCEPTABLE on 11-OCT-2011 by D. SMITH ()
 PENDING on 09-JUN-2011 by EES_PROD

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA: I 077456
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 17-AUG-2011
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 1018495 FEI: 1018495
 DSM PHARMACEUTICALS INC
 5900 MARTIN LUTHER KING JR HIGHWAYS
 GREENVILLE, NC 27834
DMF No: AADA: I 077456
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 11-OCT-2011
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment:

CFN: (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No:

AADA: I 077456

Responsibilities:

DRUG SUBSTANCE RELEASE TESTER

Profile:

CONTROL TESTING LABORATORY

OAI Status: NONE

Last Milestone:

OC RECOMMENDATION

Milestone Date:

09-JUN-2011

Decision:

ACCEPTABLE

Reason:

BASED ON PROFILE

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202192Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

ruxolitinib (JAKAFI)

Date: October 27, 2011

To: File for NDA 202192

From: John K. Leighton, PhD, DABT

Director, Division of Hematology Oncology Toxicology

Office of Hematology and Oncology Products

I have examined pharmacology/toxicology supporting review of Dr. Chen and labeling and supervisory memorandum provided by Dr. Saber. I concur with Dr Saber's conclusion that JAKAFI may be approved for the proposed indication and that no additional nonclinical studies are needed.

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

/s/

JOHN K LEIGHTON
10/27/2011

MEMORANDUM

Date: October 27, 2011
From: Haleh Saber, Ph.D.
Pharmacology/Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology Oncology Products (OHOP)
Re: Approvability for Pharmacology and Toxicology
NDA: 202,192
Drug: JAKAFI (ruxolitinib)
Indication: For treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis

Ruxolitinib is a small molecule inhibitor of Janus Associated Kinases 1 and 2 (JAK 1/2). The inhibitory activity of ruxolitinib on JAKs was demonstrated *in vitro* and in animal models containing aberrant JAK/STAT signaling. Myelofibrosis, a type of myeloproliferative disorder, is known to be associated with dysregulation of JAK 1/2. This condition may present as a primary myelofibrosis or it may be secondary to polycythemia vera or essential thrombocythemia. The pharmacologic class assigned to ruxolitinib is “kinase inhibitor”, as presented in the HIGHLIGHTS section of the label. The detailed information on the mechanism of action of the drug is under section 12.1 of the FULL PRESCRIBING INFORMATION.

Pharmacology, safety pharmacology, pharmacokinetic/ADME (absorption, distribution, metabolism and excretion), and toxicology studies were conducted in *in vitro* systems and/or in animal species. Ruxolitinib was administered orally to animals in toxicology studies, consistent with the intended route of administration in patients. Drug-related toxicities were similar after single- or repeat-dose administration, therefore only repeat-dose general toxicology studies were reviewed for this NDA. Toxicities were mostly related to pharmacology of the drug, with lymphoid depletion, and reduced size of thymus and spleen being the primary adverse effects. Single-dose administration of ruxolitinib to Beagle dogs in a safety pharmacology study resulted in reduced systolic, diastolic, and mean arterial pressure. Safety pharmacology studies also revealed CNS and respiratory effects in animals; e.g. lower body temperature, reduced activity, and increased tidal volume/decreased minute volume. While dizziness and balance disorder have been reported in patients treated with ruxolitinib, cardiovascular or respiratory adverse effects have not been observed.

When administered during the period of organogenesis, ruxolitinib was not teratogenic to rats or rabbits. Reduced fetal weight and/or increased post-implantation loss were seen in animals only at doses that resulted in maternal mortalities. In a designated fertility study, ruxolitinib did not impair male or female fertility but resulted in increased post-implantation loss. In a peri- and post-natal developmental study conducted in rats, there were no drug-related adverse findings in pups for fertility indices or for maternal or

embryofetal survival, growth, and development parameters at the doses evaluated. Reduced number of pups (F1) delivered compared to the control appears to be secondary to the post-implantation loss, as previously reported in the embryo-fetal developmental study.

Ruxolitinib was not genotoxic when tested *in vitro* or *in vivo* for mutagenic or clastogenic potential. When tested in a 6-month carcinogenicity study in Tg.rasH2 transgenic mouse, ruxolitinib was not carcinogenic. A 2-year carcinogenicity study in rat is ongoing. Considering the serious and life-threatening condition of the disease and lack of adequate therapy, the results of the 2-year carcinogenicity study may be submitted post-approval. Based on the QSAR (quantitative structure–activity relationship) models, six impurities were found to have structural alerts for genotoxicity. Further evaluation by Ames assay, showed these compounds to be negative for mutagenic potential. The Ames tests on impurities were non-GLP; however, upon further examination of the study criteria, conduct of the study, and concentrations used in the study, DHOT accepts results of the non-GLP studies for these impurity. Of note, one of the six impurities was present in the 6-month carcinogenicity study at ^{(b) (4)}

Considering the results of reproduction toxicology studies together with the negative results reported in the genetic toxicology studies, the Applicant's proposed Category C for pregnancy is acceptable.

The nonclinical studies were reviewed by Dr. Wei Chen. Results of the carcinogenicity study were reviewed by Dr. Miyun Tsai-Turton. The nonclinical findings are summarized in the "Executive Summary" of the NDA review and reflected in the product label.

Recommendation: I concur with Dr. Chen that from a nonclinical perspective, JAKAFI may be approved for the proposed indication.

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/s/

HALEH SABER
10/27/2011

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 202,192
Supporting document/s: SDN 000
Applicant's letter date: June 3, 2011
CDER stamp date: June 3, 2011
Product: Ruxolitinib phosphate
Indication: Myelofibrosis
Applicant: Incyte Corporation
Review Division: Division of Hematology Oncology Toxicology
(for Division of Hematology Products; DHP)
Reviewer: Wei Chen, Ph.D.
Supervisor/Team Leader: Haleh Saber, Ph.D.
Division Director: John Leighton, Ph.D., D.A.B.T.
(Ann Farrell, MD for DHP)
Project Manager: Amy Baird

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 202,192 are owned by Incyte Corporation or are data for Incyte Corporation has obtained a written right of reference. Any information or data necessary for approval of NDA 202,192 that Incyte Corporation does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 202,192.

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1 Executive Summary

1.1 Introduction

Ruxolitinib phosphate, a new molecular entity, is a small molecule inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs). JAKs play a role in the signal transduction following cytokine and growth factor binding to their receptors. After the receptor associates with its respective cytokine/ligand it goes through a conformational change, bringing the JAKs close enough to phosphorylate each other. Once phosphorylated/ activated, the JAKs transduce an intracellular signal by promoting and activating transcription factors called STATs. The activated STATs (signal transducer and activator of transcription) dissociate from the receptor and form dimers before translocating to the cell nucleus where they regulate transcription of selected genes [Kisseleva et al, Gene 285:1-24,(2002)]. The efficacy of ruxolitinib phosphate has been shown in *in vitro* studies and in *in vivo* nonclinical tumor models representing both hematological and solid tumors. Ruxolitinib is being developed as a monophosphate salt for the oral treatment of myelofibrosis, a type of myeloproliferative neoplasm (MPN). With this NDA, the Applicant is submitting nonclinical pharmacology, pharmacokinetic, and toxicology studies to support the approval of ruxolitinib phosphate for the treatment of myelofibrosis.

1.2 Brief Discussion of Nonclinical Findings

Ruxolitinib was rapidly absorbed in rats and dogs with a similarly short half-life after single and multiple oral dosing. The pivotal non-clinical general toxicity studies of ruxolitinib were conducted in rats and dogs, consistent with the clinical route of administration. Non-clinical studies also included safety pharmacology studies, reproductive toxicity studies, genotoxicity studies, and a carcinogenicity study. The pivotal toxicology studies were conducted in compliance with Good Laboratory Practice regulation. Nonclinical pharmacokinetic and toxicokinetic studies of ruxolitinib were also evaluated in rats and dogs.

Pharmacology

Ruxolitinib (also referred to as “INCB018424” or “INC424”) is a pyrrolo-pyrimidine derivative, and it is an inhibitor of JAKs, with relative selectivity for JAK1 and JAK2. Ruxolitinib inhibited JAK in enzyme-based and cell-based assays. Ruxolitinib showed its inhibitory activity on JAKs in animal models with aberrant JAK/STAT signaling. Ruxolitinib inhibited cell proliferation, decreased circulating inflammatory cytokines (eg, TNF- α , IL-6) and resulted in prolonged survival in the mice xenograft models of hematological malignancies.

Safety pharmacology

Safety pharmacology studies revealed adverse effects of ruxolitinib on the functions of central nervous, respiratory and cardiovascular systems. Administration of ruxolitinib resulted in various observations including lower body temperature, lower activity and observations of darkened skin and mucous membranes. Decreased respiratory frequency, increase in tidal volume and decrease in minute volume were noted in rats

following a single oral dose of INCB018424. Administration of ruxolitinib at a dose of 30 mg/kg (the highest dose tested) resulted in significantly lower pulse pressure, as well as lower systolic, diastolic, and calculated mean arterial pressure (up to 53%, 41%, 31%, and 33%, respectively) when compared to the control group.

General toxicology

The repeated dose toxicology studies in rats and dogs have shown that oral administration of ruxolitinib resulted in alterations in hematology parameters and microscopic observations of marked lymphoid depletion, which correlated with small thymus and spleen as well as low lymphocyte counts. No adverse effect of ruxolitinib on central nervous system, respiratory, or cardiovascular system was noted at the doses tested in the repeat-dose toxicology studies in rats and dogs. Clinical and anatomical pathology findings associated with the treatment of ruxolitinib were generally reversible after a recovery period. Toxicities observed are mostly direct effects based on the pharmacology of ruxolitinib.

Genetic toxicology

Ruxolitinib was not mutagenic or clastogenic in the *in vitro* and *in vivo* assays studied.

Reproductive toxicology

Ruxolitinib did not impair fertility when administered to either male or female rats prior to and during the mating time frame. However, embryo-fetal viability was reduced. Ruxolitinib was not teratogenic in either the rat or the rabbit when administered to animals during the period of organogenesis. It did, however, lead to increased postimplantation loss and/or reduced fetal weight at a maternally toxic/lethal dose. In a pre- and post-natal developmental study, ruxolitinib resulted in a slightly prolonged gestation period; the significance of this finding is unclear. Reduced number of pups (F1) delivered appears to be secondary to the increased post-implantation loss in F0 females..

Carcinogenicity studies

Treatment of Tg.rasH2 animals with ruxolitinib at daily oral doses up to 125 mg/kg for 26-weeks did not increase the incidence of neoplastic lesions.

1.3 Recommendations

1.3.1 Approvability

Recommending approval. The non-clinical studies adequately support the safety of ruxolitinib phosphate by oral route in myelofibrosis.

1.3.2 Additional Non Clinical Recommendations

Additional non-clinical studies are not needed at this time.

1.3.3 Labeling

Information needed for nonclinical sections of the label are provided in this review. Therefore, a separate labeling review is not deemed necessary.

2 Drug Information

2.1 Drug

CAS Registry Number: 941678-49-5

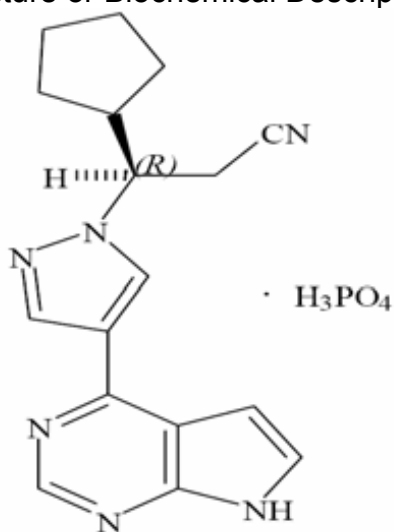
Generic Name: ruxolitinib phosphate

Code Name: INCB018424; INC424

Chemical Name: (R)-3-(4-(7H-pyrrolo [2,3-d] pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate

Molecular Formula/Molecular Weight: $C_{17}H_{21}N_6O_4P$ / 404.36

Structure or Biochemical Description



Pharmacologic Class: kinase inhibitor

Mechanism of action: inhibition of the Janus Associated Kinases 1 and 2 (JAKs 1 and 2)

2.2 Relevant INDs, NDAs, BLAs and DMFs:

IND 77456 (for myeloproliferative disorders)

IND 77101 (for psoriasis)

IND 77,455 (for rheumatoid arthritis)

DMF (b) (4)

2.3 Drug Formulation: 5mg, 10 mg, 15 mg, 20 mg, and 25 mg tablets

Composition of Ruxolitinib Phosphate Tablets, 5 mg

Component	Quality Standard	Amount (mg/tablet)	Function
Ruxolitinib Phosphate ^a	Incyte specification	(b) (4)	API
Microcrystalline Cellulose	NF/EP/JP		(b) (4)
Lactose Monohydrate	NF/EP/JP		
Colloidal Silicon Dioxide	NF/EP		
Hydroxypropyl Cellulose	NF/EP		
Povidone	USP/EP		
Sodium Starch Glycolate	NF/EP		
Magnesium Stearate	NF/EP/JP		
(b) (4)	USP/EP		
Total Tablet Weight (mg)			
(b) (4)			

2.4 Comments on Novel Excipients: N/A

2.5 Comments on Impurities/Degradants of Concern: none

2.6 Proposed Clinical Population and Dosing Regimen

Myelofibrosis, including primary myelofibrosis (PMF), post-polycythemia vera Myelofibrosis (PPV-MF), and post-essential thrombocythemia-myelofibrosis (PET-MF)

The recommended starting dose is as follows:

(b) (4)

Patients with platelet counts between 100,000 and 200,000/ μ L: 15 mg, oral, twice daily
 Patients with platelet counts > 200,000/ μ L: 20 mg, twice daily

3 Studies Submitted

Studies Reviewed

ADME

		Study no.	Folder/file
1 Title	Pharmacokinetics of INCB018424 in Dogs	INCYTE-DMB-06.182.1	M4.2.2.2
2	<i>In vitro</i> and <i>ex vivo</i> protein binding of INCB018424 in rat, cynomolgus monkey, dog, minipig, and human serum and plasma	INCYTE-DMB-07.11.1	M4.2.2.3
3	Quantitative whole-body autoradioluminography of rats following oral administration of ¹⁴ C-INCB018424	INCYTE-DMB-08.58.1	M4.2.2.3
4	Placental transfer and lacteal excretion of ¹⁴ C-INCB018424 following administration of a single oral dose to Pregnant Sprague Dawley rats	INCYTE-DMB-10.50.1	M4.2.2.3
5	The <i>in vitro</i> metabolism of INCB018424 by rat liver microsomes and individual rat recombinant cytochrome P450(s)	INCYTE-DMB-10.51.2	M4.2.2.4
6	INCB018424: material balance and metabolism in male rats	INCYTE-DMB-08.61.1	M4.2.2.4
7	Identification of <i>in vivo</i> metabolites of INCB018424 in female rat following a single oral dose of ¹⁴ C-INCB018424	INCYTE-DMB-08.169.1	M4.2.2.4
8	Identification of <i>in vivo</i> metabolites of INCB018424 in beagle dogs	INCYTE-DMB-07.14.1	M4.2.2.4
9	Metabolism of [¹⁴ C]INCB018424 in male and female beagle dogs after a single oral administration identification	INCYTE-DMB-08.149.1	M4.2.2.4
10	Excretion mass balance in female rats and pharmacokinetics of radioactivity in male and female rats following a single oral dose of [¹⁴ C]INCB018424	INCYTE-DMB-09.82.1	M4.2.2.5
11	Excretion/mass balance in male and female beagle dogs after a single oral administration of [¹⁴ C]INCB018424	INCYTE-DMB-08.62.2	M4.2.2.5

Drug interaction

		Study no.	Folder/file name
1	Title Human CYP Isozymes that are Responsible for the In Vitro Metabolism of INCB018424	INCYTE-DMB-09.93.1	M5.3.2.2
2	In vitro evaluation of INCB018424 as an inducer of cytochrome P450 expression in cultured human hepatocytes	INCYTE-DMB-11.06.1	M5.3.2.2

Toxicology studies

Repeat dose

		Study no.	Folder/file name
1	Title A 6-month oral (gavage) toxicity study of INCB018424 in rats with a 6 week recovery period	T07-10-06	M4.2.3.2
2	A 6-month oral (gavage) toxicity study with INCB018424 in beagle dogs with 6-week recovery period	T07-10-07	M4.2.3.2
3	52-week oral gavage chronic toxicity and toxicokinetic study with INCB018424 in dogs with a 6-week recovery period	T08-07-03	M4.2.3.2

carcinogenicity

		Study no.	Folder/file name
1	Title INCB018424: 26 week repeated dose oral carcinogenicity study in Tg.rasH2 mice	T09-02-03	M4.2.3.4

Reproductive toxicology

	Title	Study no.	Folder/file name
1	Oral gavage study of fertility and early embryonic development to implantation with INCB018424 in rats	8212204	M4.2.3.5
2	Oral administration of INCB018424 via gavage: definitive study for effects on embryo-fetal development in Sprague Dawley rats	T07-12-04	M4.2.3.5
3	Oral administration of INCB018424 via gavage: definitive study for effects on embryo-fetal development in New Zealand white rabbits	T07-12-05	M4.2.3.5
4	Oral gavage study for effects on pre- and post-natal development, Including maternal function with INCB018424 in rats	1001237	M4.2.3.5

Other studies

Genetic toxicology

	Title	Study no.	Folder/file name
1	(b) (4)	1012571	M4.2.3.7
2	(b) (4)	1012575	M4.2.3.7
3	(b) (4)	1012576	M4.2.3.7
4	(b) (4)	1012577	M4.2.3.7
5	(b) (4)	1012578	M4.2.3.7
6	(b) (4)	1012579	M4.2.3.7

Studies submitted, but not reviewedPharmacology

		Study no.	Folder/file name
1	In vitro activity of INCB018424 metabolites	INCYTE-IN VITRO-07.02.2	M4.2.1.1
2	In vitro activity of INCB018424 in cytokine-mediated cell-based assays	INCYTE-IN VITRO-09.08.1	M4.2.1.1
3	In vitro activity of INCB018424 metabolites	INCYTE-IN VITRO-069.11.1	M4.2.1.1
4	Pharmacological activity of metabolites of INCB018424 in rats and dogs	INCYTE-DMB- 07.15.2	M4.2.1.1
5	Pharmacodynamic activity of INCB018424 following a single oral dose in gestating rabbits	INCYTE-IN VITRO-09.13.1	M4.2.1.1
6	Summary report: effect of INCB018424 in rodent models of cancer	INCYTE-PRECLIN -10.01.1	M4.2.1.1
7	Summary report: activity of INCB018424 in rodent pharmacodynamic models	INCYTE-PRECLIN -10.02.1	M4.2.1.1
8	Summary report: activity of INCB018424 in inflammatory disease models	INCYTE-PRECLIN -10.03.1	M4.2.1.1

Secondary Pharmacodynamics

		Study no.	Folder/file name
1	<i>In Vitro</i> Pharmacology: ExpresSProfile- Study of INCB018424"	T-06-01-02	M4.2.1.2
2	<i>In Vitro</i> Pharmacology: Kinase Assays- Study of INCB018424	T-06-11-09	M4.2.1.2
3	Binding of INCB018424 to human adenosine A1, A2a and A2b receptors	INCYTE-IN VITRO-07.01.1	M4.2.1.2

ADME

		Study no.	Folder/file name
Title	<i>In vitro</i> permeation of INCB018424 in topical formulations across mouse skin	INCYTE-DMB-06.163.1	M4.2.2.2
2	Effect of Elevated Gastric pH on the Oral Absorption of INCB018424 in Cynomolgus Monkeys	INCYTE-DMB-09.60.1	M4.2.2.2
3	Pharmacokinetics of INCB018424 in CD-1 Mice After a Single Dose Oral Dose	INCYTE-DMB-08.170.1	M4.2.2.2
4	The Pharmacokinetics of INCB018424 in Rats	INCYTE-DMB-06.169.1	M4.2.2.2
5	Pharmacokinetics of INCB018424 in Cynomolgus Monkeys	INCYTE-DMB-07.08.1	M4.2.2.2
6	<i>Ex vivo</i> and <i>in vitro</i> protein binding of INCB018424 in CD-1 mouse plasma	INCYTE-DMB-08.191.1	M4.2.2.3
7	<i>Ex Vivo</i> and <i>In Vitro</i> Protein Binding of INCB018424 in CByB6F1 Hybrid (Wild-type TgRasH2) Mouse Plasma	INCYTE-DMB-08.158.1	M4.2.2.3
8	<i>In Vitro</i> and <i>Ex Vivo</i> Protein Binding of INCB018424 in Rabbit Plasma	INCYTE-DMB-09.61.1	M4.2.2.3
9	Brain and cerebrospinal fluid concentrations of INCB018424 in rats	INCYTE-DMB-07.12.1	M4.2.2.3
10	Quantitative whole-body autoradioluminography tissue distribution of ¹⁴ C-INCB018424 in Sprague Dawley rats following a single oral dose	INCYTE-DMB-07.109.1	M4.2.2.3
11	Identification of <i>in vivo</i> metabolites of INCB018424 in CD-1 mice after a single oral dose	INCYTE-DMB-08.171.1	M4.2.2.4
12	Metabolism of [¹⁴ C]INCB018424 in male and female CByB6F1-Tg(HRAS)2Jic mice after a single oral administration	INCYTE-DMB-08.154.1	M4.2.2.4
13	Identification of <i>in vivo</i> metabolites of INCB018424 in female rat following a single oral dose of ¹⁴ C-INCB018424	INCYTE-DMB-09.84.1	M4.2.2.4
14	Identification of <i>in vivo</i> metabolites of INCB018424 in rabbit	INCYTE-DMB-09.95.1	M4.2.2.4
15	Identification of <i>in vivo</i> milk and plasma metabolites of INCB018424 in female lactating rats following a single oral dose of ¹⁴ C-INCB018424	INCYTE-DMB-10.51.2	M4.2.2.4

Drug interaction

		Study no.	Folder/file name
1	Reaction phenotyping: identification of human CYP enzymes involved in the metabolism of [¹⁴ C]-VNP401101M	NCL-156	M5.3.2.2
2	Metabolic Stability of VNP40101M and VNP4090CE in Human Liver Microsomes and Cryopreserved Human Hepatocytes	NCL-147	M5.3.2.2
3	<i>In vitro</i> metabolism of [¹⁴ C]VNP40101M in cryopreserved hepatocytes from the rat, dog, and human	NCL-137	M5.3.2.2

Studies reviewed previously and referenced in this reviewSafety pharmacology

		Study no.	Folder/file name
1	Plethysmography-restrained respiratory assessment of orally administered INCB018424 to Sprague Dawley rats	T06-10-04	M4.2.1.3
2	Toxicokinetics of INCB018424 in rat acute CNS pharmacological profile study	T06-10-03	M4.2.1.3
3	Effects of INCB018424 on cloned HERG channels expressed in mammalian cells	DMB-06.187.1	M4.2.1.3
4	Cardiovascular assessment of orally administered INCB018424 to conscious radiotelemetry-instrumented beagle dogs	T06-10-01	M4.2.1.3

ADME

		Study no.	Folder/file name
4	The Pharmacokinetics of INCB018424 in Rats	INCYTE-DMB-06.169.1	M4.2.2.2

Genetic toxicology

		Study no.	Folder/file name
1	INCB018424: <i>Salmonella</i> plate incorporation mutagenicity assay Key findings: INCB01824 (free base) was not mutagenic in the <i>Salmonella</i> plate incorporation mutagenicity assay, under the conditions of this experiment	AB22ZU.501.BTL	M4.2.3.3
2	<i>Salmonella-Escherichia coli</i> /mammalian-microsome reverse mutation assay with a confirmatory assay	T06-08-01	M4.2.3.3
3	INCB018424: Chromosomal aberrations in cultured human peripheral blood lymphocytes	T06-08-02	M4.2.3.3
3	INCB018424: In vivo rat bone marrow micronucleus assay	T06-10-02	M4.2.3.3

4 Pharmacology

4.1 Primary Pharmacology

Brief summary

Ruxolitinib is an inhibitor of the Janus Associated kinases (JAKs) with selectivity for JAK1 and JAK2. Ruxolitinib was tested in cell-based assays and *in vivo* models relevant to the pathogenesis of myeloproliferative neoplasms (MPNs). Activity was observed in *in vitro* studies and in nonclinical tumor models representing both hematological and solid tumors. Ruxolitinib was shown to inhibit IL-2 stimulated phosphorylation of JAKs and STATs and IL-2 induced proliferation of T cells as well as the phosphorylation of STAT proteins and the production of pro-inflammatory factors (eg, IL-17, IL-22, MCP-1) induced by other cytokines, such as IL-23 and IL-6. Ruxolitinib inhibited splenomegaly in mice resulting from intravenous inoculation of cells expressing the clinically relevant JAK2V617F mutation. The *in vitro* pharmacological activity of eight ruxolitinib metabolites observed in human plasma was evaluated using enzyme and cell-based assays. The two major human metabolites, M18 and M27 (25% and 11% of parent based on AUC, respectively), as well as the six other metabolites tested were shown to be pharmacologically active. These metabolites had 2-5-fold weaker potency compared to that of the parent compound in a human whole blood assay measuring inhibition of IL-6 induced STAT3 phosphorylation.

In safety pharmacology assessments of ruxolitinib including respiratory and central nervous system studies in rats, and *in vitro* and *in vivo* (ECG study in conscious dogs) cardiovascular studies, treatment-related findings were lower body temperature, lower activity, observations of darkened skin and mucous membranes, decreases in minute volume in high dose female rats in the respiratory study and decreases in arterial blood pressure along with increases in heart rate at the highest dose evaluated in dogs in the cardiovascular study.

Primary pharmacodynamics

Mechanism of action:

Ruxolitinib is a small molecular inhibitor of JAKs with selectivity for JAK1 and JAK2 (IC₅₀ value at 3.3 nM and 2.8 nM respectively). The *in vitro* studies showed that ruxolitinib inhibited JAK/STAT signaling and growth of a cell line expressing the constitutively active JAK2 mutant (JAK2V617F) that has been implicated in the pathogenesis of the majority of Philadelphia chromosome negative myeloproliferative neoplasms (MPNs). Ruxolitinib treatment resulted in a suppression of phosphorylated STAT3 (pSTAT3) and tumor growth in mice xenograft model with cells expressing JAK2V617F. These results suggest that the alteration of JAK/STAT signaling pathway could contribute to the therapeutic or toxic effect of ruxolitinib.

Drug activity related to proposed indication:1- Alteration of JAK/STAT pathway is associated with myeloproliferative disorders

The Applicant cited publication

Lalentino and Pierre, *Biochem Pharmacol* (2006) 71: 715

Title: JAK/STAT signal transduction: Regulators and implication in hematological malignancies

This reference article is a commentary review paper; the following summary is copied from above review article.

Summary: Signal transducers and activators of transcription (STATs) comprise a family of several transcription factors that are activated by a variety of cytokines, hormones and growth factors. STATs are activated through tyrosine phosphorylation, mainly by JAK kinases, which lead to their dimerization, nuclear translocation and regulation of target genes expression. Stringent mechanisms of signal attenuation are essential for insuring appropriate, controlled cellular responses. Among them phosphotyrosine phosphatases (SHPs, CD45, PTP1B/TC-PTP), protein inhibitors of activated STATs (PIAS) and suppressors of cytokine signaling (SOCS) inhibit specific and distinct aspects of cytokine signal transduction.

Somatic point mutation in JH2 domain of JAK2 (JAK2V617F), leading also to constitutive tyrosine phosphorylation of JAK2 and its downstream effectors was reported in myeloproliferative disorders.

2- Effects of INCB018424 on kinase activities of JAKs and other enzymes

The Applicant cited publication

Quintas-Cardama et al. *Blood* (2010) 115: 3109

Title: Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: therapeutic implications for the treatment of myeloproliferative neoplasms

Summary: INCB018424 inhibited JAK1 and JAK2 with IC50 values of 3.3 nM and 2.8 nM, respectively. The inhibitory effect of INCB018424 on JAK1 and JAK2 was 6 times more effective comparing to Tyk2 and 130 times comparing to JAK3.

Methods: The kinase domains of human JAK1 (837-1142), JAK2 (828-1132), JAK3 (781-1124), and Tyk2 (873-1187) were cloned by PCR with N-terminal epitope tags. Recombinant proteins were expressed using Sf21 cells and baculovirus vectors and purified with affinity chromatography. JAK kinase assays used a homogeneous time-resolved fluorescence assay with the peptide substrate (-EQEDEPEGDYFEWLE). Each enzyme reaction was carried out with test compound or control, JAK enzyme, 500nM peptide, adenosine triphosphate (ATP; 1mM), and 2.0% dimethyl sulfoxide

(DMSO) for 1 hour. The 50% inhibitory concentration (IC₅₀) was calculated as the compound concentration required for inhibition of 50% of the fluorescent signal.

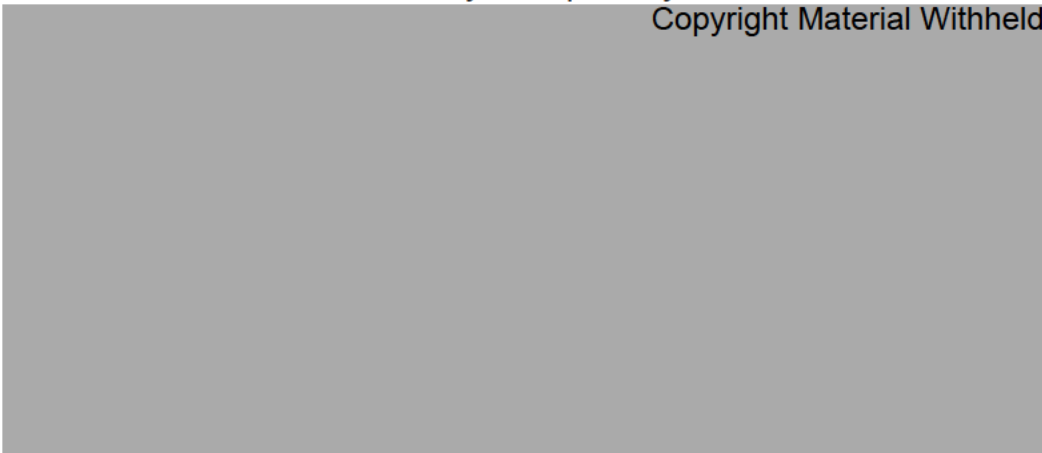
Results:

- 1) INCB018424 inhibited kinase activities of JAK1 and JAK2 with IC₅₀ values of 3.3nM and 2.8nM, respectively;
- 2) INCB018424 demonstrated inhibitory activity against Tyk2 with an IC₅₀ value of 19 nM, and inhibitory activity against JAK3 with an IC₅₀ value of 428 nM.

The following table is excerpted from this publication.

Enzymatic potency of INCB18424

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3- The reduction of cell viability by INCB018424 was associated with inhibition of JAK/STAT signaling pathway

3-a. INCB018424 inhibited protein phosphorylation associated with JAK1 and JAK2

The Applicant cited publication

Quintas-Cardama et al. Blood (2010) 115: 3109

Title: Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: therapeutic implications for the treatment of myeloproliferative neoplasms

Summary: treatment with INCB018424 reduced phosphorylation of JAK2, STAT5 and ERK1/2 in Ba/F3-EpoR-JAK2V617F cells; reduced phosphorylation of STAT3 and STAT5 in HEL cells; and reduced phosphorylation of JAK1 in primary MF patient samples.

Method: Ba/F3-EpoR-JAK2V617F or HEL cells, and primary MF patient samples were treated with increasing concentrations of INCB018424 for 2.5 hours, and extracts from these cells were subjected to immunoblot analysis for phosphorylation (p) or total forms of proteins associated with the JAK/STAT signaling pathway.

Results: There was a dose-dependent reduction in the phosphorylated form of JAK1, JAK2, STAT3 (pSTAT3), STAT5 (pSTAT5), and ERK1/2 with maximal effect at approximately 300 nM in the tested cell lines. However there was no change in total levels of the respective proteins.

The following figures are excerpted from this publication.

INCB018424 inhibited JAK2V617F-mediated signaling in Ba/F3-EpoR-JAK2V617F (A), HEL (B) cells, or primary MF patient peripheral blood mononuclear cells (C).



3-b. INCB018424 reduced cell viability

The Applicant cited publication
Quintas-Cardama et al. Blood (2010) 115: 3109

Title: Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: therapeutic implications for the treatment of myeloproliferative neoplasms

Summary: A dose-dependent reduction in viability was observed in INCB018424 treated Ba/F3-EpoR-JAK2V617F cells and HEL cells.

Method: Hel cells and Ba/F3-EpoR-JAK2V617F cells (engineered cell system: Cytokine-dependent Ba/F3 cells were transformed to growth factor independence by ectopic expression of JAK2V617F and a requisite type I cytokine receptor EpoR) were treated with INCB018424 and a viable cell number was assessed after 48 hours. Viability was measured by cellular ATP determination using the Cell-Titer Glo (Promega) luciferase reagent or viable cell counting. Values were transformed to percent inhibition relative to vehicle control, and IC50 curves were fitted according to nonlinear regression analysis of the data using PRISM GraphPad.

Results: 1) A dose-dependent reduction in viability was observed with an IC50 of 126nM in Ba/F3-EpoR-JAK2V617F cells;
2) The growth of HEL cells was also affected by INCB018424 with a 50% effective concentration (EC50) of 186 nM.

The following figure is excerpted from this publication.



3-c. INCB018424 induced apoptosis

The Applicant cited publication
Quintas-Cardama et al. Blood (2010) 115: 3109

Title: Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: therapeutic implications for the treatment of myeloproliferative neoplasms

Summary: Cells expressing JAK2V617F underwent apoptosis when treated with INCB018424.

Method: Ba/F3-EpoR-JAK2V617F cells were treated with various concentrations of INCB018424 for approximately 24 hours and analyzed for hallmarks of apoptosis by annexin V/propidium iodide staining or mitochondrial membrane depolarization. Cells treated with INCB018424 were stained with a combination of fluorescein isothiocyanate-annexin V and propidium iodide and analyzed using flow cytometry to determine the percentages of viable, early apoptotic, and late apoptotic or dead cells. The effects of JAK inhibition on mitochondrial membrane potential were determined by flow cytometry using JC-1 as a molecular probe.

Results: Treatment with INCB018424 increased apoptosis compared with DMSO, with a 4.3, 7.2-, and 13.2-fold increase at concentrations of 150, 400, and 1000 nM, respectively.

3-d. INCB018424 inhibited hematopoietic progenitor cell proliferation in primary MPN patient samples

The Applicant cited publication
Quintas-Cardama et al. Blood (2010) 115: 3109

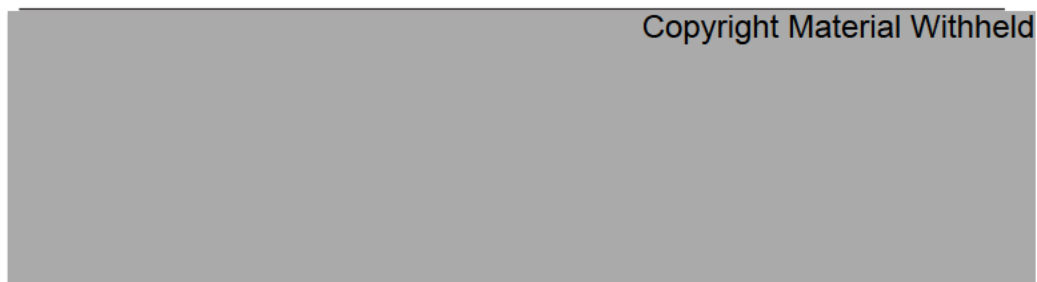
Title: Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: therapeutic implications for the treatment of myeloproliferative neoplasms

Summary: INCB018424 inhibited hematopoietic progenitor cell colony formation. Cells derived from patients with polycythemia vera (PV) with mutated JAK2 are more sensitive to JAK1/2 inhibition than normal donors, particularly in the absence of hematopoietic growth factor support.

Method: Mononuclear cells from 3 healthy controls and 3 patients with PV expressing the JAK2V617F mutant allele at frequencies more than 90% were obtained. Growth of clonogenic progenitors of erythroid (BFU-E) and myeloid origin (CFU-M) was assessed in colony-forming assays in the presence of increasing concentrations of INCB018424

Results: 1) Inhibition of the growth of erythroid and myeloid progenitors was observed with INCB018424
2) INCB018424 demonstrated potency against erythroid colony formation in JAK2V617F⁺ human MPNs

The follow table is excerpted from this publication



3-e. The effect of INCB018424 on an in vivo model of JAK2V617F-driven malignancy

The Applicant cited publication

Quintas-Cardama et al. Blood (2010) 115: 3109

Title: Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: therapeutic implications for the treatment of myeloproliferative neoplasms

Summary: Oral administration of INCB018424 inhibited JAK-STAT signaling, prevented splenomegaly, decreased JAK2V617F mutant cells in the spleen, decreased circulating inflammatory cytokines (eg, TNF- α , IL6) and resulted in prolonged survival in the mice at doses that did not cause changes of peripheral blood cell counts.

Method: 1×10^5 Ba/F3-EpoR-JAK2V617F cells were injected into the tail vein of Balb/c mice. The mice were monitored for splenomegaly and survival over a 3-week period to evaluate the impact of INCB018424 on the course of disease.

Results:

- 1) Vehicle treated animals had splenomegaly with a mean weight of 471 mg (~5 times normal), whereas spleen weights of mice treated with INCB018424 were 110 mg;
- 2) Beginning on day 15, mice from the vehicle group died of disease. By day 22, greater than 90% of the vehicle group had died, whereas, in contrast, greater than 90% of mice treated with INCB018424 survived;
- 3) Genomic PCR analysis of spleen samples showed that JAK2V617F cells were significantly decreased by treatment with INCB018424 (33%, $P < .01$);
- 4) INCB018424 normalized uncontrolled JAK/STAT signaling in spleens from mice inoculated with Ba/F3-EpoR-JAK2V617F cells;
- 5) Treatment with INCB018424 resulted in significant suppression of elevated IL-6 levels and reduction of TNF-levels to normal;

The following figures and table are excerpted from this publication

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4.2 Secondary Pharmacology

Both studies (T-06-01-02 and T-06-11-09) were non-GLP studies and are not reviewed here. The following summary is excerpted from the applicant's submission.

Ruxolitinib at 0.1 and 1 μM did not demonstrate significant ($> 50\%$) cross reactivity with any of the 50 in vitro binding assays and enzyme assays (T-06-01-02). However, 26% inhibition at 1 μM was noted for the human adenosine 1 receptor (hA1). This observation prompted determination of an IC_{50} value for ruxolitinib-mediated inhibition of binding to this adenosine receptor, and the other adenosine family of receptors. Using membranes prepared from CHO-K1 cells expressing the human A1 receptor, the IC_{50} for ruxolitinib-mediated inhibition of radioligand binding was determined to be 2.1 μM . IC_{50} values for hA2a and hA2b receptors were $> 30 \mu\text{M}$ and 11 μM respectively [INCYTE-IN VITRO-07.01.1].

Ruxolitinib was evaluated in a Cerep Kinase Assay screen (T06-11-09) at 0.2 μM to investigate the effect of ruxolitinib in 30 in vitro kinase assays. Ruxolitinib did not demonstrate significant cross reactivity (defined as > 50% inhibition) against any of the kinases tested in this panel except those of the JAK family: complete inhibition of JAK2 activity was confirmed and JAK3 activity was inhibited by 95%.

Note from reviewer: It would have been preferable if a higher concentration of INCB018424 (i.e., 10 μM) had been evaluated in the Cerep ExpressProfile screen. However, based on the data available for INCB018424, it appears that there is little risk of unintended pharmacological activity due to binding to non-specific receptors/enzymes.

4.3 Safety Pharmacology

Safety pharmacology summary:

The safety pharmacology study reports were reviewed by Dr. Barbara Hill for the treatment of rheumatoid arthritis (IND 77,455). Dr. Hill summarized the safety pharmacology study results as follows.

- The NOAEL for central nervous systemic pharmacological effects noted in rats (lower body temperature and reduced total and ambulatory activity counts) following a single oral dose of INCB018424 was identified as 15 mg/kg for males and 50 mg/kg for females, under the conditions of this study;
- The NOAEL for respiratory effects noted in rats (decreased respiratory frequency, increase in tidal volume and increase in minute volume) following a single oral dose of INCB018424 was identified as 15 mg/kg for males and 50 mg/kg for females, under the conditions of this study;
- The IC_{50} for INCB018424 HERG potassium current was 131.6 μM , under the conditions of this study. The NOAEL for cardiovascular effects noted in male dogs (significant increase in heart rate, significant shortening of PR interval, slight increase in lengthening of the QRS complex, significant shortening of the RR interval and a slight prolongation of the heart-rate corrected QT interval) following a single oral dose of INCB018424 was identified as 10 mg/kg, under the conditions of this study.

Neurological effects:

From Dr. Hill's review

The neuropharmacologic effects of INCB018424 were evaluated in an oral rat GLP study using a Functional Observation Battery (FOB) and locomotor activity measurements. Single oral (gavage) doses of 0, 15, 50 and 150 mg/kg INCB018424 were administered to Sprague-Dawley rats (10/sex/group). Separate toxicokinetic groups for low-, mid- and high-dose groups were included in this study. Toxicology parameters included assessment of mortality. FOB (sensorimotor, neuromuscular and physiological observations) and locomotor activity (measured for a 60 minute interval; home cage, handling and open field observations) were recorded for all animals prior to

dose administration and 30 minutes post dose (T_{max}). Blood samples for toxicokinetic analysis were collected from 6 animals/sex/group at 0, 0.5, 1, 2, 4 and 8 hours post-dose.

No treatment related mortality was noted in this study. No treatment related effects on FOB or locomotor activity were noted in low-dose animals and mid dose females. The only treatment related effect on FOB was noted in high-dose females. A significant lower body temperature was noted in high-dose females (35.1°C) compared to control females (37.1°C) at 30 minutes post-dose. Total and ambulatory activity counts during the first 15 minutes of the 1-hour session were significantly reduced in mid dose males and high-dose animals. A summary of the mean pharmacokinetic parameters for INCB018424 measured in this study is provided in the following table.

Dose (mg/kg/day)	T_{max} (hr)		C_{max} (µM/ml)		$AUC_{0-8\text{ hr}}$ (µM·hr)	
	Males	Females	Males	Females	Males	Females
15	0.5	0.5	0.15	1.02	0.14	1.29
50	0.5	0.5	0.68	2.85	1.15	9.62
150	0.5	0.5	1.94	13.6	4.0	36.1

A dose-related increase in systemic exposure was noted in this study. Females exhibited a greater systemic exposure compared to males. The NOAEL for central nervous systemic pharmacological effects noted in rats following a single oral dose of INCB018424 was identified as 15 mg/kg for males and 50 mg/kg for females, under the conditions of this study.

Respiratory effects:

From Dr. Hill's review

The respiratory effects of INCB018424 were evaluated in an oral rat GLP study using head-out neck-sealed plethysmography chambers. Single oral (gavage) doses of 0, 15, 50 and 150 mg/kg INCB018424 were administered to Sprague-Dawley rats (8/sex/group). Respiratory parameters included respiratory rate, tidal volume and derived minute volume. Data was captured from 60 minutes pre-dose and continuously for 4 hours post dose.

No treatment-related effects on mortality or clinical signs were noted in this study. A significant decrease in respiratory frequency was noted in high-dose animals. This effect lasted for up to 3 hours post dose with a maximum decrease of 23% in high dose males and 21% in high dose females. A significant increase in tidal volume was noted in mid-dose males and high-dose animals. This effect lasted for up to 4 hours post dose with a maximum increase of 21% in mid-dose males, 34% in high-dose males and 18% in high dose females. The higher tidal volume noted in high-dose animals may reflect a compensatory response to the lower respiratory frequency. A significant decrease in minute volume was noted in high-dose females (up to 17% noted at three timepoints from 0.75 to 1.75 hours post-dose). The NOAEL for respiratory effects noted in rats following a single oral dose of INCB018424 was identified as 15 mg/kg for males and 50 mg/kg for females, under the conditions of this study.

Cardiovascular effects:

From Dr. Hill's review

The effects of INCB018424 on the cardiovascular system were evaluated in a GLP *in vitro* HERG assay and in a GLP *in vivo* cardiovascular safety pharmacology study conducted in Beagle dogs.

INCB018424 (10, 100 and 300 μ M) was tested for HERG-channel inhibition in embryonic kidney cells (HEK293). INCB018424 inhibited HERG current by (mean $\pm$ SEM): $3.8 \pm 0.2\%$ at 10 μ M, $40.3 \pm 1.6\%$ at 100 μ M and by $74.1 \pm 0.2\%$ at 300 μ M versus $0.6 \pm 0.5\%$ for the vehicle control. Significant inhibition of HERG current was noted at 100 and 300 μ M INCB018424 compared to vehicle control. The IC₅₀ for INCB018424 HERG potassium current was 131.6 μ M, under the conditions of this study. The positive control (60 nM terfenadine) inhibited HERG potassium current by 83.1% in this assay.

Four adult naïve male conscious radiotelemetry-implanted Beagle dogs were used in the *in vivo* cardiovascular safety pharmacology study. The sponsor states that only male dogs were used in this study because toxicokinetic parameters were similar in male and female dogs. Single oral doses of 0, 3, 10 and 30 mg/kg INCB018424 (dose volume = 10 ml/kg; vehicle: 0.5% methylcellulose) were administered in a Latin-square design. A 3-4 day washout period was incorporated between each dose. Heart rate, arterial blood pressure (systolic, diastolic), body temperature and ECG were collected for a 30-second period every 10 minutes for 24 hours post dose.

No treatment-related effects on mortality were noted in this study. Emesis was noted after dose administration in high-dose animals. A significantly lower pulse pressure as well as systolic, diastolic and calculated mean pressure (up to 53%, 41%, 31% and 33%, respectively) was noted in high-dose animals compared to control animals. These changes peaked approximately 2-3 hours post dose after which mean arterial blood pressure values began to recover. However, lower values for arterial blood pressure were still noted 24 hours post dose in high-dose animals. No treatment related effects on systolic, diastolic or mean pulse pressure were noted in low and mid-dose animals.

A significant increase in heart rate (increase up to 117% during hour 2) that lasted up to 10 hours post dose was noted in high-dose animals compared to vehicle control. The observed increase in heart rate may reflect a compensatory response to the decreases in arterial blood pressure noted in high-dose animals. No treatment-related effects on heart rate were noted in low- and mid-dose animals. A slight decrease in body temperature was noted at 3 and 4 hours (0.24°C and 0.22°C lower, respectively) in high-dose animals. No treatment-related effects on body temperature were noted in low- and mid-dose animals. A significant shortening of PR interval for up to 6 hours post dose (up to 21% shorter) was noted in high dose animals compared to vehicle control animals. The study report states that these changes in the PR interval were considered to be a consequence of the increases in heart rate. No treatment-related effects on PR interval were noted in low- and mid-dose animals. A slight increase in lengthening of the

QRS complex for up to 18 hours post-dose (up to 9% or 3.2 msec during hour 3) was noted in high-dose animals compared to vehicle control animals. No treatment related effects on QRS complex were noted in low and mid dose animals. A significant shortening of the RR interval for up to 6 hours post dose (up to 54% shorter during hour 2) was noted in high dose animals compared to vehicle control animals. The study report states that these changes in the RR interval were considered to be a consequence of the increases in heart rate. No treatment related effects on RR interval were noted in low and mid dose animals. A slight prolongation of the heart rate corrected QT interval (QTcV) was noted between hours 11 – 14 (5%) and 19 – 24 (3%) in high- dose animals compared to vehicle control animals. No treatment-related effects on QTcV were noted in low- and mid-dose animals.

Acute cardiovascular effects of INCB018424 after oral administration to high-dose dogs included decreased pulse pressure, systolic, diastolic and mean arterial pressure and increased heart rate. Additional treatment-related effects noted in high-dose dogs included shortening of the RR and PR interval, which may have been related to increased heart rate. A slight lengthening of the QRS complex and corrected QT interval was noted in high dose dogs. The NOAEL for cardiovascular effects noted in male dogs following a single oral dose of INCB018424 was identified as 10 mg/kg, under the conditions of this study.

Renal effects: no study conducted

Gastrointestinal effects: no study conducted

Abuse liability: no study conducted

Reviewer comment: The maximum daily dose proposed for BID dosing of ruxolitinib phosphate would be 50 mg/day, equivalent to 29.4 mg/m²/day, based on a 1.7 m² surface area individual. The NOAEL identified in the conducted safety pharmacology studies (10-50 mg/kg or 60-300 mg/m² in rats, 10 mg/kg or 200 mg/m² in dogs) is 2-10 folds of the maximum daily dose proposed. Based on single dose toxicokinetics (rat: INCYTE-DMB-06.174.1; dog: T-07-10-07], the projected C_{max} level in female rats at the NOAEL dose of 50 mg/kg is 2.85 μM (0.51 μM unbound), and the projected C_{max} level in dogs at the NOAEL of 10 mg/kg is approximately 7.99 μM (0.77 μM unbound), which are 10.4-fold and 15.7-fold, respectively, of the C_{max} at the highest proposed therapeutic dose in humans (25 mg bid) associated with a C_{max} value of 1.48 μM (0.049 μM unbound, INCYTE-DMB-10.56.3). In addition, the adverse effects observed in the safety pharmacology studies were not noted in the repeated dose toxicology studies. Clinical studies have not recapitulated these findings at clinically relevant doses. Therefore, the potential for ruxolitinib to cause adverse alterations in respiratory, neurologic, and cardiovascular parameters in humans is considered to be low.

PHARMACOLOGY TABULATED SUMMARY

In Vitro Potency of Ruxolitinib in Cell Lines Relevant to MPNs

Cell Type	Stimulator	Measured Parameter	IC ₅₀ for ruxolitinib (mean ± standard deviation) ^a
INA-6	IL-6	STAT3 Phosphorylation	< 125 nM
	IL-6	Cell Proliferation	141 ± 43 nM
	BMSC	Cell Proliferation	185 nM
TF-1	GM-CSF	Cell Proliferation	80 ± 30 nM
Bcr-Abl TF-1	-	Cell Proliferation	> 25000 nM ^b
Ba/F3-JAK2V617F	-	JAK2/STAT5/ERK Phosphorylation	128-320 nM ^b
Ba/F3-JAK2V617F	-	Cell Proliferation	127 ± 17 nM ^b
HEL	-	STAT5 Phosphorylation	< 300 nM ^b
HEL	-	STAT3 Phosphorylation	< 300 nM ^b

INCB018424 had anti-tumor effect on the following tested cell lines
in vitro- or in vivo

IL-6 dependent INA-6 cell line (plasma cell leukemia cells)
 TF-1 (leukemia cells)
 Ba/F3-JAK2V617F cell line (murine leukemia Ba/F3 cells expressing JAK2V617F with the erythropoietin (EPO) receptor)
 HEL (human erythroleukemia cell line)
 Progenitor colonies derived from mononuclear cells from patients with PV
 INA-6 multiple myeloma mouse xenograft model
 HH human T-cell cutaneous lymphoma xenograft model, mouse
 Mouse xenograft model with cells expressing Ba/F3-JAK2V617F mutation
 22Rv1 Tumor Model, hormone refractory prostate cancer xenograft tumor model, mouse
 MM1.S Model, myeloma mouse xenograft model

5 Pharmacokinetics/ADME/Toxicokinetics**5.1 PK/ADME**

Note: PK studies conducted in minipigs are not reviewed.

Brief summary

Pharmacokinetic studies were performed in various species after either oral or intravenous administration of ruxolitinib. The PK of ruxolitinib is characterized by a rapid absorption with T_{max} value of 0.4-2 h, and a generally short terminal elimination half-life, ranging from 1.5 h to 2 h in rats and dogs. There was no accumulation with 1-month repeated daily dosing, however there was a small accumulation with 6-month

repeated daily dosing. The absolute oral bioavailability was variable across the nonclinical species, 29% in male rats and 105% in female rats, around 50% in dogs. There were generally no gender differences in exposure of ruxolitinib and its metabolites in dogs. In rats, the C_{max} and AUC values were several-fold higher in females compared to males.

In rats, after a single oral dose of ^{14}C -ruxolitinib, drug-derived radioactivity was widely distributed with highest concentration in the GI system, and no detectable levels in the CNS. Ruxolitinib was eliminated from most tissues rapidly and completely. In pregnant rats administered a single oral dose of ^{14}C -ruxolitinib, the fetal:maternal plasma and fetal tissue:maternal plasma concentration ratios were less than one for all fetal tissues indicating that fetal exposure was limited. The plasma protein binding of ruxolitinib was 3.3% in human.

Oxidation was the predominant metabolic pathways in rats and dogs. In vitro studies suggest that CYP3A4 is the predominant CYP isozyme responsible for the metabolism of ruxolitinib. Ruxolitinib is metabolized by isozymes including CYP1A2, CYP2C6 and CYP2D1 found in both male rats and female rats. In rat liver microsomes, ruxolitinib is metabolized to a greater extent in males compared to females, consistent with ruxolitinib being metabolized by the male-rat-specific isozymes CYP2C11, CYP2C13 and CYP3A2.

In rat, dog and human ^{14}C mass balance studies, elimination of drug-derived radioactivity after oral and IV dosing was similarly rapid and complete with excretion via urine, bile and feces. In rats, ruxolitinib-derived radioactivity preferentially partitions into milk with the qualitative metabolite profile being similar to plasma. Milk concentrations were less than 1% of C_{max} by 24 h. Ruxolitinib and M18 are not potent inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in human liver microsomes. In vitro data suggest that ruxolitinib is not an inducer of CYP1A2, CYP2B6 or CYP3A activity at therapeutically relevant concentrations.

Methods of Analysis

[See under individual study reviews]

Absorption

The pharmacokinetics of INCB018424 in rats

This study (study#INCYTE-DMB-06.169.1) was reviewed by Dr. Barbara Hill. The following summary is excerpted from Dr. Hill's review.

The pharmacokinetics of INCB018424 was determined in male and female rats given a single 10 mg/kg iv dose (2/sex) or a single 50 mg/kg oral dose (2/sex) of INCB018424 phosphate. The mean systemic plasma clearance of INCB018424 for males (9.4 L/hr/kg) and females (4.8 L/h/kg) were very high and approximated about 3- and 1.5- fold the hepatic blood flow in rats, respectively. The average clearance in males was about 2-fold greater than in females. The mean C_{max} and AUC values after oral administration of 50 mg/kg INCB018424 were 2.24 μM and 5.40 $\mu M \cdot hr$, respectively, in males and 30.4 μM and 39.3 $\mu M \cdot hr$, respectively, in females. This

indicates an approximately 8-fold difference in oral clearance between male and female rats. The mean AUC values after iv administration of 10 mg/kg INCB018424 were 3.75 $\mu\text{M}\cdot\text{hr}$ and 7.49 $\mu\text{M}\cdot\text{hr}$ in males and females, respectively. The mean volumes of distribution in male and female rats were 3.8 and 1.6 L/kg, respectively, indicating that INCB018424 was distributed beyond the total volume of body water (0.7 L/kg) in rats. The apparent terminal disposition half-life of INCB018424 following oral dosing (1.5 hr) was longer than following iv dosing (0.4 hr), but did not show much difference between male and female rats. The average oral bioavailability of INCB018424 was 29% in male rats and 105% in female rats.

Study title: A 6-month oral (gavage) toxicity study of INCB018424 in rats with a 6 week recovery period

Key Study Findings:

- Plasma C_{max} and AUC_{0-t} values generally increased in a dose-proportional manner at doses ≥ 15 mg/kg, but increased not in a dose-proportional manner at doses < 15 mg/kg;
- C_{max} and AUC_{0-t} values were similar on study days 0 and 27; on study day 181, C_{max} and AUC_{0-t} values were higher than values on study days 0 and 27;
- Exposures were several fold higher in females than in males;
- The T_{max} was 0.5 h for all groups, while half-life values were short and not dose dependent, ranging from 0.358 to 1.98 h

Study no.: (b) (4)-519048

Volume #, and page #: electronic submission, Module 4,

Conducting laboratory and location: (b) (4)

Date of study initiation: 1 October 2007

GLP compliance: yes

QA report: yes (x) no ()

Drug, lot #, and % purity: INCB018424

Lot number: SS-IN3-139

Purity: 99.9%

Methods

Species/strain: Rat/Crl:CD(SD)

#/sex/group: 5/sex for control, 11/sex/group for treatment group

Schedule: once daily for 182 days

Doses in administered units: 0, 5, 10, 20/15 mg/kg, at the dose volume of 10 mL/kg

Route: oral gavage

Blood samples collection: prior to dosing and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours
after dose administration on study days 0, 27 and 181

Results: The table below is excerpted from the sponsor's application
Summary of INCB018424 Toxicokinetics in Male and Female Rats Given Daily Oral
Doses of 5, 15, 30 and 60 mg/kg of INCB018424

Gender	Day	Parameter	5 mg/kg	15 mg/kg	30 mg/kg	60 mg/kg
Male	0*	C _{max} (μM)	0.0116	0.0918	0.209	0.501
		T _{max} (h)	0.500	0.500	0.500	0.500
		AUC _{0-∞}	0.00823	0.0902	0.298	1.07
		t _{1/2} (h)	NC	0.358	1.07	0.787
	27	C _{max} (μM)	0.0139	0.0707	0.188	0.400
		T _{max} (h)	0.500	0.500	0.500	0.500
		AUC _{0-∞}	0.00919	0.0924	0.237	0.720
		t _{1/2} (h)	NC	0.887	1.94	0.899
	181	C _{max} (μM)	0.0492	0.165	0.445	0.707
		T _{max} (h)	0.500	0.500	0.500	0.500
		AUC _{0-∞}	0.0533	0.296	0.662	1.32
		t _{1/2} (h)	1.04	1.33	1.11	1.77
Female	0*	C _{max} (μM)	0.0968	0.660	2.83	3.03
		T _{max} (h)	0.500	0.500	0.500	0.500
		AUC _{0-∞}	0.113	0.832	3.33	14.1
		t _{1/2} (h)	0.931	1.98	1.22	1.07
	27	C _{max} (μM)	0.116	0.821	1.11	2.65
		T _{max} (h)	0.500	0.500	0.500	0.500
		AUC _{0-∞}	0.130	1.03	2.41	10.1
		t _{1/2} (h)	0.829	1.10	1.26	1.15
	181	C _{max} (μM)	0.209	1.72	4.98	6.11
		T _{max} (h)	0.500	0.500	0.500	0.500
		AUC _{0-∞}	0.361	2.33	7.40	25.8
		t _{1/2} (h)	1.79	1.66	1.47	1.40

* = Day 0 corresponds with the first day of dosing
NC = not calculated due to insufficient time points to determine the terminal phase

Study Title: Pharmacokinetics of INCB018424 in Dogs

Key Study Finding:

- The time profile following oral dosing was similar to that with IV dosing;
- The disposition half-life of INCB018424 was about same in both the PO and IV groups;
- The systemic plasma clearance was 0.48 L/hr/kg
- The bioavailability was 57% if plasma exposure was considered to increase in proportional manner with the dose escalation (see reviewer's comment below).

Study no: INCYTE-DMB-06.182.1

Volume #, and page #: electronic submission, page 1-9

Conducting laboratory and location: (b) (4)

Date of study initiation: July 10, 2006

GLP compliance: no, (no information provided)

QA report: yes () no (x)

Drug, lot #, radiolabel, and % purity: INCB018424

Lot No.: SS-IN2-175

Purity: not provided

Formulation/vehicle:

IV study-1 mg/mL of INCB018424 in normal saline,

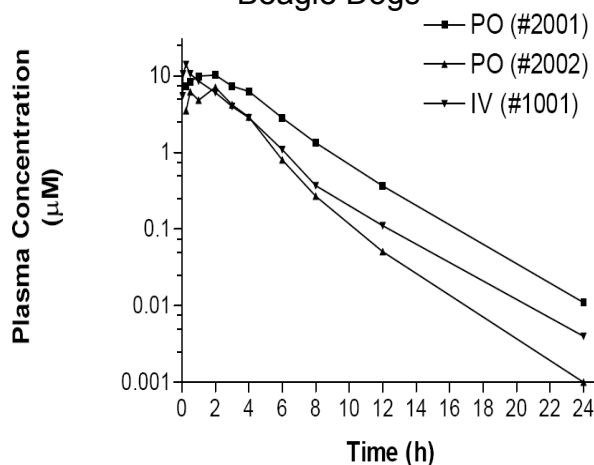
PO study-2 mg/mL of INCB018424 in 0.5% methylcellulose aqueous

solution

Methods: Two male beagle dogs were given a single PO dose of 10 mg/kg and one male beagle dog was given a single IV dose of 5 mg/kg of INCB018424 (free base

equivalent). Blood samples were collected at predose, 15 min, 30 min, 1, 2, 3, 4, 6, 8, 12 and 24 h post-dose in the PO group, and predose, 2.5, 5, 15, 30 min, 1, 2, 3, 4, 6, 8, 12 and 24 h post-dose in the IV group. Analyses for ruxolitinib concentrations in plasma were conducted by liquid chromatographic tandem mass spectrometry (LC-MS/MS). The plasma concentration-time data was used to determine the pharmacokinetic parameters by standard non-compartmental methods using WinNonlin® version 5.0.1

Results: The following figures were copied from the sponsor's submission
Plasma Concentration-Time Profile Following IV (5 mg/kg) or PO (10 mg/kg) Dosing in Beagle Dogs



PK parameters

Plasma Concentrations (µM) and Pharmacokinetics of INCB018424 in Beagle dogs
Given a 10 mg/kg PO Dose or 5 mg/kg IV Dose of INCB018424

PO			IV		
Time (h)	#2001	#2002	Mean	Time (h)	#1001
0	BQL	BQL	BQL	0	BQL
0.25	7.41	3.51	5.46	0.042	5.52
0.5	8.47	6.21	7.34	0.083	10.7
1.0	9.98	4.83	7.41	0.25	14.2
2.0	10.3	7.11	8.71	0.5	10.7
3.0	7.37	4.21	5.79	1.0	8.62
4.0	6.31	2.92	4.62	2.0	6.12
6.0	2.84	0.802	1.82	3.0	4.00
8.0	1.34	0.273	0.807	4.0	2.86
12	0.367	0.051	0.209	6.0	1.09
24	0.011	0.001	0.006	8.0	0.370
				12	0.111
				24	0.004
C_{max} (μM)	10.3	7.11	8.71	AUC ($\mu\text{M}^*\text{h}$)	34.1
T_{max} (h)	2.0	2.0	2.0	CL (L/h/kg)	0.48
AUC* ($\mu\text{M}^*\text{h}$)	52.3	25.4	38.9	V_{ss} (L/kg)	1.1
$T_{1/2}$ (h)	2.3	2.1	2.2	$T_{1/2}$ (h)	2.5
F (%)	77	37	57	% dose in urine [#]	<1

BQL, below quantifiable limit of 0.001 μM ; [#] As unchanged parent

Reviewer comment:

It appears that the sponsor compared the $\frac{1}{2}$ of the AUC from 10 mg/kg oral dosing to the AUC from 5 mg/kg IV dosing to determine bioavailability (57%). Considering the sample size and the PK profile from other conducted studies showing that AUC was not increased in a proportional manner with dose escalation, therefore the bioavailability claimed by the sponsor (57%) may not accurate by using above calculating method.

Study title: A 6-month oral (gavage) toxicity study with INCB018424 in beagle dogs with 6-week recovery period

Key Study Findings:

- Plasma C_{max} and AUC generally increased in a dose proportional manner at doses ≤ 5 mg/kg, increased greater than dose proportional escalation at dose > 5 mg/kg in both males and females;
- C_{max} and AUC values were generally similar on study days 0 and 40, but higher on study day 175;
- The mean T_{max} and half-life values were generally similar for all dose groups ranging from 0.500 to 1.17 hours and 0.640 to 2.09 hours, respectively;
- TK parameters were generally comparable between males and females

Study no.: (b) (4)-519049

Volume #, and page #: electronic submission, Module 4,

Conducting laboratory and location: (b) (4)

Date of study initiation: 26 September 2007

GLP compliance: yes

QA report: yes (x) no ()

Drug, lot #, and % purity: INCB018424

Lot number: SS-IN3-139

Purity: 99.9%

Methods

Species/strain: Beagle dogs

#/sex/group: 7/sex/group

Schedule: daily for a total 6 months

Doses in administered units: 0.5, 2.5, 5.0 and 10 mg/kg/day

Route: oral gavage

Blood samples collection: prior to dosing and at 0.5, 1, 2, 4, 8, 12 and 24 hours after dose administration on study days 0, 40 and 175

Results: The following summary table was excerpted from the Sponsor's application

Summary of INCB018424 Toxicokinetics in Male and Female Beagle Dogs Given Daily Oral Doses of 0.5, 2.5, 5 or 10 mg/kg of INCB018424

Gender	Day ^a	Parameter	Mean ± SD (N=7)			
			0.5 mg/kg	2.5 mg/kg	5 mg/kg	10 mg/kg ^c
Male	0	C _{max} (μM)	0.515 ± 0.32	2.24 ± 0.72	3.90 ± 1.5	7.99 ± 3.6
		T _{max} (h)	0.500 ± 0.0	0.500 ± 0.0	0.571 ± 0.19	0.714 ± 0.27
		AUC _{0-t} (μM*h)	0.752 ± 0.67	2.79 ± 0.96	7.38 ± 2.4	18.3 ± 6.4
		t _{1/2} (h)	NC	0.640 ± 0.14	0.818 ± 0.13	1.21 ± 0.16
	40	C _{max} (μM)	0.471 ± 0.14	1.94 ± 0.36	3.51 ± 0.98	9.70 ± 3.3
		T _{max} (h)	0.500 ± 0.0	0.500 ± 0.0	0.643 ± 0.24	0.714 ± 0.27
		AUC _{0-t} (μM*h)	0.690 ± 0.52	2.75 ± 0.71	8.29 ± 2.4	27.5 ± 9.6
		t _{1/2} (h)	NC	0.705 ± 0.17	1.04 ± 0.20	1.31 ± 0.36
	175	C _{max} (μM)	0.627 ± 0.23	3.01 ± 0.63	6.19 ± 0.79	15.0 ± 7.0
		T _{max} (h)	0.500 ± 0.0	0.643 ± 0.24	0.857 ± 0.24	1.17 ± 0.41
		AUC _{0-t} (μM*h)	1.16 ± 0.49	7.54 ± 2.0	18.3 ± 5.8	72.8 ± 55
		t _{1/2} (h)	0.923 ± 0.26	1.16 ± 0.21	1.22 ± 0.25	2.09 ± 0.82
Female	0	C _{max} (μM)	0.491 ± 0.26	2.35 ± 1.1	4.24 ± 0.55	7.67 ± 2.4
		T _{max} (h)	0.500 ± 0.0	0.500 ± 0.0	0.500 ± 0.0	0.571 ± 0.19
		AUC _{0-t} (μM*h)	0.621 ± 0.48	4.16 ± 2.4	6.35 ± 2.0	21.0 ± 11
		t _{1/2} (h)	NC	0.936 ± 0.32	0.686 ± 0.17	1.19 ± 0.41
	40	C _{max} (μM)	0.448 ± 0.25	2.14 ± 0.82	3.87 ± 0.99	9.53 ± 3.8
		T _{max} (h)	0.571 ± 0.19	0.500 ± 0.0	0.500 ± 0.0	0.786 ± 0.27
		AUC _{0-t} (μM*h)	0.663 ± 0.49	3.63 ± 2.0	6.19 ± 1.5	26.3 ± 17
		t _{1/2} (h)	NC	0.846 ± 0.24	0.752 ± 0.16	1.23 ± 0.44
	175	C _{max} (μM)	0.588 ± 0.19	3.48 ± 1.1	4.46 ± 0.89	11.5 ± 7.3
		T _{max} (h)	0.571 ± 0.19	0.643 ± 0.24	0.786 ± 0.27	0.917 ± 0.20
		AUC _{0-t} (μM*h)	1.07 ± 0.72	8.10 ± 3.9	11.0 ± 2.2	38.8 ± 22
		t _{1/2} (h)	0.965 ± 0.22 ^b	1.08 ± 0.24	1.09 ± 0.21	1.48 ± 0.28

NC: Not calculated due to insufficient time points in the terminal phase in > 4 dogs in this group

a: Day 0 was the first day of dosing

b: N=5; two dogs had insufficient time points in the terminal phase to calculate t_{1/2}

c: N=6 for Day 175

Study title: 52-week oral gavage chronic toxicity and toxicokinetic study with INCB018424 in dogs with a 6-week recovery period

Key Study Findings:

- The mean plasma C_{max} and AUC values generally increased dose proportionally or slightly greater between 0.75 and 6 mg/kg;
- The C_{max} values on Day 1 and after multiple dosing were similar, while AUC values after multiple dosing were slightly higher at all doses in male dogs, but only at 6 mg/kg in females;
- The terminal half-life values were not dose-dependent and were slightly increase with multiple dosings;
- The mean T_{max} Were generally similar for all dose groups ranging from 0.500 to 1.14 hours;
- TK parameters were generally comparable between males and females

Note: The AUC values in this study were consistent with corresponding values from the 6 month study

Study no.: 7456-271

Volume #, and page #: electronic submission, Module 4,

Conducting laboratory and location:

(b) (4)

Date of study initiation: 02 July 2008

GLP compliance: yes

QA report: yes (x) no ()

Drug, lot #, and % purity: INCB018424

Lot number: BPR-07-101-B2-21

Purity: 97.89%

Methods

Species/strain: Beagle dogs

#/sex/group: 7/sex/group

Schedule: daily for a total 52 weeks

Doses in administered units: 0.75, 1.5, 3, and 6 mg/kg/day

Route: oral gavage

Toxicokinetic analysis: Day 1 and during Weeks 4, 13, 26, and 52 of the dosing phase. All animals will be bled predose (within 1 hour of dosing) and approximately 0.5, 1, 2, 4, 8, 12, and 24 hour postdose.

Results: The following summary table was excerpted from the Sponsor's application

Summary of INCB018424 Toxicokinetics in Male Beagle Dogs Given
Daily Oral Doses of 0.75, 1.5, 3 or 6 mg/kg of INCB018424

Gender	Day	Parameter	Mean ± SD (N=7)			
			0.75 mg/kg	1.5 mg/kg	3 mg/kg	6 mg/kg
Male	1	C _{max} (µM)	0.310 ± 0.13	0.486 ± 0.39	1.06 ± 0.62	3.97 ± 2.3
		T _{max} (h)	0.500 ± 0.0	0.500 ± 0.0	0.500 ± 0.0	0.571 ± 0.19
		AUC ₀₋₄ (µM*h)	0.463 ± 0.20	0.833 ± 0.75	2.31 ± 1.9	9.38 ± 8.1
		AUC ₀₋₂₄ (µM*h)	0.541 ± 0.21	0.897 ± 0.80	2.39 ± 1.9	9.61 ± 8.1
		t _{1/2} (h)	1.16 ± 0.54	0.985 ± 0.40 ^a	1.29 ± 0.67	1.02 ± 0.40
	28	C _{max} (µM)	0.262 ± 0.044	0.399 ± 0.24	0.958 ± 0.29	2.29 ± 1.5
		T _{max} (h)	0.571 ± 0.19	0.643 ± 0.24	0.643 ± 0.24	1.14 ± 0.63
		AUC ₀₋₄ (µM*h)	0.605 ± 0.19	1.15 ± 0.82	3.10 ± 1.4	11.0 ± 10
		AUC ₀₋₂₄ (µM*h)	0.673 ± 0.21	1.20 ± 0.82	3.21 ± 1.5	11.4 ± 10
		t _{1/2} (h)	1.58 ± 0.41	1.33 ± 0.20	1.73 ± 0.37	1.95 ± 0.87
	87	C _{max} (µM)	0.294 ± 0.19	0.663 ± 0.31	1.74 ± 0.82	3.11 ± 1.7
		T _{max} (h)	0.643 ± 0.24	0.643 ± 0.24	0.500 ± 0.0	1.14 ± 0.63
		AUC ₀₋₄ (µM*h)	0.745 ± 0.46	1.86 ± 1.4	6.46 ± 2.8	15.9 ± 12
		AUC ₀₋₂₄ (µM*h)	0.784 ± 0.48	2.00 ± 1.4	6.59 ± 2.8	16.7 ± 13
		t _{1/2} (h)	1.45 ± 0.49 ^a	1.46 ± 0.43	1.63 ± 0.21	2.02 ± 0.60
176 ^b	C _{max} (µM)	0.326 ± 0.096	0.569 ± 0.25	1.49 ± 0.91	4.03 ± 1.6	
	T _{max} (h)	0.571 ± 0.19	0.571 ± 0.19	0.643 ± 0.24	1.10 ± 0.55	
	AUC ₀₋₄ (µM*h)	0.953 ± 0.21	2.13 ± 1.5	5.84 ± 3.3	18.5 ± 9.7	
	AUC ₀₋₂₄ (µM*h)	1.02 ± 0.23	2.23 ± 1.7	6.08 ± 3.4	19.4 ± 10	
	t _{1/2} (h)	1.92 ± 0.73	2.07 ± 0.60	2.07 ± 0.68	2.01 ± 0.68	
357 ^c	C _{max} (µM)	0.398 ± 0.12	0.630 ± 0.26	1.32 ± 0.57	4.91 ± 1.6	
	T _{max} (h)	0.786 ± 0.27	0.929 ± 0.53	1.00 ± 0.50	0.875 ± 0.75	
	AUC ₀₋₄ (µM*h)	1.12 ± 0.36	2.27 ± 1.2	5.90 ± 3.1	16.5 ± 8.4	
	AUC ₀₋₂₄ (µM*h)	1.21 ± 0.37	2.36 ± 1.2	6.23 ± 3.2	16.8 ± 8.4	
	t _{1/2} (h)	1.68 ± 0.73	1.89 ± 0.19	2.48 ± 1.0	1.57 ± 0.37	

a: N=6; one dog had insufficient time points in the terminal phase to calculate t_{1/2}
b: For 6 mg/kg group, N=5
c: Day 196 for 6 mg/kg (N=4)

Summary of INCB018424 Toxicokinetics in Female Beagle Dogs Given
Daily Oral Doses of 0.75, 1.5, 3 or 6 mg/kg of INCB018424

Gender	Day	Parameter	Mean $\pm$ SD (N=7)			
			0.75 mg/kg	1.5 mg/kg	3 mg/kg	6 mg/kg
Male	1	C _{max} (μ M)	0.511 $\pm$ 0.29	0.798 $\pm$ 0.62	1.68 $\pm$ 0.77	3.47 $\pm$ 1.1
		T _{max} (h)	0.571 $\pm$ 0.19	0.786 $\pm$ 0.57	0.714 $\pm$ 0.57	0.643 $\pm$ 0.24
		AUC ₀₋₄ (μ M*h)	0.983 $\pm$ 0.58	1.78 $\pm$ 1.7	5.28 $\pm$ 4.3	8.58 $\pm$ 5.3
		AUC ₀₋₂₄ (μ M*h)	1.05 $\pm$ 0.59	1.87 $\pm$ 1.7	5.38 $\pm$ 4.3	8.94 $\pm$ 5.8
		t _{1/2} (h)	1.04 $\pm$ 0.57	1.20 $\pm$ 0.22	1.14 $\pm$ 0.22	1.42 $\pm$ 0.87
		28	C _{max} (μ M)	0.280 $\pm$ 0.10	0.518 $\pm$ 0.37	1.10 $\pm$ 0.59
	T _{max} (h)		0.714 $\pm$ 0.27	0.571 $\pm$ 0.19	1.00 $\pm$ 0.71	0.714 $\pm$ 0.27
	AUC ₀₋₄ (μ M*h)		0.785 $\pm$ 0.34	1.38 $\pm$ 0.91	4.84 $\pm$ 2.7	8.74 $\pm$ 3.5
	AUC ₀₋₂₄ (μ M*h)		0.855 $\pm$ 0.38	1.47 $\pm$ 0.89	5.08 $\pm$ 2.7	9.06 $\pm$ 3.8
	t _{1/2} (h)		1.59 $\pm$ 0.48	1.83 $\pm$ 0.64	2.31 $\pm$ 1.1	1.84 $\pm$ 0.44
	87	C _{max} (μ M)	0.328 $\pm$ 0.13	0.552 $\pm$ 0.25	1.76 $\pm$ 0.50	3.31 $\pm$ 1.0
		T _{max} (h)	0.643 $\pm$ 0.24	0.571 $\pm$ 0.19	0.929 $\pm$ 0.53	0.786 $\pm$ 0.57
		AUC ₀₋₄ (μ M*h)	0.828 $\pm$ 0.45	1.82 $\pm$ 1.2	7.15 $\pm$ 3.8	13.1 $\pm$ 4.5
		AUC ₀₋₂₄ (μ M*h)	0.878 $\pm$ 0.46	1.91 $\pm$ 1.2	7.46 $\pm$ 4.0	13.5 $\pm$ 4.8
		t _{1/2} (h)	1.46 $\pm$ 0.46	1.73 $\pm$ 0.31	1.94 $\pm$ 0.49	1.72 $\pm$ 0.57
176	C _{max} (μ M)	0.304 $\pm$ 0.15	0.578 $\pm$ 0.19	1.41 $\pm$ 0.96	3.57 $\pm$ 2.4	
	T _{max} (h)	0.857 $\pm$ 0.24	0.643 $\pm$ 0.24	0.714 $\pm$ 0.27	0.857 $\pm$ 0.24	
	AUC ₀₋₄ (μ M*h)	1.06 $\pm$ 0.56	2.33 $\pm$ 1.1	6.59 $\pm$ 5.5	17.6 $\pm$ 8.8	
	AUC ₀₋₂₄ (μ M*h)	1.14 $\pm$ 0.57	2.48 $\pm$ 1.1	6.83 $\pm$ 5.7	19.1 $\pm$ 9.4	
	t _{1/2} (h)	2.17 $\pm$ 0.88	2.41 $\pm$ 0.54	1.84 $\pm$ 0.53	3.21 $\pm$ 3.1	
357 ^b	C _{max} (μ M)	0.304 $\pm$ 0.26	0.844 $\pm$ 0.33	1.29 $\pm$ 0.51	3.90 $\pm$ 1.4	
	T _{max} (h)	1.00 $\pm$ 0.55 ^a	0.786 $\pm$ 0.27	0.786 $\pm$ 0.57	0.833 $\pm$ 0.26	
	AUC ₀₋₄ (μ M*h)	0.515 $\pm$ 0.69	2.22 $\pm$ 1.6	4.30 $\pm$ 2.7	16.4 $\pm$ 7.3	
	AUC ₀₋₂₄ (μ M*h)	0.688 $\pm$ 0.83	2.57 $\pm$ 1.6	4.83 $\pm$ 2.9	17.1 $\pm$ 7.7	
	t _{1/2} (h)	1.44 $\pm$ 0.15 ^c	1.50 $\pm$ 0.41	1.90 $\pm$ 0.86	2.00 $\pm$ 0.50	

a: N=6; could not be calculated for one dog due to insufficient time points

b: For 6 mg/kg group, N=6

c: N=4; could not be calculated for three dogs due to insufficient time points

Distribution**Quantitative whole-body autoradiography of rats following oral administration of ¹⁴C-INCB018424****Key Study Findings:**

- Radioactivity was mainly in the liver, bile, large intestine, small intestine, and uveal tract in both male and female rats; relative high exposure of radiation was also noted in the adrenal gland, renal cortex and renal medulla in female rats;
- Highest concentration of radiation in tissues was observed at 2 hours postdose;
- Radioactivity concentrations in central nervous system tissues (cerebellum, cerebrum, medulla, olfactory lobe, and spinal cord) were not measurable at any sampling time;
- Fecal, hepatobiliary, and renal excretion were indicated as elimination pathways;
- In general, elimination of administered radioactivity was rapid in most tissues, most tissue concentrations were below the limit of quantitation at 24 hours postdose and no ¹⁴C-INCB018424-derived radioactivity was detected by 336 hours postdose;
- Low concentrations of ¹⁴C-INCB018424-derived radioactivity were measured in the testis and accessory sex organs of male rats and the ovary and uterus of female rats, but concentrations were below the limit of quantitation by 8 hours postdose;
- Peak tissue concentrations of radioactivity tended to be higher in female rats than males, consistent with higher peak blood and plasma levels;
- The maximum blood and plasma concentrations of ¹⁴C-INCB018424-derived radioactivity were measured at 2 hours postdose, and declined steadily throughout the experimental timeframe. Blood radioactivity was not partitioned preferentially in plasma;
- Percentage of dosed radioactivity in blood and tissues was 80% in males and 53% in females at 8 hours postdose

Study no: (b) (4) 7456-241**Volume #, and page #:** electronic submission, page 1-103**Conducting laboratory and location:** (b) (4)**Date of study initiation:** September 13, 2007**GLP compliance:** yes**QA report:** yes (x) no ()**Drug, lot #, radiolabel, and % purity:** ¹⁴C-INCB018424

Lot No.: 3562192

Purity: 96.8% (radiochemical purity)

INCB018424

Lot No.: SS-IN2-175

Purity: not provided

Formulation/vehicle: 0.5% methylcellulose in reverse osmosis water

Methods:*Group Designations and Dose Levels*

Group	Number of Animals		Dose Route	Target Dose Level (mg/kg)	Target Dose Volume (mL/kg)	Samples Collected
	Male	Female				
1	5 LE	5 LE	Oral	25	10	Carcass for WBA

LE Long Evans, pigmented rats

WBA Whole-body autoradiography.

Note: The dose was approximately 100 μ Ci/kg.

One animal/sex/time point was sacrificed at 2, 8, 24, 168, and 336 hours postdose. Blood was collected and plasma was harvested at specified time points and carcasses were prepared for quantitative whole-body autoradiography (QWBA). Blood and plasma were analyzed for concentrations of radioactivity using liquid scintillation counting (LSC). Exposed screens were scanned using a Storm scanner for QWBA.

Dosing:

Species/strain: Long Evans, pigmented rats (HsdBlu:LE)

#/sex/group or time point: 5/sex

Weight: 179-199 g

Doses in administered units: 25 mg/kg, 100 μ Ci

Route, form, volume, and infusion rate: oral gavage at dose volume of 10 mL/kg

Results: The following tables are excerpted from Applicant's submission

Concentrations of radioactivity in blood and tissues determined by whole-body autoradiography at specified times after a single oral administration of ¹⁴C-INCB018424 to male rats (Group 1, 25 mg/kg)

Matrix	ng Equivalents ¹⁴ C-INCB018424/g				
	Animal Number (Sacrifice Time)				
	B05630 (2 Hours)	B05631 (8 Hours)	B05632 (24 Hours)	B05633 (168 Hours)	B05634 (336 Hours)
Adrenal gland	2120	ND	ND	ND	ND
Bile	30200	ND	ND	ND	ND
Blood	ND	ND	ND	ND	ND
Bone	BLQ	ND	ND	ND	ND
Bone marrow	950	ND	ND	ND	ND
Cecum	5710	121000	ND	ND	ND
Cecum contents	91500	498000	1550	ND	ND
Cerebellum	BLQ	ND	ND	ND	ND
Cerebrum	BLQ	ND	ND	ND	ND
Diaphragm	1420	ND	ND	ND	ND
Epididymis	1080	ND	ND	ND	ND
Esophageal contents	1400	ND	ND	ND	ND
Esophagus	5010	ND	ND	ND	ND
Exorbital lacrimal gland	754	ND	ND	ND	ND
Eye	2170	852	BLQ	BLQ	ND
Eye (lens)	BLQ	BLQ	BLQ	ND	ND
Fat (abdominal)	BLQ	ND	ND	ND	ND
Fat (brown)	844	ND	ND	ND	ND
Harderian gland	1010	ND	ND	ND	ND
Intra-orbital lacrimal gland	1030	ND	ND	ND	ND
Kidney	5420	673	ND	ND	ND
Large intestinal contents	1060	634000	4060	ND	ND
Large intestine	10500	31400	ND	ND	ND
Liver	9710	2140	BLQ	ND	ND
Lung	1060	ND	ND	ND	ND
Lymph nodes	ND	ND	ND	ND	ND
Medulla	BLQ	ND	ND	ND	ND
Muscle	1460	ND	ND	ND	ND
Myocardium	ND	ND	ND	ND	ND
Nasal turbinates	613	ND	ND	ND	ND
Olfactory lobe	BLQ	ND	ND	ND	ND
Pancreas	1550	BLQ	ND	ND	ND
Pituitary gland	835	ND	ND	ND	ND
Preputial gland	1410	590	ND	ND	ND

BLQ Below the limit of quantitation (<398 ng equivalents ¹⁴C-INCB018424/g).

ND Not detectable (sample not discernible from background or surrounding tissue)

Note: ng Equivalent/g values are reported to three significant figures with a maximum of three decimal places.

Continued from last page

Matrix	ng Equivalents ¹⁴ C-INCB018424/g				
	Animal Number (Sacrifice Time)				
	B05630 (2 Hours)	B05631 (8 Hours)	B05632 (24 Hours)	B05633 (168 Hours)	B05634 (336 Hours)
Prostate	1240	ND	ND	ND	ND
Renal cortex	4910	ND	ND	ND	ND
Renal medulla	5950	ND	ND	ND	ND
Salivary gland	1250	ND	ND	ND	ND
Seminal vesicle	1080	ND	ND	ND	ND
Skin (nonpigmented)	1300	ND	ND	ND	ND
Skin (pigmented)	5860	3310	1400	ND	ND
Small intestinal contents	3980000 ^a	26700	ND	ND	ND
Small intestine	104000	1370	ND	ND	ND
Spinal cord	BLQ	ND	ND	ND	ND
Spleen	1190	ND	ND	ND	ND
Stomach	1910	ND	ND	ND	ND
Stomach contents	65000	ND	BLQ	ND	ND
Testis	753	ND	ND	ND	ND
Thymus	1120	ND	ND	ND	ND
Thyroid	ND	ND	ND	ND	ND
Urinary bladder	ND	ND	ND	ND	ND
Urine	46600	ND	ND	ND	ND
Uveal tract	14400	6240	3320	1090	ND

BLQ Below the limit of quantitation (<398 ng equivalents ¹⁴C-INCB018424/g).

ND Not detectable (sample not discernible from background or surrounding tissue)

Note: ng Equivalent/g values are reported to three significant figures with a maximum of three decimal places.

a One or more samples were above the upper limit of quantitation (>2230000 ng equivalents ¹⁴C-INCB018424/g).

Concentrations of radioactivity in blood and tissues determined by whole-body autoradiography at specified times after a single oral administration of ¹⁴C-INCB018424 to female rats (Group 1, 25 mg/kg)

Matrix	ng Equivalents ¹⁴ C-INCB018424/g				
	Animal Number (Sacrifice Time)				
	B05635 (2 Hours)	B05636 (8 Hours)	B05637 (24 Hours)	B05638 (168 Hours)	B05639 (336 Hours)
Adrenal gland	12200	409	ND	ND	ND
Bile	111000	ND	ND	ND	ND
Blood	3200	ND	ND	ND	ND
Bone	492	ND	ND	ND	ND
Bone marrow	3060	ND	ND	ND	ND
Cecum	15700	58900	ND	ND	ND
Cecum contents	73400	329000	7220	ND	ND
Cerebellum	BLQ	ND	ND	ND	ND
Cerebrum	BLQ	ND	ND	ND	ND
Diaphragm	5120	ND	ND	ND	ND
Esophageal contents	35100	ND	ND	ND	ND
Esophagus	5500	ND	ND	ND	ND
Exorbital lacrimal gland	5010	ND	ND	ND	ND
Eye	2910	1010	477	BLQ	ND
Eye (lens)	BLQ	BLQ	BLQ	ND	ND
Fat (abdominal)	515	ND	ND	ND	ND
Fat (brown)	5120	ND	ND	ND	ND
Harderian gland	5320	ND	ND	ND	ND
Intra-orbital lacrimal gland	4630	ND	ND	ND	ND
Kidney	18700	1020	ND	ND	ND
Large intestinal contents	1330	415000	9480	ND	ND
Large intestine	14600	27300	ND	ND	ND
Liver	25300	3070	449	ND	ND
Lung	3520	ND	ND	ND	ND
Lymph nodes	4050	ND	ND	ND	ND
Medulla	BLQ	ND	ND	ND	ND
Muscle	4160	ND	ND	ND	ND
Myocardium	5980	ND	ND	ND	ND
Nasal turbinates	2440	ND	ND	ND	ND
Olfactory lobe	BLQ	ND	ND	ND	ND
Ovary	1850	ND	ND	ND	ND
Pancreas	5920	ND	ND	ND	ND
Pituitary gland	4450	ND	ND	ND	ND
Preputial gland	3510	ND	ND	ND	ND

BLQ Below the limit of quantitation (<398 ng equivalents ¹⁴C-INCB018424/g).

ND Not detectable (sample not discernible from background or surrounding tissue).

Note: ng Equivalent/g values are reported to three significant figures with a maximum of three decimal places.

Continued from last page

Matrix	ng Equivalents ¹⁴ C-INCB018424/g				
	Animal Number (Sacrifice Time)				
	B05635 (2 Hours)	B05636 (8 Hours)	B05637 (24 Hours)	B05638 (168 Hours)	B05639 (336 Hours)
Renal cortex	19500	1120	ND	ND	ND
Renal medulla	15900	739	ND	ND	ND
Salivary gland	5520	ND	ND	ND	ND
Skin (nonpigmented)	4680	ND	ND	ND	ND
Skin (pigmented)	6120	ND	ND	ND	ND
Small intestinal contents	2890000 ^a	16400	ND	ND	ND
Small intestine	98500	ND	ND	ND	ND
Spinal cord	BLQ	ND	ND	ND	ND
Spleen	4400	ND	ND	ND	ND
Stomach	7660	ND	ND	ND	ND
Stomach contents	363000	1010	ND	ND	ND
Thymus	4070	ND	ND	ND	ND
Thyroid	4140	ND	ND	ND	ND
Urinary bladder	ND	ND	ND	ND	ND
Urine	138000	7150	ND	ND	ND
Uterus	3690	ND	ND	ND	ND
Uveal tract	19000	7360	3630	2350	ND

BLQ Below the limit of quantitation (<398 ng equivalents ¹⁴C-INCB018424/g).

ND Not detectable (sample not discernible from background or surrounding tissue).

Note: ng Equivalent/g values are reported to three significant figures with a maximum of three decimal places.

a One or more samples were above the upper limit of quantitation (>2230000 ng equivalents ¹⁴C-INCB018424/g).

Percent of radioactive dose in blood and tissues determined by whole-body
autoradiography at specified times after a single oral administration of
¹⁴C-INCB018424 to male rats (Group 1, 25 mg/kg)

Matrix	Percent of Radioactive Dose				
	Animal Number (Sacrifice Time)				
	B05630 (2 Hours)	B05631 (8 Hours)	B05632 (24 Hours)	B05633 (168 Hours)	B05634 (336 Hours)
Adrenal gland	0.00	NA	NA	NA	NA
Bile	NA	NA	NA	NA	NA
Blood	NA	NA	NA	NA	NA
Bone	NA	NA	NA	NA	NA
Bone marrow	0.01	NA	NA	NA	NA
Cecum	0.08	1.72	NA	NA	NA
Cecum contents	8.08	44.41	0.14	NA	NA
Cerebellum	NA	NA	NA	NA	NA
Cerebrum	NA	NA	NA	NA	NA
Diaphragm	NA	NA	NA	NA	NA
Epididymis	0.01	NA	NA	NA	NA
Esophageal contents	NA	NA	NA	NA	NA
Esophagus	NA	NA	NA	NA	NA
Exorbital lacrimal gland	NA	NA	NA	NA	NA
Eye	0.01	0.00	NA	NA	NA
Eye (lens)	NA	NA	NA	NA	NA
Fat (abdominal)	NA	NA	NA	NA	NA
Fat (brown)	0.00	NA	NA	NA	NA
Harderian gland	0.00	NA	NA	NA	NA
Intra-orbital lacrimal gland	NA	NA	NA	NA	NA
Kidney	0.18	0.02	NA	NA	NA
Large intestinal contents	0.05	27.53	0.18	NA	NA
Large intestine	0.28	0.85	NA	NA	NA
Liver	1.90	0.42	NA	NA	NA
Lung	0.02	NA	NA	NA	NA
Lymph nodes	NA	NA	NA	NA	NA
Medulla	NA	NA	NA	NA	NA
Muscle	2.57	NA	NA	NA	NA
Myocardium	NA	NA	NA	NA	NA
Nasal turbinates	NA	NA	NA	NA	NA
Olfactory lobe	NA	NA	NA	NA	NA
Pancreas	0.02	NA	NA	NA	NA
Pituitary gland	0.00	NA	NA	NA	NA
Preputial gland	0.00	0.00	NA	NA	NA

NA Not applicable.
SD Standard deviation

Continued from last page

Matrix	Percent of Radioactive Dose				
	Animal Number (Sacrifice Time)				
	B05630 (2 Hours)	B05631 (8 Hours)	B05632 (24 Hours)	B05633 (168 Hours)	B05634 (336 Hours)
Prostate	0.00	NA	NA	NA	NA
Renal cortex	0.16	NA	NA	NA	NA
Renal medulla	0.20	NA	NA	NA	NA
Salivary gland	0.01	NA	NA	NA	NA
Seminal vesicle	0.01	NA	NA	NA	NA
Skin (nonpigmented)	1.19	NA	NA	NA	NA
Skin (pigmented)	5.36	3.06	1.32	NA	NA
Small intestinal contents	314.56 ^a	2.13	NA	NA	NA
Small intestine	8.86	0.12	NA	NA	NA
Spinal cord	NA	NA	NA	NA	NA
Spleen	0.01	NA	NA	NA	NA
Stomach	0.04	NA	NA	NA	NA
Stomach contents	6.67	NA	NA	NA	NA
Testis	0.03	NA	NA	NA	NA
Thymus	0.01	NA	NA	NA	NA
Thyroid	NA	NA	NA	NA	NA
Urinary bladder	NA	NA	NA	NA	NA
Urine	NA	NA	NA	NA	NA
Uveal tract	0.05	0.02	0.01	0.00	NA
Total	350.38 ^a	80.28	1.65	0.00	0.00

NA Not applicable.

SD Standard deviation.

a One or more samples were above the upper limit of quantitation (>2230000 ng equivalents ¹⁴C-INCB018424/g).

Percent of radioactive dose in blood and tissues determined by whole-body autoradiography at specified times after a single oral administration of ¹⁴C-INCB018424 to female rats (Group 1, 25 mg/kg)

Matrix	Percent of Radioactive Dose				
	Animal Number (Sacrifice Time)				
	B05635 (2 Hours)	B05636 (8 Hours)	B05637 (24 Hours)	B05638 (168 Hours)	B05639 (336 Hours)
Adrenal gland	0.01	0.00	NA	NA	NA
Bile	NA	NA	NA	NA	NA
Blood	0.88	NA	NA	NA	NA
Bone	0.10	NA	NA	NA	NA
Bone marrow	0.04	NA	NA	NA	NA
Cecum	0.23	0.86	NA	NA	NA
Cecum contents	6.62	29.63	0.65	NA	NA
Cerebellum	NA	NA	NA	NA	NA
Cerebrum	NA	NA	NA	NA	NA
Diaphragm	NA	NA	NA	NA	NA
Esophageal contents	NA	NA	NA	NA	NA
Esophagus	NA	NA	NA	NA	NA
Exorbital lacrimal gland	NA	NA	NA	NA	NA
Eye	0.02	0.01	0.00	NA	NA
Eye (lens)	NA	NA	NA	NA	NA
Fat (abdominal)	0.15	NA	NA	NA	NA
Fat (brown)	0.03	NA	NA	NA	NA
Harderian gland	0.02	NA	NA	NA	NA
Intra-orbital lacrimal gland	NA	NA	NA	NA	NA
Kidney	0.70	0.04	NA	NA	NA
Large intestinal contents	0.06	19.58	0.44	NA	NA
Large intestine	0.41	0.77	NA	NA	NA
Liver	4.70	0.57	0.08	NA	NA
Lung	0.07	NA	NA	NA	NA
Lymph nodes	NA	NA	NA	NA	NA
Medulla	NA	NA	NA	NA	NA
Muscle	7.45	NA	NA	NA	NA
Myocardium	0.08	NA	NA	NA	NA
Nasal turbinates	NA	NA	NA	NA	NA
Olfactory lobe	NA	NA	NA	NA	NA
Ovary	0.00	NA	NA	NA	NA
Pancreas	0.10	NA	NA	NA	NA
Pituitary gland	0.00	NA	NA	NA	NA
Preputial gland	0.01	NA	NA	NA	NA

NA Not applicable.
SD Standard deviation.

Continued from last page

Percent of radioactive dose in blood and tissues determined by whole-body autoradiography at specified times after a single oral administration of ¹⁴C-INCB018424 to female rats (Group 1, 25 mg/kg)

Matrix	Percent of Radioactive Dose				
	Animal Number (Sacrifice Time)				
	B05635 (2 Hours)	B05636 (8 Hours)	B05637 (24 Hours)	B05638 (168 Hours)	B05639 (336 Hours)
Renal cortex	0.73	0.04	NA	NA	NA
Renal medulla	0.59	0.03	NA	NA	NA
Salivary gland	0.04	NA	NA	NA	NA
Skin (nonpigmented)	4.35	NA	NA	NA	NA
Skin (pigmented)	5.69	NA	NA	NA	NA
Small intestinal contents	254.86 ^a	1.44	NA	NA	NA
Small intestine	10.04	NA	NA	NA	NA
Spinal cord	NA	NA	NA	NA	NA
Spleen	0.05	NA	NA	NA	NA
Stomach	0.16	NA	NA	NA	NA
Stomach contents	35.30	0.10	NA	NA	NA
Thymus	0.04	NA	NA	NA	NA
Thyroid	0.00	NA	NA	NA	NA
Urinary bladder	NA	NA	NA	NA	NA
Urine	NA	NA	NA	NA	NA
Uterus	0.03	NA	NA	NA	NA
Uveal tract	0.10	0.04	0.02	0.01	NA
Total	333.64 ^a	53.11	1.20	0.01	0.00

NA Not applicable.

SD Standard deviation.

^a One or more samples were above the upper limit of quantitation (>2230000 ng equivalents ¹⁴C-INCB018424/g).

Concentrations of radioactivity in blood, plasma, and cellular fraction at specified times after a single oral administration of ¹⁴C-INCB018424 to male and female rats (Group 1, 25 mg/kg)

Collection Time Point	ng Equivalents ¹⁴ C-INCB018424/g									
	Animal Number									
	Males					Females				
(hours)	B05630	B05631	B05632	B05633	B05634	B05635	B05636	B05637	B05638	B05639
	<u>Blood</u>									
2	1400	-	-	-	-	4830	-	-	-	-
8	-	178	-	-	-	-	183	-	-	-
24	-	-	44.8	-	-	-	-	40.7	-	-
168	-	-	-	14.6	-	-	-	-	14.4	-
336	-	-	-	-	BLQ	-	-	-	-	BLQ
	<u>Plasma</u>									
2	1420	-	-	-	-	5130	-	-	-	-
8	-	170	-	-	-	-	163	-	-	-
24	-	-	33.3	-	-	-	-	36.3	-	-
168	-	-	-	BLQ	-	-	-	-	BLQ	-
336	-	-	-	-	BLQ	-	-	-	-	BLQ
	<u>Cellular Fraction</u>									
2	1410	-	-	-	-	4710	-	-	-	-
8	-	172	-	-	-	-	197	-	-	-
24	-	-	54.7	-	-	-	-	54.3	-	-
168	-	-	-	26.1	-	-	-	-	25.4	-
336	-	-	-	-	16.9	-	-	-	-	16.4

BLQ Below the limit of quantitation.

- Not scheduled for collection.

**Percent of radioactive dose in blood and tissues determined by whole-body
autoradiography at specified times after a single oral administration of
¹⁴C-INCB018424 to male rats (Group 1, 25 mg/kg)**

Matrix	Percent of Radioactive Dose				
	Animal Number (Sacrifice Time)				
	B05630 (2 Hours)	B05631 (8 Hours)	B05632 (24 Hours)	B05633 (168 Hours)	B05634 (336 Hours)
Adrenal gland	0.00	NA	NA	NA	NA
Bile	NA	NA	NA	NA	NA
Blood	NA	NA	NA	NA	NA
Bone	NA	NA	NA	NA	NA
Bone marrow	0.01	NA	NA	NA	NA
Cecum	0.08	1.72	NA	NA	NA
Cecum contents	8.08	44.41	0.14	NA	NA
Cerebellum	NA	NA	NA	NA	NA
Cerebrum	NA	NA	NA	NA	NA
Diaphragm	NA	NA	NA	NA	NA
Epididymis	0.01	NA	NA	NA	NA
Esophageal contents	NA	NA	NA	NA	NA
Esophagus	NA	NA	NA	NA	NA
Exorbital lacrimal gland	NA	NA	NA	NA	NA
Eye	0.01	0.00	NA	NA	NA
Eye (lens)	NA	NA	NA	NA	NA
Fat (abdominal)	NA	NA	NA	NA	NA
Fat (brown)	0.00	NA	NA	NA	NA
Harderian gland	0.00	NA	NA	NA	NA
Intra-orbital lacrimal gland	NA	NA	NA	NA	NA
Kidney	0.18	0.02	NA	NA	NA
Large intestinal contents	0.05	27.53	0.18	NA	NA
Large intestine	0.28	0.85	NA	NA	NA
Liver	1.90	0.42	NA	NA	NA
Lung	0.02	NA	NA	NA	NA
Lymph nodes	NA	NA	NA	NA	NA
Medulla	NA	NA	NA	NA	NA
Muscle	2.57	NA	NA	NA	NA
Myocardium	NA	NA	NA	NA	NA
Nasal turbinates	NA	NA	NA	NA	NA
Olfactory lobe	NA	NA	NA	NA	NA
Pancreas	0.02	NA	NA	NA	NA
Pituitary gland	0.00	NA	NA	NA	NA
Preputial gland	0.00	0.00	NA	NA	NA

NA Not applicable.

SD Standard deviation

Continued from last page

Percent of radioactive dose in blood and tissues determined by whole-body autoradiography at specified times after a single oral administration of ¹⁴C-INCB018424 to male rats (Group 1, 25 mg/kg)

Matrix	Percent of Radioactive Dose				
	Animal Number (Sacrifice Time)				
	B05630 (2 Hours)	B05631 (8 Hours)	B05632 (24 Hours)	B05633 (168 Hours)	B05634 (336 Hours)
Prostate	0.00	NA	NA	NA	NA
Renal cortex	0.16	NA	NA	NA	NA
Renal medulla	0.20	NA	NA	NA	NA
Salivary gland	0.01	NA	NA	NA	NA
Seminal vesicle	0.01	NA	NA	NA	NA
Skin (nonpigmented)	1.19	NA	NA	NA	NA
Skin (pigmented)	5.36	3.06	1.32	NA	NA
Small intestinal contents	314.56 ^a	2.13	NA	NA	NA
Small intestine	8.86	0.12	NA	NA	NA
Spinal cord	NA	NA	NA	NA	NA
Spleen	0.01	NA	NA	NA	NA
Stomach	0.04	NA	NA	NA	NA
Stomach contents	6.67	NA	NA	NA	NA
Testis	0.03	NA	NA	NA	NA
Thymus	0.01	NA	NA	NA	NA
Thyroid	NA	NA	NA	NA	NA
Urinary bladder	NA	NA	NA	NA	NA
Urine	NA	NA	NA	NA	NA
Uveal tract	0.05	0.02	0.01	0.00	NA
Total	350.38 ^a	80.28	1.65	0.00	0.00

NA Not applicable.

SD Standard deviation.

a One or more samples were above the upper limit of quantitation (>2230000 ng equivalents ¹⁴C-INCB018424/g).

Percent of radioactive dose in blood and tissues determined by whole-body autoradiography at specified times after a single oral administration of ¹⁴C-INCB018424 to female rats (Group 1, 25 mg/kg)

Matrix	Percent of Radioactive Dose				
	Animal Number (Sacrifice Time)				
	B05635 (2 Hours)	B05636 (8 Hours)	B05637 (24 Hours)	B05638 (168 Hours)	B05639 (336 Hours)
Adrenal gland	0.01	0.00	NA	NA	NA
Bile	NA	NA	NA	NA	NA
Blood	0.88	NA	NA	NA	NA
Bone	0.10	NA	NA	NA	NA
Bone marrow	0.04	NA	NA	NA	NA
Cecum	0.23	0.86	NA	NA	NA
Cecum contents	6.62	29.63	0.65	NA	NA
Cerebellum	NA	NA	NA	NA	NA
Cerebrum	NA	NA	NA	NA	NA
Diaphragm	NA	NA	NA	NA	NA
Esophageal contents	NA	NA	NA	NA	NA
Esophagus	NA	NA	NA	NA	NA
Exorbital lacrimal gland	NA	NA	NA	NA	NA
Eye	0.02	0.01	0.00	NA	NA
Eye (lens)	NA	NA	NA	NA	NA
Fat (abdominal)	0.15	NA	NA	NA	NA
Fat (brown)	0.03	NA	NA	NA	NA
Harderian gland	0.02	NA	NA	NA	NA
Intra-orbital lacrimal gland	NA	NA	NA	NA	NA
Kidney	0.70	0.04	NA	NA	NA
Large intestinal contents	0.06	19.58	0.44	NA	NA
Large intestine	0.41	0.77	NA	NA	NA
Liver	4.70	0.57	0.08	NA	NA
Lung	0.07	NA	NA	NA	NA
Lymph nodes	NA	NA	NA	NA	NA
Medulla	NA	NA	NA	NA	NA
Muscle	7.45	NA	NA	NA	NA
Myocardium	0.08	NA	NA	NA	NA
Nasal turbinates	NA	NA	NA	NA	NA
Olfactory lobe	NA	NA	NA	NA	NA
Ovary	0.00	NA	NA	NA	NA
Pancreas	0.10	NA	NA	NA	NA
Pituitary gland	0.00	NA	NA	NA	NA
Preputial gland	0.01	NA	NA	NA	NA

NA Not applicable.

SD Standard deviation.

Continued from last page

Percent of radioactive dose in blood and tissues determined by whole-body autoradiography at specified times after a single oral administration of ¹⁴C-INCB018424 to female rats (Group 1, 25 mg/kg)

Matrix	Percent of Radioactive Dose				
	Animal Number (Sacrifice Time)				
	B05635 (2 Hours)	B05636 (8 Hours)	B05637 (24 Hours)	B05638 (168 Hours)	B05639 (336 Hours)
Renal cortex	0.73	0.04	NA	NA	NA
Renal medulla	0.59	0.03	NA	NA	NA
Salivary gland	0.04	NA	NA	NA	NA
Skin (nonpigmented)	4.35	NA	NA	NA	NA
Skin (pigmented)	5.69	NA	NA	NA	NA
Small intestinal contents	254.86a	1.44	NA	NA	NA
Small intestine	10.04	NA	NA	NA	NA
Spinal cord	NA	NA	NA	NA	NA
Spleen	0.05	NA	NA	NA	NA
Stomach	0.16	NA	NA	NA	NA
Stomach contents	35.30	0.10	NA	NA	NA
Thymus	0.04	NA	NA	NA	NA
Thyroid	0.00	NA	NA	NA	NA
Urinary bladder	NA	NA	NA	NA	NA
Urine	NA	NA	NA	NA	NA
Uterus	0.03	NA	NA	NA	NA
Uveal tract	0.10	0.04	0.02	0.01	NA
Total	333.64 ^a	53.11	1.20	0.01	0.00

NA Not applicable.

SD Standard deviation.

a One or more samples were above the upper limit of quantitation (>2230000 ng equivalents ¹⁴C-INCB018424/g).

***In Vitro* and *Ex Vivo* protein binding of INCB018424 in rat, cynomolgus monkey, dog, minipig, and human serum and plasma**

Key Study Findings

- In serum: the *in vitro* unbound fractions of INCB018424 in human, rat, cynomolgus monkey, dog and minipig serum were 3.2, 15, 5.6, 9.5 and 28%, respectively;
- In plasma: the *in vitro* unbound fractions of INCB018424 in human, rat, dog and minipig plasma were 3.3, 14, 12 and 26%, respectively;
- The *ex vivo* unbound fractions of INCB018424 in rat, dog and minipig plasma were 18, 9.7 and 33%, respectively.

Study no: INCYTE-DMB-07.11.1

Volume #, and page #: electronic submission, page 1-11

Conducting laboratory and location: no information provided

Date of study initiation: October 20, 2005

GLP compliance: no,

QA report: yes () no (x)

Drug, lot #, radiolabel, and % purity: INCB018424

Lot No.: 2, 7, 8, 9, 10 and SS-IN2-175;

Purity: not provided

Formulation/vehicle: not provided

Methods: The *in vitro* protein binding of INCB018424 was determined using serum and plasma from rats, cynomolgus monkeys (serum only), dogs, minipigs, and humans. The *ex vivo* protein binding of INCB018424 was determined using pooled plasma from rats (single oral or IV dose in rat pharmacokinetic study, INCYTE-DMB-06.169.1), minipigs (pharmacokinetic study in Gottingen minipigs administered a single IV dose of 18424, INCYTE-DMB-07.10.1) and dogs (10-day multiple oral dose toxicokinetic study in dogs, INCYTE-DMB-06.185.1). The Multi-Equilibrium Dialyzer System™ and diachema membranes from Harvard Apparatus (Holliston, MA) were used for the experiment.

Results: the following tables are excerpted from the Applicant's submission

Summary of *In Vitro* and *Ex Vivo* Fraction Unbound (f_u) of INCB018424 in Serum and Plasma from Human, Rat, Cynomolgus Monkey, Dog and minipig

Species	Matrix	Type	INCB018424 Concentration (μ M)	Lot #	f_u (%)	Mean $\pm$ SD (%)	Overall Mean $\pm$ SD (%)		
Human	serum	<i>in vitro</i>	3.0	2	4.1	3.6 $\pm$ 0.4	3.2		
			3.0	2	3.3				
			3.0	8	3.5				
			10	9	2.4	2.6			
			10	9	2.8				
	plasma	<i>in vitro</i>	10	9	2.9	3.3	3.3		
			10	9	3.7				
Rat	serum	<i>in vitro</i>	3.0	2	20	15 $\pm$ 4	15		
			3.0	2	17				
			3.0	9	9.4				
			10	8	17	14 $\pm$ 5			
			10	9	7.9				
			10	9	16				
	plasma	<i>in vitro</i>	3.0	10	17	17	14		
			1.0	10	12			12	
			<i>ex vivo</i>	4.3	7	18		18	18
Cyno	serum	<i>in vitro</i>	3.0	2	5.6	5.6	5.6		
Dog	serum	<i>in vitro</i>	3.0	2	8.9	9.2	9.5 $\pm$ 0.7		
			3.0	10	9.5				
			10	10	10	10			
	plasma	<i>in vitro</i>	1.0	8	11	11	12 $\pm$ 1		
			10	8	13			13	
			10	8	12				
			<i>ex vivo</i>	0.39	SS-IN2-175	7.3		7.3	9.7
4.8	SS-IN2-175	12		12					
Minipig	serum	<i>in vitro</i>	3.0	2	31	30	28		
			3.0	10	29				
			10	8	25	25			
	plasma	<i>in vitro</i>	3.0	10	26	26	26		
			<i>ex vivo</i>	1.1	SS-IN2-175	33		33	33

Placental transfer and lacteal excretion of ¹⁴C-INCB018424 following administration of a single oral dose to pregnant Sprague Dawley rats**Key Study Findings**

- Peak tissue concentrations occurred at 1 hour postdose in most maternal and fetal tissues and then declined with time;
- Low concentrations of drug-derived radioactivity crossed the placenta and resulted in limited fetal exposure;
- Radioactivity concentrations in maternal central nervous system tissues were very low and only quantifiable in the Day 18 dams at 1 hour postdose;
- With the exceptions of fetal brain, fetal spinal cord, and fetal eye, radioactivity concentrations in fetal tissues were lower than the equivalent maternal tissues and were at BLQ by 8 hours postdose;
- Maternal elimination was nearly complete by 24 hours postdose;
- Peak radioactivity concentrations occurred at 1 hour postdose in plasma and blood and at 2 hours postdose in milk. The milk:plasma concentration ratios ranged from 4.02 to 24.8 (13.4 based on AUC_{0-∞}), indicating that ¹⁴C-INCB018424-related radioactivity preferentially partitioned into milk of rats.

Study no: INCYTE-DMB-10.50.1**Volume #, and page #:** electronic submission, page 1-95**Conducting laboratory and location:** (b) (4)**Date of study initiation:** March 23, 2010**GLP compliance:** yes,**QA report:** yes (x) no ()**Drug, lot #, radiolabel, and % purity:**

14C-INCB018424

Lot No.: 65359001

Purity: Chemical purity: 99.6%

Radiopurity: 99.18%

INCB018424

Lot No.: BPR-09-134-B1-12

Purity: 98.9%

Formulation/vehicle: 0.5% methylcellulose in reverse osmosis water

Methods: The tissue distribution and lacteal excretion of ¹⁴C-INCB018424-derived radioactivity were assessed following a single oral administration of ¹⁴C-INCB018424 to timed-pregnant and lactating female Sprague Dawley (SD) rats. One animal/group/time point was sacrificed at 1, 2, 4, 8, and 24 hours postdose to examine tissue distribution of radioactivity in maternal and fetal tissues on Day 13 (Group 1) and Day 18 (Group 2) of gestation by whole-body autoradiography (WBA). Milk, blood, and plasma were collected from 3 animals/time point (Group 3) at 10

days postpartum and analyzed for concentrations of radioactivity using liquid scintillation counting (LSC) to assess the lacteal excretion of ¹⁴C-INCB018424-derived radioactivity.

The following summary table is copied from the sponsor.

Group	Number of Female Animals ^a	Dose Route	Target Dose Level (mg/kg)	Target Dose Volume (mL/kg)	Samples Collected
1 ^b	5	Oral	30	10	Blood, Carcass for WBA
2 ^c	5	Oral	30	10	Blood, Carcass for WBA
3 ^d	15	Oral	30	10	Blood, Plasma, and Milk
1R ^{b,e}	4	Oral	30	10	Blood, Carcass for WBA

WBA Whole-body autoradiography.

Notes: The dose was approximately 50 µCi/kg.

a Animals were timed-pregnant.

b Animals were dosed on Day 13 of gestation.

c Animals were dosed on Day 18 of gestation.

d Animals were dosed approximately 10 days postpartum (the actual number of days postpartum was recorded in the data).

e Animals in Group 1 sacrificed at 1 and 8 hours postdose were either not pregnant or had few fetuses; data from the Group 1, 8-hour animal was not reported and only the radioanalysis data from the Group 1, 1-hour animal was reported. The Group 1, 1- and 8-hour animals were repeated as Group 1R. Two animals in Group 1R were sacrificed at 1 and 8 hours postdose, respectively.

Dosing:

Species/strain: pregnant Sprague Dawley rats (Hsd:Sprague Dawley SD)

Age: 15-17 weeks

#/sex/group or time point: see the table in Method section

Weight: 234-352 g

Doses in administered units: 30 mg/kg, ~50 µCi

Route, form, volume, and infusion rate: oral gavage at dose volume of 10 mL/kg

Results: the following tables were excerpted from the sponsor's submission

**Pharmacokinetic parameters for radioactivity in blood and tissues collected from
timed-pregnant rats after a single oral administration of ¹⁴C-INCB018424 on
Gestation Day 13 (Groups 1 and 1R, 30 mg/kg)**

Matrix or Tissue	C _{max} (ng-eq/g)	T _{max} (Hours)	Half-Life (Hours)	AUC _{0-t} (ng-eq·hour/g)	AUC _{0-∞} (ng-eq·hour/g)
Adrenal gland	11900	1.00	2.41	43770	48538
Amniotic fluid	NC	NC	NC	NC	NC
Amniotic sac	10100	4.00	NC	67460	NC
Aorta	7470	1.00	44.0	59855	150616
Bile	36200	4.00	NC	108850	NC
Blood	2860	1.00	NC	7045	NC
Bone	NC	NC	NC	NC	NC
Bone marrow	3410	1.00	NC	7420	NC
Brain cerebellum	NC	NC	NC	NC	NC
Brain cerebrum	NC	NC	NC	NC	NC
Brain choroid plexus	2090	4.00	NC	4370	NC
Brain medulla	NC	NC	NC	NC	NC
Brain olfactory lobe	NC	NC	NC	NC	NC
Cecum	7860	2.00	7.63	75786	86214
Contents, cecum	547000	8.00	NC	6524220	NC
Contents, esophageal	113000	4.00	NC	150220	NC
Contents, large intestinal	289000	8.00	NC	3289530	NC
Contents, small intestinal	806000	2.00	NC	3219800	NC
Contents, stomach	1440000	1.00	0.484	3399380	3400559
Diaphragm	4240	1.00	1.87	19869	21956
Esophagus	4050	1.00	NC	10420	NC
Exorbital lacrimal gland	4540	1.00	NC	10935	NC
Eye	NC	NC	NC	NC	NC
Eye lens	NC	NC	NC	NC	NC
Eye uveal tract	2730	1.00	NC	4768	NC
Fat (abdominal)	NC	NC	NC	NC	NC
Fat (brown)	2940	1.00	NC	8005	NC
Fetal blood	NC	NC	NC	NC	NC
Fetal brain	NC	NC	NC	NC	NC
Fetal eye	NC	NC	NC	NC	NC
Fetal gastrointestinal tract	NC	NC	NC	NC	NC
Fetal heart	NC	NC	NC	NC	NC
Fetal kidney	NC	NC	NC	NC	NC
Fetal liver	NC	NC	NC	NC	NC
Fetal lung	NC	NC	NC	NC	NC
Fetal muscle	NC	NC	NC	NC	NC
Fetal spinal cord	NC	NC	NC	NC	NC
Fetus	923	1.00	7.97	1634	9808
Harderian gland	5490	1.00	8.10	30806	40883
Intra-orbital lacrimal gland	4470	1.00	NC	10050	NC
Kidney	17500	1.00	1.63	74400	80130
Kidney cortex	17400	1.00	1.67	78150	84568
Kidney medulla	15400	1.00	1.42	66950	70604

NC Not calculated.

Continued from last page

**Pharmacokinetic parameters for radioactivity in blood and tissues collected from
timed-pregnant rats after a single oral administration of ¹⁴C-INCB018424 on
Gestation Day 13 (Groups 1 and 1R, 30 mg/kg)**

Matrix or Tissue	C _{max} (ng-eq/g)	T _{max} (Hours)	Half-Life (Hours)	AUC _{0-t} (ng-eq·hour/g)	AUC _{0-∞} (ng-eq·hour/g)
Large intestine	3790	4.00	37.9	51540	135212
Liver	26200	4.00	17.6	187430	252590
Lung	3000	1.00	NC	8175	NC
Lymph nodes	2770	1.00	NC	7260	NC
Mammary gland	2360	1.00	9.35	11250	26495
Muscle	2930	1.00	NC	7870	NC
Myocardium	5220	1.00	NC	13190	NC
Nasal turbinates	1080	4.00	NC	1860	NC
Ovary	1520	1.00	NC	4260	NC
Pancreas	5680	1.00	NC	13630	NC
Pituitary gland	3720	1.00	NC	10555	NC
Placenta	2770	1.00	NC	5825	NC
Preputial gland	6300	1.00	4.57	26700	41746
Salivary gland	4300	1.00	NC	11285	NC
Skin	2480	1.00	11.6	33552	44728
Small intestine	11000	2.00	4.49	67700	103037
Spinal cord	NC	NC	NC	NC	NC
Spleen	3560	1.00	NC	9105	NC
Stomach	4220	1.00	7.73	13470	50392
Thymus	3300	1.00	NC	8125	NC
Thyroid	4280	4.00	NC	25425	NC
Urinary bladder	8350	1.00	NC	31315	NC
Urine	243000	1.00	2.79	794000	929711
Uterus	4360	1.00	NC	8660	NC

NC Not calculated.

**Pharmacokinetic parameters for radioactivity in blood and tissues collected from
timed-pregnant rats after a single oral administration of ¹⁴C-INCB018424 on
Gestation Day 18 (Group 2, 30 mg/kg)**

Matrix or Tissue	C _{max} (ng-eq/g)	T _{max} (Hours)	Half-Life (Hours)	AUC _{0-t} (ng-eq-hour/g)	AUC _{0-∞} (ng-eq-hour/g)
Adrenal gland	14600	4.00	NC	67415	NC
Amniotic fluid	NC	NC	NC	NC	NC
Amniotic sac	5770	4.00	25.0	43842	72274
Aorta	9660	1.00	14.0	83755	110019
Bile	84200	1.00	2.09	324250	364363
Blood	3540	1.00	NC	9045	NC
Bone	NC	NC	NC	NC	NC
Bone marrow	4620	1.00	1.58	21022	22552
Brain cerebellum	652	1.00	NC	NC	NC
Brain cerebrum	624	1.00	NC	NC	NC
Brain choroid plexus	NC	NC	NC	NC	NC
Brain medulla	NC	NC	NC	NC	NC
Brain olfactory lobe	855	1.00	NC	NC	NC
Cecum	13900	4.00	NC	25950	NC
Contents, cecum	498000	8.00	NC	5962020	NC
Contents, esophageal	19100	4.00	NC	30956	NC
Contents, large intestinal	470000	8.00	NC	5097340	NC
Contents, small intestinal	642000	2.00	2.58	2811980	2817232
Contents, stomach	1180000	2.00	0.624	3617280	3619658
Diaphragm	5730	1.00	1.95	26230	29406
Esophagus	7140	1.00	1.75	25705	27842
Exorbital lacrimal gland	5850	4.00	1.53	29670	31761
Eye	904	1.00	NC	NC	NC
Eye lens	NC	NC	NC	NC	NC
Eye uveal tract	3690	1.00	NC	7145	NC
Fat (abdominal)	682	4.00	NC	1332	NC
Fat (brown)	4270	1.00	NC	9915	NC
Fetal blood	1770	1.00	NC	4473	NC
Fetal brain	1730	1.00	NC	4539	NC
Fetal eye	2530	4.00	NC	6780	NC
Fetal gastrointestinal tract	2390	1.00	1.26	3080	5593
Fetal heart	3250	4.00	NC	9030	NC
Fetal kidney	2660	1.00	1.25	3425	6191
Fetal liver	3380	4.00	1.65	16806	18298
Fetal lung	2470	4.00	NC	6660	NC
Fetal muscle	2530	1.00	NC	NC	NC
Fetal spinal cord	2020	1.00	NC	5104	NC
Fetus	2260	4.00	NC	6210	NC
Harderian gland	8060	4.00	30.2	60996	103606
Intra-orbital lacrimal gland	6510	1.00	NC	16820	NC
Kidney	19700	1.00	5.40	127086	134071
Kidney cortex	20900	1.00	1.74	91975	100488
Kidney medulla	17400	1.00	2.40	82875	98443

NC Not calculated.

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**Pharmacokinetic parameters for radioactivity in blood and tissues collected from
timed-pregnant rats after a single oral administration of ¹⁴C-INCB018424 on
Gestation Day 18 (Group 2, 30 mg/kg)**

Matrix or Tissue	C _{max} (ng-eq/g)	T _{max} (Hours)	Half-Life (Hours)	AUC _{0-t} (ng-eq·hour/g)	AUC _{0-∞} (ng-eq·hour/g)
Large intestine	8970	4.00	4.43	46040	76747
Liver	26200	1.00	7.75	254950	292965
Lung	5270	1.00	NC	13480	NC
Lymph nodes	4480	1.00	1.49	21407	22789
Mammary gland	6840	4.00	4.87	39235	66415
Muscle	4250	1.00	1.67	22439	24346
Myocardium	7430	1.00	1.65	32900	35475
Nasal turbinates	1900	1.00	NC	4249	NC
Ovary	2420	1.00	NC	6635	NC
Pancreas	7060	1.00	1.42	32748	34504
Pituitary gland	7470	1.00	1.66	25762	27583
Placenta	4280	1.00	1.52	20470	21839
Preputial gland	5290	1.00	3.05	10739	13780
Salivary gland	6520	1.00	1.50	28650	30428
Skin	4310	4.00	NC	21705	NC
Small intestine	12700	4.00	4.46	69135	113012
Spinal cord	NC	NC	NC	NC	NC
Spleen	5640	1.00	1.47	24480	25912
Stomach	6770	1.00	2.49	30040	34280
Thymus	4410	1.00	NC	12285	NC
Thyroid	7070	4.00	22.2	76315	129886
Urinary bladder	7720	1.00	0.458	8570	9693
Urine	27100	1.00	2.53	37400	112516
Uterus	4150	1.00	2.04	16063	17948

NC Not calculated.

Concentrations of radioactivity in blood, plasma, and milk as determined by LSC at specified times after a single oral administration of ¹⁴C-INCB018424 to lactating female rats (Group 3, 30 mg/kg)

Sample	Time Point	ng Equivalents ¹⁴ C-INCB018424/g				SD
		1	2	3	Mean	
Blood ^a	1 h	2210	2920	3590	2910	691
Blood ^b	2 h	1960	2080	1970	2000	69.0
Blood ^c	4 h	818	980	1190	996	187
Blood ^d	8 h	275	384	251	303	71.2
Blood ^e	24 h	BLQ	BLQ	BLQ	0.00 ^f	0.00
Plasma ^a	1 h	2290	3010	3750	3020	730
Plasma ^b	2 h	2120	2090	2060	2090	28.1
Plasma ^c	4 h	812	1010	1240	1020	212
Plasma ^d	8 h	285	400	237	307	83.6
Plasma ^e	24 h	BLQ	BLQ	BLQ	0.00 ^f	0.00
Milk ^a	1 h	10500	10500	15000	12000	2600
Milk ^b	2 h	12600	16700	12800	14000	2280
Milk ^c	4 h	10800	13100	14200	12700	1750
Milk ^d	8 h	7990	6840	6910	7250	648
Milk ^e	24 h	105	132	147	128	21.5

BLQ Below the limit of quantitation. (<49.8 ng equivalents ¹⁴C-INCB018424/g, blood)
(<43.2 ng equivalents ¹⁴C-INCB018424/g, plasma)
(<51.1 ng equivalents ¹⁴C-INCB018424/g, milk)

h Hours.

SD Standard deviation.

a Samples collected from Animal Nos. B20396, B20397, and B20398.

b Samples collected from Animal Nos. B20399, B20400, and B20401.

c Samples collected from Animal Nos. B20402, B20403, and B20404.

d Samples collected from Animal Nos. B20405, B20406, and B20407.

e Samples collected from Animal Nos. B20408, B20409, and B20410.

f BLQ was assigned a value of 0.00 for calculations.

Milk:plasma concentration ratios at specified times after a single oral administration of ¹⁴C-INCB018424 to lactating female rats (Group 3, 30 mg/kg)

Time Point	Milk:Plasma Concentration Ratio				
	1	2	3	Mean	SD
1 h ^a	4.59	3.48	4.00	4.02	0.559
2 h ^b	5.97	7.98	6.22	6.72	1.09
4 h ^c	13.3	13.0	11.5	12.6	0.946
8 h ^d	28.0	17.1	29.1	24.8	6.65
24 h ^e	N.A.	N.A.	N.A.	N.A.	N.A.

h Hours.

N.A. Not applicable.

SD Standard deviation.

a Samples collected from Animal Nos. B20396, B20397, and B20398.

b Samples collected from Animal Nos. B20399, B20400, and B20401.

c Samples collected from Animal Nos. B20402, B20403, and B20404.

d Samples collected from Animal Nos. B20405, B20406, and B20407.

e Samples collected from Animal Nos. B20408, B20409, and B20410.

Pharmacokinetic parameters for radioactivity in blood, plasma, and milk, as applicable, collected from timed-pregnant or lactating rats after a single oral administration of ¹⁴C-INCB018424 (Groups 1, 1R, 2, and 3, 30 mg/kg)

Matrix	C _{max} (ng-eq/g)	T _{max} (Hours)	Half-Life (Hours)	AUC _{0-t} (ng-eq·hour/g)	AUC _{0-∞} (ng-eq·hour/g)
<u>Groups 1 and 1R^a</u>					
Blood	3140	1.00	2.66	14627	16377
Plasma	3180	1.00	3.73	19637	19890
<u>Group 2</u>					
Blood	4640	1.00	3.55	27796	28085
Plasma	4570	1.00	3.37	27737	27963
<u>Group 3^b</u>					
Blood	2910	1.00	2.22	9504	10475
Plasma	3020	1.00	2.19	9829	10798
Milk	14000	2.00	2.93	144624	145166

a Data from the 1-hour replacement animal (Animal No. B22229, Group 1R) was used to calculate pharmacokinetic parameters.

b Pharmacokinetic parameters were calculated using the mean concentrations obtained from 3 animals/time point.

Metabolism**The in vitro metabolism of INCB018424 by rat liver microsomes and individual rat recombinant cytochrome P450(s)****Key Study Findings:**

- Liver microsomes from male rats metabolized INCB018424 *in vitro* to a greater extent than females;
- INCB018424 was metabolized by the following isozymes in both female and male rats; CYP1A2, CYP2C6 and CYP2D1
- INCB018424 was metabolized extensively by the male specific rat CYP isozymes CYP2C11, CYP2C13 and CYP3A2.

Study number: INCYTE-DMB-07.01.2-153**Volume #, and page #:** Electronic submission; page 108

M4/42-stud-rep/422-pk/4224-metab/ncl-153.pdf, page 1-43

Conducting laboratory and location: Incyte Corporation**Date of study initiation:** August 7, 2006**GLP compliance:** no,**QA report:** yes (x) no (x)**Drug, lot #, radiolabel, and % purity:** INCB018424

Lot SS-IN2-175

Purity: not provided

Formulation/vehicle: 50 mM potassium phosphate buffer (pH 7.4), 2mM NADPH,**Methods:**Metabolism by Rat Liver Microsomes

INCB018424 was incubated in triplicate with either female or male rat liver microsomes at 37°C. Each incubation contained 0.5 mg/mL of the either female (pool of 10 rats) or male (pool of 10 rats) rat liver microsome, 50 mM potassium phosphate buffer (pH 7.4), 2mM NADPH, and INCB018424 (1 µM). Aliquots were taken at 0, 10, 20 and 30 minutes, deproteinized with acetonitrile and stored at -20°C until analysis.

Metabolism by Individual Rat Recombinant CYP Isozymes

INCB018424 was incubated in triplicate with individual rat cytochrome P-450 (CYP) isozymes at 37°C. Each incubation contained 5 pmols of the individual isozyme, 50 mM potassium phosphate buffer (pH 7.4), 2mM NADPH, and INCB018424 (1 µM). Aliquots were taken at 0, 30 and 60 minutes, deproteinized with acetonitrile and stored at -20°C until analysis.

Results: The Applicant only presented the summary table. The following summary tables are excerpted from the Applicant's submission.

Extrapolated *In Vivo* Parameters Based on the *In Vitro* Rate of Metabolism of INCB018424 by Rat Liver Microsomes

	Extrapolated <i>In Vivo</i> Parameter	
Gender	CL (L/h/kg)	Hepatic Extraction Ratio
Female	1.02	0.35
Male	2.54	0.88

The *In Vitro* Metabolism of INCB018424 by Individual Rat Recombinant Cytochrome P450s

CYP Isozyme	Gender	Percent of INCB018424 Remaining	
		0 minutes	60 minutes
CYP1A2	Male/Female	100	5 ± 1
CYP2B1	Male/Female	100	102 ± 3
CYP2C6	Male/Female	100	1 ± 0
CYP2C11	Male	100	2 ± 1
CYP2C12	Female	100	101 ± 4
CYP2C13	Male	100	78 ± 4
CYP2D1	Male/Female	100	42 ± 1
CYP3A2	Male	100	2 ± 1

INCB018424: Material Balance and Metabolism in Male Rats

Key Study Findings:

- The route and extent of elimination was similar between orally and intravenously dosed rats with urine being the most significant route (~50%);
- INCB018424 was also excreted via bile and feces;
- Elimination was rapid; most of the dose was eliminated within 12 hrs of dosing (92% and 87%, respectively);
- The metabolic profile was similar between dosing routes;
- Metabolite breakdown was extensive with very few single metabolites accounting for more than 5% of the dose.

Study number: (b) (4)-22603; INCYte-DMB-08.61.1

Volume #, and page #: Electronic submission; page 1-82

Conducting laboratory and location: (b) (4)

Date of study initiation: March 20, 2007

GLP compliance: no,

QA report: yes () no (x)

Drug, lot #, radiolabel, and % purity: INCB018424

Lot SS-IN2-175

Purity: not provided

[¹⁴C]INCB018424

Lot 3562192

Purity: 99% (radiochemical purity)

Formulation/vehicle: 50 mM potassium phosphate buffer (pH 7.4), 2mM NADPH,

Methods: INCB018424 was administered by the oral and intravenous routes to male Crl:CD(SD) rats. Dose solutions were prepared as follows:

Dose Route	Dose Level (mg/kg bw)	Dose Volume (mL/kg bw)	Radiochemical Dose (μCi/kg bw)	Specific Activity in Dose (μCi/mg)	Chemical Concentration (mg/mL)	Radiochemical Concentration (μCi/mL)
Oral	50	10	600	12	5	60
Intravenous	10	5	300	30	2	60

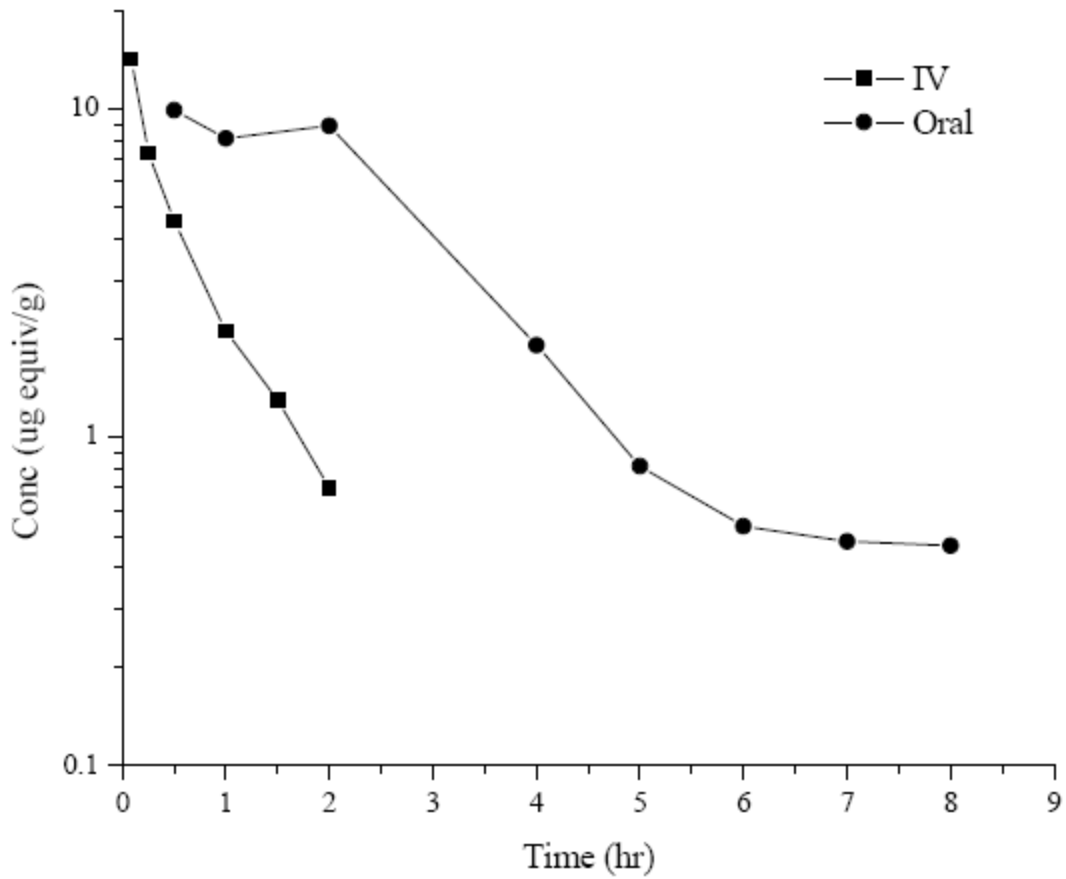
Study design is summarized in the following table:

Experiment	Dose Route	Dose Level (mg/kg bw)	Number of Animals	Time of Sacrifice (hours)	Samples
Mass Balance and Pharmacokinetics	Oral	50	4M	96	Urine, Feces, Bile, Carcass, Cage Wash, Metabolite profile in selected samples
	Intravenous	10	4M	96	
Metabolite Identification	Oral	50	2M	3	Metabolite profile in plasma

Following dosing, rats were housed individually in metabolism units suitable for the collection of urine and feces up to a maximum of 4 days. Blood samples were collected pre-dose, and at 5, 15, 30, 60, 90, and 120 minutes post-dose for the intravenous group, and 0.5, 1, 2, 4, 5, 6, 7, and 8 hours post-dose for the oral group. Urine, feces, bile and/or plasma samples were analyzed by HPLC and mass spectroscopy to determine the molecular weight of any radioactively labeled metabolites.

Results: the following figures and tables are excerpted from the Applicant's submission.

Total ¹⁴C Concentration in Plasma Following Oral or Intravenous Dosing



Pharmacokinetic Parameters

Nominal Dose		Half-Life	Tmax	Cmax	Observed AUC
Oral (50 mg/kg)	Mean	1.338	1.25	11.342	30.325
	SD	0.257	0.866	2.913	9.03
IV (10 mg/kg)	Mean	0.579	0.083	58.557	13.002
	SD	0.072	0	88.633	7.45

Percent Recovery

Sample		Oral		IV	
		Mean	SD	Mean	SD
urine	Predose	N.A.	N.A.	N.A.	N.A.
urine	4 h	28.813	7.697	35.172	5.712
urine	8 h	17.05	9.136	9.009	2.679
urine	12 h	4.089	2.39	1.601	1.034
urine	24 h	1.6	0.771	2.553	1.102
urine	48 h	0.387	0.261	0.303	0.157
urine	72 h	0.067	0.038	0.102	0.085
urine	96 h	0.025	0.014	0.021	0.008
	Subtotal ^a	52.03	4.285	48.76	5.548
feces	Predose	N.A.	N.A.	N.A.	N.A.
feces	4 h	N.A.	N.A.	N.A.	N.A.
feces	8 h	1.302	1.018	N.A.	N.A.
feces	12 h	4.788	4.81	5.079	0.81
feces	24 h	6.465	2.91	7.845	1.978
feces	48 h	0.583	0.405	1.18	1.085
feces	72 h	0.206	0.227	0.1	0.055
feces	96 h	0.11	0.09	0.163	0.265
	Subtotal ^a	11.931	0.916	11.826	0.766
bile	Predose	N.A.	N.A.	N.A.	N.A.
bile	4 h	29.321	5.674	34.691	1.155
bile	8 h	4.594	1.545	0.943	0.177
bile	12 h	1.723	2.262	0.325	0.015
bile	24 h	0.867	0.412	0.383	0.137
bile	48 h	0.121	0.035	0.122	0.03
bile	72 h	0.042	0.016	0.031	0.003
bile	96 h	0.019	0.006	0.024	0.014
	Subtotal ^a	36.687	5.778	36.518	1.122
cage wash	24 h	1.042	0.618	6.501	3.741
cage wash	48 h	0.382	0.312	0.535	0.566
cage wash	72 h	0.068	0.048	0.201	0.09
cage wash	96 h	0.08	0.024	0.366	0.219
	Subtotal ^a	1.571	0.885	7.368	4.072
	Total	102.22	1.312	104.47	4.709

^a The subtotals are the average of the subtotals from each animal, not the sum of the values listed here. Please see appendix data for individual values.

Metabolites observed in pooled bile, urine, and feces after oral and intravenous dosing

Designation	RT (min) ^a	m/z	Metabolite description	Matrix observed ^b
M1	3.25	357	Tri-hydroxylation and reduction	U
M2	4.25	357	Tri-hydroxylation and reduction	U (IV)
M3	4.25	339	Di-hydroxylation of cyclopentyl	U (oral)
M4	4.75	339	Di-hydroxylation of cyclopentyl	U
M5	4.75	499	O-glucuronidation of 3-cyclopentyl	U (oral), B
M6	5.25	499	O-glucuronidation of 3-cyclopentyl	B
M7	5.42	323	3-hydroxylation of cyclopentyl	U, B, F
(INCB025257)				
M9	5.75	321	3-ketone on cyclopentyl	U, B (oral), F (oral)
(INCB025255)				
M10	5.75	499	O-glucuronidation of 3-cyclopentyl	B
M11	5.92	321	3-ketone on cyclopentyl	U, F
(INCB025256)				
M12	5.92	325	2-hydroxylation of cyclopentyl and reduction	U (oral)
M13	5.92	339	Dihydroxylation	U
M14	5.92	323	2-hydroxylation of cyclopentyl	U (IV), F
(INCB027596)				
M15	6.25	499	O-glucuronidation of 3-cyclopentyl	B (oral)
M16	6.75	323	3-hydroxylation of cyclopentyl	U, F (oral)
(INCB025264)				
M17	6.75	499	O-glucuronidation of 3-cyclopentyl	U, B
M18	7.25	323	2-hydroxylation of cyclopentyl	U
(INCB027598)				
M19	7.25	341	Di-hydroxylation of pyrazol or pyrolopyrimidine and reduction	U
M20	8.08	339	Hydroxylation on cyclopentyl and pyrazol or pyrolopyrimidine	U
M21	8.42	339	Hydroxylation on cyclopentyl and pyrazol or pyrolopyrimidine	U
M22	8.42	403	Sulfate of 3-hydroxylated cyclopentyl	U (IV)
18424	10.3	307	None	U, F

a approximate retention time based on radiochromatograms for urine under experimental conditions

b Unless noted in parentheses, metabolite observed after oral and IV dosing for the indicated matrix

U = urine

B = bile

F = feces

Percent of peaks and metabolite identification of pooled bile, urine, and feces after oral dosing

Bile			Urine			Feces		
Run Time (min)	Peak ID	% of Dose	Run Time (min)	Peak ID	% of Dose	Run Time (min)	Peak ID	% of Dose
			3.25	M1	4.88			
			4.25	M3	1.58			
4.917	M5	1.91	4.75	M4,M5	2.25			
5.25	M6, M7	1.99	5.417	M7	14.76	5.583	M7	4.03
5.75	M9, M10	2.49	5.917	M9, M11, M12, M13	14.05	5.917	M9	1.05
6.25	M15	3.12	6.75	M16, M17	1.98	6.25	M11, M14	2.60
6.75	M17	8.45	7.25	M18, M19	1.15	6.917	M16	0.77
			8.083	M20	1.82	10.583	18424	0.55
			8.417	M21	1.54			
			10.25	18424	0.15			

Percent of peaks and metabolite identification of pooled bile, urine, and feces after intravenous dosing

Bile			Urine			Feces		
Run Time (min)	Peak ID	% of Dose	Run Time (min)	Peak ID	% of Dose	Run Time (min)	Peak ID	% of Dose
			3.25	M1	2.40			
4.917	M5	2.78	4.25	M2	1.42	5.583	M7	4.87
5.25	M6,M7	2.33	4.75	M4	2.38	6.25	M11,M14	2.11
5.75	M10	2.72	5.417	M7	9.93	10.583	18424	0.34
6.75	M17	6.11	5.917	M9,M11,M13,M14	9.90			
			6.75	M16,M17	2.17			
			7.25	M18,M19	2.94			
			8.083	M20	1.23			
			8.417	M21,M22	1.31			
			10.25	18424	1.99			

Identification of rat plasma metabolites of INCB018424 after a single oral dose of ¹⁴C-INCB018424

Key study findings:

- INCB018424 was present in plasma from the 1 and 4 hour timepoints, with 12 radiochromatographic peaks related to INCB018424 observed;
- A total of seven metabolites of INCB018424 were identified and confirmed using previously isolated or synthesized metabolites of INCB018424;
- The two most abundant circulating plasma metabolites were INCB025258 (M8), a 3-hydroxyl metabolite of the cyclopentyl ring and INCB025256 (M11), a 3-oxocyclopentyl metabolite.

Study no: INCYTE-DMB-08.169.1

Volume #, and page #: electronic submission, page 1-43

Conducting laboratory and location: INCYTE

Date of study initiation: September 13, 2008

GLP compliance: no,

QA report: yes () no (x)

Drug, lot #, radiolabel, and % purity: INCB018424

Lot SS-IN2-175

Purity: not provided

¹⁴C-INCB018424

Lot 3562192

Purity: not provided

Formulation/vehicle: not provided

Methods: Plasma samples from male rats orally dosed with 25 mg/200 µCi/kg ¹⁴C-INCB018424 were obtained on day 1 of a single dose tissue distribution study conducted at (b) (4) study # 59N-070. Residual plasma samples collected 1, 4 and 24 h post-dose from each rat were pooled by time point. Samples were assayed using electrospray ionization LC-MS with a Thermo Finnigan LCQ Deca-XP Plus Ion-Trap Mass Spectrometer (Thermo-Fisher Scientific Waltham MA), operated in positive ionization mode.

Source of Study Samples for Biotransformation Experiments

Subject ID	Study #	Total Dose	¹⁴ C Dose	Time Point
1 and 2	59N-0701	25 mg/kg	200 µCi/kg	1 Hour
3 and 4	59N-0701	25 mg/kg	200 µCi/kg	4 Hour
5 and 6	59N-0701	25 mg/kg	200 µCi/kg	24 Hour

Results:

Summary Table of Metabolites of INCB018424 Found in Male Rat Plasma at 1 Hour Post-Dose

1 Hour Post-Dose Sample	RT	m/z	Average DPM	% of Parent	Plasma DPM/Gram	Plasma uCi/gram	Plasma ug/gram
Metabolite M41	7.4	339	1577	110	2896	0.00130	0.1819
Metabolite M43	10.7	339	639	43	1172	0.00053	0.0737
INCB025257 (M7)	13.8	323	2225	150	4084	0.00184	0.2566
INCB025258 (M8)	14.7	323	4201	280	7713	0.00347	0.4846
INCB025255 (M9)	17.9	321	3102	210	5696	0.00257	0.3579
INCB025264 (M16)	20.1	323	1501	100	2756	0.00124	0.1732
INCB025256 (M11)	21.0	321	4046	270	7428	0.00335	0.4667
INCB032568 (M48)	27.5	323	1067	72	1958	0.00088	0.1230
INCB027598 (M18)	32.8	323	387	26	711	0.00032	0.0446
Metabolite M52	45.5	312	385	26	707	0.00032	0.0444
Metabolite M53	51.2	305	599	40	1100	0.00050	0.0691
INCB018424	52.0	307	1492	100	2739	0.00123	0.1721
Sum =			22202				

Sample Mass Extracted (g)	2.014
Extraction Efficiency (%)	90.14
Recon Volume (µL)	100
Injection Volume (µL)	30
Mass Eq. of Plasma on Column (g)	0.545

Specific Activity of Dose = 7.169 uCi/mg
0.00717 uCi/ug

Summary Table of Metabolites of INCB018424 Found in Male Rat
Plasma at 4 Hours Post-Dose

4 Hour Post-Dose Sample	RT	m/z	Average DPM	% of Parent	Plasma DPM/Gram	Plasma uCi/gram	Plasma ug/gram
Metabolite M41	7.4	339	237	6800	435	0.00020	0.0273
Metabolite M43	10.7	339	61	1700	112	0.00005	0.0071
INCB025257 (M7)	13.8	323	142	4100	261	0.00012	0.0164
INCB025258 (M8)	14.7	323	538	15000	989	0.00045	0.0621
INCB025255 (M9)	17.9	321	297	8500	545	0.00025	0.0343
INCB025264 (M16)	20.1	323	171	4900	315	0.00014	0.0198
INCB025256 (M11)	21.0	321	535	15000	984	0.00044	0.0618
INCB032568 (M48)	27.5	323	174	5000	320	0.00014	0.0201
INCB027598 (M18)	32.8	323	70	2000	129	0.00006	0.0081
Metabolite M52	45.5	312	0	0	0	0.00000	0.0000
Metabolite M53	51.2	305	18	510	33	0.00001	0.0021
INCB018424	52.0	307	4	100	6	0.00000	0.0004
Sum =			2245				

Sample Mass Extracted (g) 2.01
 Extraction Efficiency (%) 90.14
 Recon Volume (µL) 100
 Injection Volume (µL) 30
 Mass Eq. of Plasma on Column (g) 0.544

Specific Activity of Dose = 7.169 uCi/mg
 0.00717 uCi/ug

Identification of in vivo metabolites of INCB018424 in female rat following a single oral dose of ¹⁴C-INCB018424

Key study findings:

- INCB018424 was present in plasma from female rat at the 1, 2, and 4 hour timepoints, with a total of 18 radiochromatographic peaks related to INCB018424 observed;
- Concentrations of metabolites in plasma were low (less than 0.8 µg) equivalents/g in all cases;
- There were eight circulating plasma metabolites present at 1 or 2 hours post-dose at levels that were >10% of parent (based on radiochemical detection) in order of decreasing amount: INCB025258 (M8); INCB025256 (M11); INCB018424 (M7),
- Structures for INCB025257 (M7); INCB032568 (M48); INCB025264(M16); INCB027598 (M18); INCB025262 (M27); and M35 have not been elucidated;
- The overall metabolic profile is similar in males and females, with the three most abundant metabolites of INCB025258 (M8), INCB025256 (M11), and INCB025257 (M7), in decreasing amount, respectively.

Study no: INCYTE-DMB-08.169.1

Volume #, and page #: electronic submission, page 1-120

Conducting laboratory and location: INCYTE

Date of study initiation: September 22, 2009

GLP compliance: no,

QA report: yes () no (x)

Drug, lot #, radiolabel, and % purity: INCB018424

Lot BPR-07-101-B2-21

Purity: not provided

¹⁴C-INCB018424

Lot 65359001

Purity: not provided

Formulation/vehicle: not provided

Methods:

Source of Study Samples for Biotransformation Experiments

Species	Gender	Dose / Route	Study # / Group	Matrix
Rat (intact)	F, M	25 mg/kg PO	59N-0901 / 2, 3	Plasma
Rat (bile duct-cannulated)	F	25 mg/kg PO	59N-0901 / 1	Bile, Urine, Feces

Plasma, bile, urine, feces obtained from either male or female Sprague-Dawley rats were prepared by pooling each sample obtained from individual animals at the following collection time points:

Plasma: 1, 2, 4, 8, 24, hours for females; 1, and 4 hours for male rats

Urine, bile and feces: 0-8, 8-24, 24-48, 48-72, 72-96 hours for female rats

Samples were assayed using electrospray ionization LC-MS with a Thermo Finnigan

LCQ Deca-XP Plus Ion-Trap Mass Spectrometer (Thermo-Fisher Scientific Waltham MA), operated in positive ionization mode.

Results:

Quantitative Summary (as % of Parent Present and µg equivalent/g) of Metabolites of ¹⁴C-INCB018424 Found in Female Rat Plasma Following a Single 25 mg/kg Oral Dose

Metabolite	RT	m/z	1 Hour		2 Hour		4 Hour	
			% of Parent	µg/gram	% of Parent	µg/gram	% of Parent	µg/gram
Unknown	7.3	Unk	0.6	0.009	1.31	0.02	104.56	0.04
Unknown	8.0	Unk	2.6	0.035	2.60	0.03	57.40	0.02
M1	8.1	357	N/F	N/F	N/F	N/F	N/F	N/F
M2	12.2	357	N/F	N/F	N/F	N/F	N/F	N/F
M54	12.3	367	3.3	0.044	4.26	0.06	79.92	0.03
Di-Hydroxyl (m/z 339)	13.5	339	3.5	0.047	2.53	0.03	48.76	0.02
M2-B	14.4	357	N/F	N/F	N/F	N/F	N/F	N/F
M10	15.4	499	N/F	N/F	N/F	N/F	N/F	N/F
Unknown	16.6	Unk	1.4	0.020	2.28	0.03	22.30	0.01
M15	17.2	499	N/F	N/F	N/F	N/F	N/F	N/F
M3	17.7	339	N/F	N/F	N/F	N/F	N/F	N/F
Quad-Hydroxyl (m/z 371)	18.0	371	4.6	0.062	5.80	0.08	84.36	0.04
INCB025257 (M7)	19.9	323	12.3	0.166	15.93	0.21	102.42	0.04
M4	20.9	339	N/F	N/F	N/F	N/F	N/F	N/F
M53	21.1	305	N/F	N/F	N/F	N/F	N/F	N/F
INCB025255 (M9)	21.9	321	6.6	0.089	8.49	0.11	63.28	0.03
INCB025258 (M8)	24.0	323	58.6	0.795	46.00	0.62	374.20	0.16
M25	24.3	499	N/F	N/F	N/F	N/F	N/F	N/F
INCB025256 (M11)	26.0	321	32.8	0.445	39.79	0.53	416.45	0.18
M35	26.9	355	9.5	0.128	9.44	0.13	63.14	0.03
INCB025264 (M16)	27.9	323	11.1	0.151	7.22	0.10	27.51	0.01
M19	28.6	341	N/F	N/F	N/F	N/F	N/F	N/F
INCB025262 (M27)	29.6	323	9.8	0.133	9.44	0.13	168.91	0.07
M26	31.2	499	N/F	N/F	N/F	N/F	N/F	N/F
Oxo Metabolite (m/z 321)	31.6	321	0.4	0.005	N/F	N/F	0.98	0.00
M20	35.6	339	N/F	N/F	N/F	N/F	N/F	N/F
M28	36.9	499	N/F	N/F	N/F	N/F	N/F	N/F
M21	38.0	339	N/F	N/F	N/F	N/F	N/F	N/F
INCB032568 (M48)	38.8	323	11.9	0.161	14.46	0.19	103.34	0.04
Glycosylation of 323	42.5	485	3.4	0.047	2.52	0.03	77.82	0.03
INCB027598 (M18)	43.0	323	10.6	0.144	7.87	0.11	64.52	0.03
M50-B	57.1	323	6.6	0.090	5.17	0.07	187.02	0.08
INCB018424	64.7	307	100.0	1.356	100.00	1.34	100.00	0.04

* Quantitative data for the metabolism of INCB018424 in Male Rat Plasma for this study may be found in [Table 10](#), and [Appendix A, Tables 19 and 20](#).

** No drug related material was radiochemically detected in the 8 and 24 hour post-dose plasma samples.

Quantitative Summary (as % of Administered Radioactivity) of Metabolites of ¹⁴C-
INCB018424 Found in Female Rat Excreta Following a Single 25 mg/kg Oral Dose

Metabolite	RT	m/z	Urine	Bile	Feces	Total
Unknown	7.3	Unk	0.39	1.63	N/F	2.02
Unknown	8.0	Unk	0.10	N/F	1.29	1.39
M1	8.1	357	1.06	1.60	N/F	2.65
M2	12.2	357	0.43	0.91	N/F	1.34
M54	12.3	367	N/F	N/F	N/F	N/F
Di-Hydroxyl (m/z 339)	13.5	339	N/F	N/F	N/F	N/F
M2-B	14.4	357	1.02	0.52	N/F	1.54
M10	15.4	499	N/F	1.16	N/F	1.16
Unknown	16.6	Unk	N/F	0.19	N/F	0.19
M15	17.2	499	N/F	3.38	N/F	3.38
M3	17.7	339	2.38	N/F	N/F	2.38
Quad-Hydroxyl (m/z 371)	18.0	371	N/F	1.83	N/F	1.83
INCB025257 (M7)	19.9	323	2.44	1.26	2.63	6.33
M4	20.9	339	1.42	N/F	0.69	2.11
M53	21.1	305	N/F	1.34	N/F	1.34
INCB025255 (M9)	21.9	321	2.26	0.64	0.48	3.38
INCB025258 (M8)	24.0	323	7.89	N/F	5.46	13.35
M25	24.3	499	N/F	5.07	N/F	5.07
INCB025256 (M11)	26.0	321	8.59	2.42	1.04	12.05
M35	26.9	355	N/F	N/F	N/F	0.00
INCB025264 (M16)	27.9	323	1.54	0.47	1.05	3.06
M19	28.6	341	4.88	1.73	0.90	7.51
INCB025262 (M27)	29.6	323	2.62	N/F	2.29	4.92
M26	31.2	499	N/F	1.44	N/F	1.44
Oxo Metabolite (m/z 321)	31.6	321	0.12	0.27	N/F	0.39
M20	35.6	339	1.15	N/F	N/F	1.15
M28	36.9	499	N/F	8.30	N/F	8.30
M21	38.0	339	1.37	N/F	N/F	1.37
INCB032568 (M48)	38.8	323	1.03	N/F	0.51	1.54
Glycosylation of 323	42.5	485	N/F	N/F	N/F	0.00
INCB027598 (M18)	43.0	323	0.27	N/F	0.18	0.45
M50-B	57.1	323	1.42	N/F	N/F	1.42
INCB018424	64.7	307	0.05	0.04	0.26	0.35

Quantitative Summary of Metabolites of ¹⁴C-INCB018424 (as µg equivalents/g and % of Administered Dose) Found in Female Rat Urine Following a Single 25 mg/kg Oral Dose (0-24 Hour)

Metabolite	RT	m/z	(µg/g equivalents)		% of Dose
			0-8 Hr	8-24 Hr	0-24 Hrs
Unknown	7.3	Unk	4.570	0.220	0.4
Unknown	8.0	Unk	N/F	0.557	0.1
M1	8.1	357	13.578	N/F	1.1
M2	12.2	357	5.556	N/F	0.4
M54	12.3	367	N/F	N/F	N/F
Di-Hydroxyl (m/z 339)	13.5	339	N/F	N/F	N/F
M2-B	14.4	357	13.061	N/F	1.0
M10	15.4	499	N/F	N/F	N/F
Unknown	16.6	Unk	N/F	N/F	N/F
M15	17.2	499	N/F	N/F	N/F
M3	17.7	339	26.758	1.688	2.4
Quad-Hydroxyl (m/z 371)	18.0	371	N/F	N/F	N/F
INCB025257 (M7)	19.9	323	25.680	2.482	2.4
M4	20.9	339	18.213	N/F	1.4
M53	21.1	305	N/F	N/F	N/F
INCB025255 (M9)	21.9	321	26.059	1.298	2.3
INCB025258 (M8)	24.0	323	91.592	4.249	7.9
M25	24.3	499	N/F	N/F	N/F
INCB025256 (M11)	26.0	321	98.392	5.235	8.6
M35	26.9	355	N/F	N/F	N/F
INCB025264 (M16)	27.9	323	17.513	0.968	1.5
M19 (DiHydrodiol)	28.6	341	62.120	0.196	4.9
INCB025262 (M27)	29.6	323	29.400	1.887	2.6
M26	31.2	499	N/F	N/F	N/F
Oxo Metabolite (m/z 321)	31.6	321	1.087	0.198	0.1
M20	35.6	339	13.015	0.757	1.1
M28	36.9	499	N/F	N/F	N/F
M21	38.0	339	15.000	1.146	1.4
INCB032568 (M48)	38.8	323	11.317	0.815	1.0
Glycosylation of m/z 323	42.5	485	N/F	N/F	N/F
INCB027598 (M18)	43.0	323	3.308	0.077	0.3
M50-B	57.1	323	14.882	1.457	1.4
INCB018424	64.7	307	0.662	N/F	0.1

Quantitative Summary of Metabolites of ¹⁴C-INCB018424 (as µg equivalents/g and % of Administered Dose) Found in Female Rat Bile Following a Single 25 mg/kg Oral Dose (0-24 Hour)

Metabolite	RT	m/z	(µg/g equivalents)		% of Dose 0-24 Hrs
			0-8 Hr	8-24 Hr	
Unknown	7.3	Unk	13.360	N/F	1.6
Unknown	8.0	Unk	N/F	N/F	N/F
M1	8.1	357	13.117	N/F	1.6
M2	12.2	357	7.443	N/F	0.9
M54	12.3	367	N/F	N/F	N/F
Di-Hydroxyl (m/z 339)	13.5	339	N/F	N/F	N/F
M2-B	14.4	357	4.286	N/F	0.5
M10	15.4	499	9.574	N/F	1.2
Unknown	16.6	Unk	N/F	0.376	0.2
M15	17.2	499	27.812	N/F	3.4
M3	17.7	339	N/F	N/F	N/F
Quad-Hydroxyl (m/z 371)	18.0	371	15.029	N/F	1.8
INCB025257 (M7)	19.9	323	10.383	N/F	1.3
M4	20.9	339	N/F	N/F	N/F
M53	21.1	305	11.006	N/F	1.3
INCB025255 (M9)	21.9	321	5.238	N/F	0.6
INCB025258 (M8)	24.0	323	N/F	N/F	N/F
M25	24.3	499	38.279	0.833	5.1
INCB025256 (M11)	26.0	321	19.917	N/F	2.4
M35	26.9	355	N/F	N/F	N/F
INCB025264 (M16)	27.9	323	3.891	N/F	0.5
M19	28.6	341	14.213	N/F	1.7
INCB025262 (M27)	29.6	323	N/F	N/F	N/F
M26	31.2	499	11.300	0.131	1.4
Oxo Metabolite (m/z 321)	31.6	321	N/F	0.547	0.3
M20	35.6	339	N/F	N/F	N/F
M28	36.9	499	66.573	0.403	8.3
M21	38.0	339	N/F	N/F	N/F
INCB032568 (M48)	38.8	323	N/F	N/F	N/F
Glycosylation of 323	42.5	485	N/F	N/F	N/F
INCB027598 (M18)	43.0	323	N/F	N/F	N/F
M50-B	57.1	323	N/F	N/F	N/F
INCB018424	64.7	307	0.349	N/F	0.0

Quantitative Summary of Metabolites of ¹⁴C-INCB018424 (as µg equivalents/g and % of Administered Dose) Found in Female Rat Feces Following a Single 25 mg/kg Oral Dose (0-24 Hour)

Metabolite	RT	m/z	(µg/g equivalents) 0-24 Hr	% of Dose 0-24 Hrs
Unknown	7.3	Unk	N/F	N/F
Unknown	8.0	Unk	1.966	1.3
M1	8.1	357	N/F	N/F
M2	12.2	357	N/F	N/F
M54	12.3	367	N/F	N/F
Di-Hydroxyl (m/z 339)	13.5	339	N/F	N/F
M2-B	14.4	357	N/F	N/F
M10	15.4	499	N/F	N/F
Unknown	16.6	Unk	N/F	N/F
M15	17.2	499	N/F	N/F
M3	17.7	339	N/F	N/F
Quad-Hydroxyl (m/z 371)	18.0	371	N/F	N/F
INCB025257 (M7)	19.9	323	3.992	2.6
M4	20.9	339	1.045	0.7
M53	21.1	305	N/F	N/F
INCB025255 (M9)	21.9	321	0.734	0.5
INCB025258 (M8)	24.0	323	8.299	5.5
M25	24.3	499	N/F	N/F
INCB025256 (M11)	26.0	321	1.576	1.0
M35	26.9	355	N/F	N/F
INCB025264 (M16)	27.9	323	1.599	1.1
M19	28.6	341	1.372	0.9
INCB025262 (M27)	29.6	323	3.483	2.3
M26	31.2	499	N/F	N/F
Oxo Metabolite (m/z 321)	31.6	321	N/F	N/F
M20	35.6	339	N/F	N/F
M28	36.9	499	N/F	N/F
M21	38.0	339	N/F	N/F
INCB032568 (M48)	38.8	323	0.779	0.5
Glycosylation of 323	42.5	485	N/F	N/F
INCB027598 (M18)	43.0	323	0.269	0.2
M50-B	57.1	323	N/F	N/F
INCB018424	64.7	307	0.389	0.3

Identification of in vivo metabolites of INCB018424 in beagle dogs**Key study findings:**

- INCB018424 underwent extensive metabolism, and the major metabolites were derived from oxidation and subsequent glucuronidation.

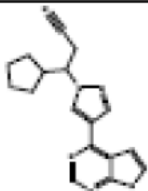
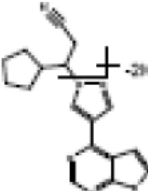
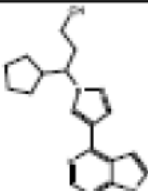
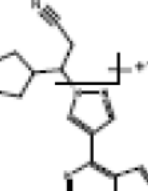
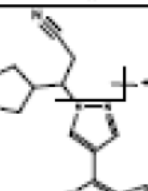
Study no: INCYTE-DMB-07.14.1**Volume #, and page #:** electronic submission, page 1-48**Conducting laboratory and location:** INCYTE**Date of study initiation:** January 7, 2007**GLP compliance:** no,**QA report:** yes () no (x)**Drug, lot #, radiolabel, and % purity:** INCB0018424

Lot # SS-IN2-175

Formulation/vehicle: not provided**Methods:** The plasma and urine samples were obtained from the beagle dogs following a single intravenous administration of INCB018424 at 5 mg/kg (Report: INCYTE-DMB-06.182.1). The residual plasma samples from this pharmacokinetic study were pooled from individual dogs and time points to generate samples of ample volume to characterize the metabolic profile. Samples were analyzed by liquid chromatography tandem mass spectrometry (LC/MS/MS).

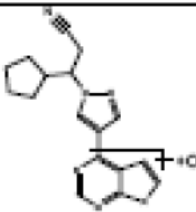
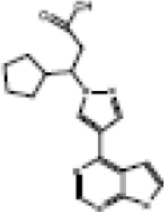
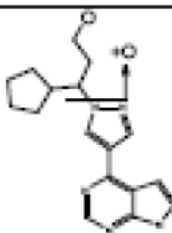
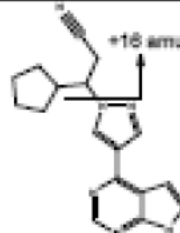
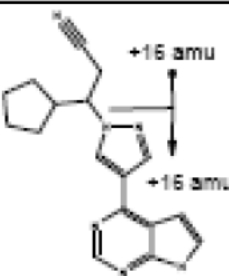
Results:

Metabolites Observed in Beagle Dog Plasma and Urine Samples

[MH] ⁺	Inference	Beagle dog Plasma t _R (min)	Beagle dog Urine t _R (min)
307 INCB018424 Parent drug		23.3	23.5
M1 m/z 305 (-2 amu)		22.6 22.8	22.6 22.8
M3 m/z 312 (+5 amu)		19.8 22.5	22.3
M4 m/z 314 (+7 amu)	No assignment	∅	10.3 12.0 13.0 15.8 16.4 16.6
M5 m/z 321 +14 amu		12.7 14.3 15.2 17.2 18.8	11.2 13.1 14.8 15.8 16.3 17.8 19.6
M6a m/z 323 +16 amu		13.3 13.7 14.9 15.5 17.3 18.6 18.9	13.7 14.1 15.8 18.0 19.2 19.6

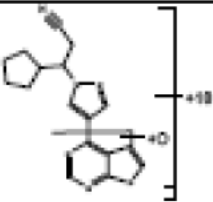
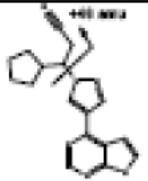
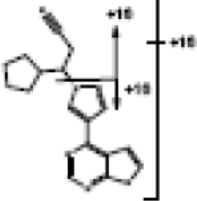
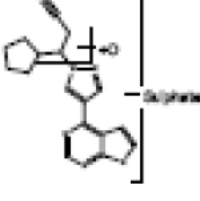
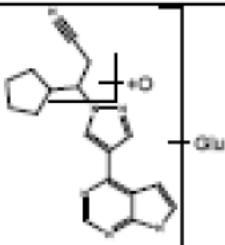
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M6b <i>m/z</i> 323 +16 amu		22.8 23.9	21.5 23.1
M9 <i>m/z</i> 326 +19 amu		x	trace
M10 <i>m/z</i> 328 +21 amu		x	11.4 13.2 16.3 16.9
M12a <i>m/z</i> 339 [+32 amu]		9.4 10.4 10.6 11.2 11.4 11.8 14.2	7.4 9.7 10.3 10.7 10.9 12.6 14.8
M12b <i>m/z</i> 339 [+32 amu]		15.1 15.5 17.1 19.3 20.3 22.2	13.8 14.4 15.4 15.8 17.4 18.9 19.2 19.4 20.2 20.4

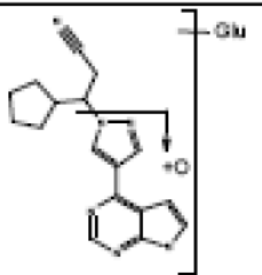
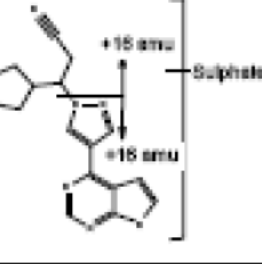
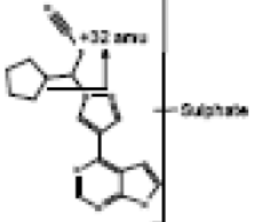
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M13 m/z 341 +34 amu		18.3 18.8	18.5 18.8 19.0
M14 m/z 353 [+46 amu]		∞	11.2 17.6 20.4
M15 m/z 355 [+48 amu]		∞	11.2 12.2 12.4 12.9
M16 m/z 403 [+16 +80 amu]		13.2 21.3	10.8 11.9 12.7 14.1 14.7 17.0 21.5
M17 m/z 483 [+176 amu]	Glucuronide of Parent Drug	19.1 21.6	21.8
M21a m/z 499 [+16 +176 amu]		12.2 15.2 16.0 17.2	11.0 12.6 14.2 15.4 18.0

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M21b m/z 499 [+16 +176 amu]		17.9 23.1	16.4 18.5
M25a m/z 419 [+112 amu]		%	9.2 10.3 12.4 13.3 15.5 16.1 16.4
M25b m/z 419 [+112 amu]		%	9.8 10.4 10.8

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Metabolism of [14C]INCB018424 in Male and Female Beagle Dogs after a Single Oral Administration

Key study findings:

- Several peaks were observed in plasma, urine and feces;
- The number of components and the profile patterns in urine, feces and plasma were similar between male and female dogs;
- These results indicate that oxidation, primarily resulting in hydroxylated and ketone metabolites, is the major Phase I metabolic pathway for INCB018424 and that the hydroxylated metabolites can undergo conjugation (e.g. glucuronidation).

Study no: INCYTE-DMB-08.149.1, (b) (4) Study No. 63161

Volume #, and page #: electronic submission, page 1-76

Conducting laboratory and location: (b) (4)

Date of study initiation: September 28, 2007

GLP compliance: no,

QA report: yes () no (x)

Drug, lot #, radiolabel, and % purity: INCB018424 Phosphate
 Lot # SS-IN2-175
 Purity: 99%

[14C]INCB018424
 Lot#356219
 Purity: 99%

Formulation/vehicle: not provided

Methods:

Group Designations and Sample Collection Times.

Study Type ^a	Number of Animals/ Sex/Animal ID	Dose Route and Level	Matrix	Sample Collection Times
MB ^a	2♂ (1M1 and 1M2) 2♀ (1F1 and 1F2)	PO ^a 3 mg/kg BW 10 µCi/kg BW	Whole Blood (Blood Cells and Plasma)	Predose, 1, 2, 4, 8, 24, 48, 72 and 96 hours post dose administration.
			Urine	Predose, 0-4, 4-12, 12-24, 24-48, 48-72 and 72-96 hour interval after dose administration.
			Feces	Predose, 0-24, 24-48, 48-72 and 72-96 hour interval after dose administration.
			Cage wash and Cage wipes	Approximately 24, 48, 72 and 96 hour after dose administration.

^a MB = Mass Balance; PO = Oral

Selected plasma, urine and fecal samples were analyzed by HPLC for metabolite characterization.

Excretion

Excretion Mass Balance in Female Rats and Pharmacokinetics of Radioactivity in Male and Female Rats Following a Single Oral Dose of [14C]INCB018424

Key Study Findings:

- Elimination of INCB018424-derived radioactivity occurred via the urine, bile and feces, accounting for an average of 45%, 40% and 20% of the administered dose, respectively;
- Excretion of radioactivity in urine and bile was rapid, with 40% of the dose recovered in the 0-8 h urine specimen, 37% in the 0-8 h bile specimen and 19% in the 0-24 h feces specimen
- The pharmacokinetics of blood and plasma total radioactivity were similar;

- Maximum plasma and blood radioactivity concentrations were observed at 1.0 h after oral dosing of [¹⁴C]INCB018424 in male and female rats, the first blood collection time.

Study no: INCYTE-DMB-09.82.1 (b)(4) **Study Number:** 59N-0901

Volume #, and page #: electronic submission, page 1-70

Conducting laboratory and location: (b)(4)

Date of study initiation: August 12, 2009

GLP compliance: no

QA report: yes () no (x)

Drug, lot #, radiolabel, and % purity:

INCB018424

Lot No.: BPR-07-101-B2-21

Purity: 97.8%

[Pyrimidine-2-¹⁴C]INCB018424

Lot#6535900

Purity: 99.18% (radiochemical purity)

Formulation/vehicle: 30% ethyl alcohol, 70% polyethylene glycol 300, 6 mg/mL

citric acid, and 5% dextrose in water (D5W)

Methods: Sprague Dawley rats were used in the study. Each animal was administered a single oral dose of [¹⁴C]INCB018424 by gavage using a dosing volume of 10 mL/kg. A summary of groups and doses is presented in the following table (excerpted from the Applicant's submission):

Group & Gender	N	Dose Route	Target Dose Level (mg/kg)	Target Dose Volume (mL/kg)	Target Dose Conc. (mg/mL)	Target Radioactivity Level (μCi/kg)
1 (BDC) Female	4	PO	25	10	2.5	200
2 (Intact) Female	15	PO	25	10	2.5	200
3 (Intact) Male	6	PO	25	10	2.5	200

Bile, urine, feces, and plasma samples were collected at the time points shown in the table below:

Sample Collection Summary

Group	Bile	Urine	Feces	Cage Residue	Blood and Plasma*
1	Pre-dose, 0-8, 8-24, 24-48, 48-72, and 72-96 h	Pre-dose, 0-8, 8-24, 24-48, 48-72, and 72-96 h	Pre-dose, 0-24, 24-48, 48-72, and 72-96 h	Rinse at 24, 48, 72 h; wash & wipe at study termination	No Sample
2	No Sample	No Sample	No Sample	No Sample	1, 2, 4, 8, 24 h
3	No Sample	No Sample	No Sample	No Sample	1, 4 h

* Terminal sample collections from 3 animals per sample time

The radioactivity content was then quantified by LSC. All LSC analyses were performed using a Model 2800TR liquid scintillation analyzer (Perkin Elmer), counting for at least 5 min or 100,000 counts.

Dosing:

Species/strain: Sprague-Dawley rats

#/sex/group or time point: see the table above

Age: not provided

Weight: 242-256 g

Doses in administered units: 25 mg/kg; 200 μ Ci/rat

Route, volume: oral gavage at dose volume of 10 mL/kg

Results: The following figure was submitted by the Applicant

Recovery of Radioactivity for Group 1 Female Rats Following Oral Administration of
 $[^{14}\text{C}]$ INCB018424 at a Target Dose of 25 mg/kg

Matrix	Collection Time	% of Dose Recovered						Cumulative
		Rat #1	Rat #2	Rat #3A	Rat #4	Mean	SD	
Feces	Pre-dose	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	0-24 h	20.374	17.562	19.240	17.076	18.563	1.522	18.563
	24-48 h	0.869	1.503	1.544	1.068	1.246	0.331	19.809
	48-72 h	0.146	0.242	0.215	0.139	0.186	0.051	19.995
	72-96 h	0.075	0.077	0.123	0.066	0.085	0.026	20.080
	Sub-total		21.464	19.384	21.122	18.349	20.080	1.470
Urine	Pre-dose	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	0-8 h	43.969	40.865	30.249	45.464	40.137	6.864	40.137
	8-24 h	4.652	5.624	4.321	4.039	4.659	0.690	44.796
	24-48 h	0.485	0.376	0.356	0.316	0.383	0.072	45.179
	48-72 h	0.193	0.184	0.185	0.113	0.169	0.037	45.348
	72-96 h	0.100	0.068	0.063	0.073	0.076	0.017	45.424
Sub-total		49.399	47.117	35.174	50.005	45.424	6.945	
Bile	Pre-dose	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	0-8 h	31.619	34.907	43.811	36.714	36.763	5.150	36.763
	8-24 h	2.339	3.101	1.753	2.114	2.327	0.570	39.090
	24-48 h	0.214	0.317	0.250	0.253	0.259	0.043	39.348
	48-72 h	0.115	0.097	0.103	0.131	0.112	0.015	39.460
	72-96 h	0.063	0.041	0.045	0.017	0.042	0.019	39.501
Sub-total		34.350	38.463	45.962	39.229	39.501	4.811	
Cage Rinse	0-24 h	1.695	0.590	0.624	0.322	0.808	0.607	0.808
	24-48 h	0.152	0.096	0.077	0.088	0.103	0.033	0.911
	48-72 h	0.050	0.026	0.062	0.021	0.040	0.020	0.951
	Sub-total		1.897	0.712	0.763	0.431	0.951	0.648
Cage Wash/ Wipe	96 h	0.069	0.060	0.149	0.150	0.107	0.049	0.107
	96 h	0.142	0.067	0.119	0.049	0.094	0.044	0.094
Total		107.321	105.803	103.289	108.213	106.157	2.155	

Plasma and Blood Concentrations of Total Radioactivity in Group 2 Female Rats Following Oral Administration of [14C]INCB018424 at a Target Dose of 25mg/kg

Time (h)	Plasma μg Equivalents/mL				
	Rat 5	Rat 6	Rat 7	Mean	SD
1	11.405	7.123	10.191	9.573	2.207
2	Rat 8	Rat 9	Rat 10	8.881	2.144
	9.477	10.663	6.502		
4	Rat 11	Rat 12	Rat 13	2.926	0.548
	3.313	3.167	2.299		
8	Rat 14	Rat 15	Rat 16	0.575	0.070
	0.519	0.654	0.552		
24	Rat 17	Rat 18	Rat 19	0.065	0.007
	0.072	0.058	0.065		

Time (h)	Blood μg Equivalents/mL				
	Rat 5	Rat 6	Rat 7	Mean	SD
1	9.438	4.943	7.390	7.257	2.250
2	Rat 8	Rat 9	Rat 10	7.192	1.711
	7.941	8.401	5.234		
4	Rat 11	Rat 12	Rat 13	2.142	0.436
	2.516	2.247	1.663		
8	Rat 14	Rat 15	Rat 16	0.408	0.040
	0.376	0.453	0.394		
24	Rat 17	Rat 18	Rat 19	BQL	ND
	BQL	BQL	BQL		

Plasma and Blood Concentrations (Mean and SD, μg equivalents/mL) of Total Radioactivity in Group 2 Female and Group 3 Male Rats Following Oral Administration of [^{14}C]INCB018424 at a Target Dose of 25 mg/kg

Time (h)	Group 2, Females			
	Plasma		Blood	
	Mean	SD	Mean	SD
1	9.573	2.207	7.257	2.250
2	8.881	2.144	7.192	1.711
4	2.926	0.548	2.142	0.436
8	0.575	0.070	0.408	0.040
24	0.065	0.007	BQL	ND
C_{max} (μg equiv/mL)	9.573		7.257	
T_{max} (h)	1.0		1.0	
AUC ₀₋₂₄ (μg equiv*h/mL)	37.94		28.55	
$t_{1/2}$ (h)	3.4		1.5	
Time (h)	Group 3, Males			
	Plasma		Blood	
	Mean	SD	Mean	SD
1	10.146	2.085	8.767	1.813
4	0.586	0.033	0.441	0.024

BQL: Below quantitation limit ($<0.123 \mu\text{g}$ equivalents/mL) and assigned a value of 0 for calculations

Blood / Plasma Total Radioactivity Concentration Ratios Following Administration of [¹⁴C]INCB018424 at a Target Dose of 25 mg/kg to Group 2 Female and Group 3 Male Rats

Group 2, Female

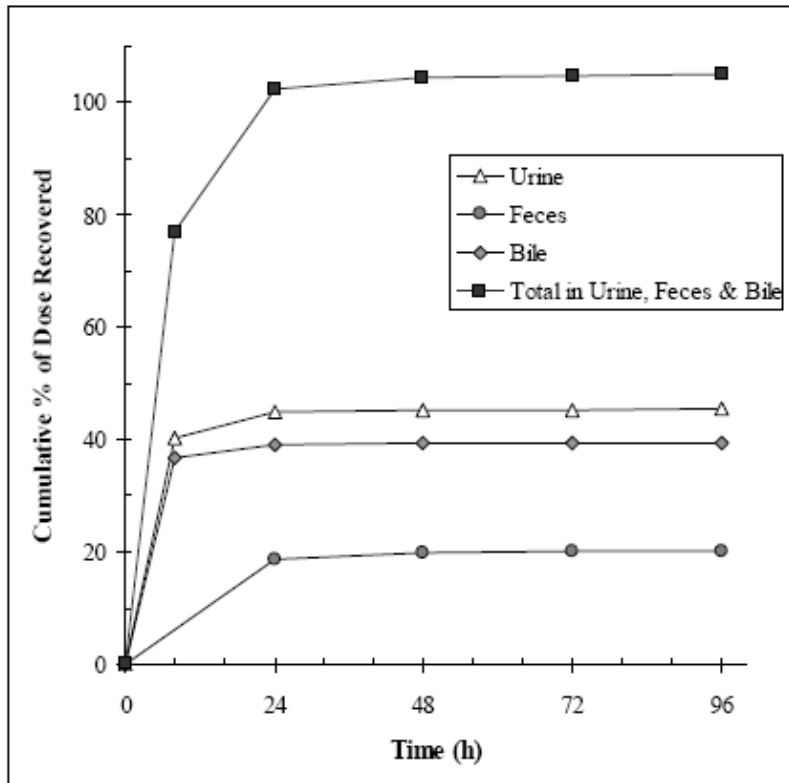
Time (h)	Blood / Plasma Ratio				
	Rat 5	Rat 6	Rat 7	Mean	SD
1	0.828	0.694	0.725	0.749	0.070
2	Rat 8	Rat 9	Rat 10	0.810	0.025
	0.838	0.788	0.805		
4	Rat 11	Rat 12	Rat 13	0.731	0.026
	0.759	0.710	0.723		
8	Rat 14	Rat 15	Rat 16	0.710	0.016
	0.724	0.693	0.714		
24	Rat 17	Rat 18	Rat 19	ND	ND
	ND	ND	ND		

ND Not Determined

Group 3, Male

Time (h)	Blood / Plasma Ratio				
	Rat 20	Rat 21	Rat 22	Mean	SD
1	0.861	0.867	0.864	0.864	0.003
4	Rat 23	Rat 24	Rat 25	0.753	0.002
	0.755	0.752	0.752		

Time Course of Excretion of Radioactivity by Group 1 (Bile Cannulated) Female Rats Following Oral Administration of [¹⁴C]INCB018424 at a Target Dose of 25 mg/kg



Excretion/Mass Balance in Male and Female Beagle Dogs after a Single Oral Administration of [¹⁴C]INCB018424

Key Study Findings:

- INCB018424 equivalent concentrations and elimination rate in blood cells were similar in male and female dogs; The INCB018424 concentration and elimination rate in plasma was similar to that of blood cells
- The excretion pattern of dosed INCB018424 radioactivity was consistent in both male and female Beagle dogs;
- The peak concentration was reached in blood cells at 1 hr post dose, the concentration decreased dramatically from 1 hr through 8 hrs post dose;
- Feces was the main route for excretion, which accounted for 54.8% and 57.9% of the dose in male and female, respectively. In urine, 34.4% and 36.3% of the dose was recovered for male and female, respectively.

Study no: INCYTE-DMB-08.62.2, (b) (4) Study No. 63161

Volume #, and page #: electronic submission, page 1-37

Conducting laboratory and location: (b) (4)

Date of study initiation: September 28, 2007

GLP compliance: no

QA report: yes () no (x)

Drug, lot #, radiolabel, and % purity:

INCB018424

Lot No.: BPR-07-101-B2-21

Purity: 97.8%

[Pyrimidine-2-¹⁴C]INCB018424

Lot#6535900

Purity: 99.18% (radiochemical purity)

Formulation/vehicle: 0.5% methylcellulose in H₂O

Methods: Two male and two female Beagle dogs received a single PO administration of [¹²+¹⁴C]INCB018424. The blood samples were collected from each animal before dose administration and at specified timepoints after dosing. The urine, feces, cage wash and cage wipes were collected from each animal for excretion and mass balance determination. See below the study design as provided by the Applicant. The radioactivity analysis was performed with collected samples by either direct liquid scintillation counting (LSC) of duplicate aliquots or oxidization (combustion) of duplicate aliquots followed by LSC.

Study Type ^a	Number of Animals/Sex	Dose Route/Level ^b	Matrix	Sample Collection Times
<u>MB</u>	2♂ 2♀	PO 3 mg/kg BW 10 µCi/kg BW	Whole Blood ^c , (Blood Cells and Plasma)	Predose, 1, 2, 4, 8, 24, 48, 72 and 96 hrs post dose administration.
			Urine ^d ,	Predose, 0-4, 4-12, 12-24, 24-48, 48-72 and 72-96 hr interval after dose administration.
			Feces ^e ,	Predose, 0-24, 24-48, 48-72 and 72-96 hr interval after dose administration.
			Cage Wash ^f , and Cage Wipes ^g	Approximately 24, 48, 72 and 96 hr after dose administration.

Dosing:

Species/strain: Beagle dog
 #/sex/group or time point: see the table above
 Age: 6 to 12 months
 Weight: 7.9 to 9.8 kg
 Doses in administered units: 3 mg/kg, 10 µCi/kg
 Route, volume: oral gavage at dose volume of 10 mL/kg

Results (presented for total radioactivity only):

[¹⁴C]INCB018424 Radioactivity in Blood Cells Collected from Male and Female Beagle Dogs after a Single PO Administration of INCB018424 at Approximately 3 mg/kg Body Weight

Blood Collection Time Interval	¹⁴ C]INCB018424 Radioactivity Concentration in Blood Cells (dpm/g)								
	Male Beagle Dogs				Female Beagle Dogs				
	(hr)	1M1	1M2	Average	%Difference	1F1	1F2	Average	%Difference
0	na	na	na	na	na	na	na	na	na
1	13775	14930	14353	4.0%	14414	17952	16183	10.9%	
2	10647	10625	10636	0.1%	9734	13443	11588	16.0%	
4	6322	5492	5907	7.0%	5214	8140	6677	21.9%	
8	2232	1673	1952	14.3%	2337	3153	2745	14.9%	
24	494	398	446	10.8%	519	714	617	15.9%	
48	313	254	284	10.4%	277	422	349	20.8%	
72	254	180	217	17.0%	227	318	273	16.6%	
96	214	162	188	13.8%	189	243	216	12.5%	

na = not applicable.

[¹⁴C]INCB018424 Radioactivity in Plasma Collected from Male and Female Beagle Dogs after a Single PO Administration of INCB018424 at Approximately 3 mg/kg Body Weight

Blood Collection Time Interval	¹⁴ C]INCB018424 Radioactivity Concentration in Plasma (dpm/g)								
	Male Beagle Dogs				Female Beagle Dogs				
	(hr)	1M1	1M2	Average	%Difference	1F1	1F2	Average	%Difference
0	na	na	na	na	na	na	na	na	na
1	15436	12651	14044	9.9%	11225	14542	12884	12.9%	
2	11369	9452	10410	9.2%	9024	11723	10374	13.0%	
4	7302	5367	6335	15.3%	4214	7146	5680	25.8%	
8	2099	1425	1762	19.1%	1928	2794	2361	18.3%	
24	290	210	250	15.9%	389	439	414	6.0%	
48	70	83	77	8.4%	56	220	138	59.4%	
72	125	105	115	8.8%	63	139	101	37.2%	
96	68	60	64	5.9%	87	92	90	3.0%	

na = not applicable.

Total Recovery of Dosed Radioactivity in Male and Female Beagle Dogs after Administration of INCB018424 at Approximately 3 mg/kg Body Weight

Matrix	Time point (hr)	Total Dose % Recovery from Urine, Feces, Cage Wash and Cage Wipes					
		Male Beagle Dogs			Female Beagle Dogs		
		1M1	1M2	Average	1F1	1F2	Average
Urine	Predose	NA	NA	NA	NA	NA	NA
	0-4	7.1%	13.6%	10.3%	10.8%	0.6%	5.4%
	4-12	18.5%	12.6%	15.6%	12.3%	1.2%	6.7%
	12-24	4.8%	7.5%	6.2%	6.6%	34.8%	20.7%
	24-48	1.6%	2.1%	1.8%	1.6%	4.4%	3.0%
	48-72	0.3%	0.4%	0.4%	0.3%	0.6%	0.4%
	24-48	0.2%	0.1%	0.1%	0.1%	0.1%	0.1%
Urine Subtotal		32.5%	36.4%	34.4%	31.5%	41.1%	36.3%
Feces	Predose	NA	NA	NA	NA	NA	NA
	0-24	48.5%	45.2%	46.8%	51.9%	39.0%	45.5%
	24-48	6.5%	6.1%	6.3%	11.1%	1.7%	6.4%
	48-72	1.0%	1.8%	1.4%	1.2%	9.5%	5.4%
	72-96	0.2%	0.2%	0.2%	0.1%	1.1%	0.6%
Fecal Subtotal		56.2%	53.4%	54.8%	64.4%	51.3%	57.9%
Cage Wash	24	4.6%	2.3%	3.5%	1.7%	1.1%	1.4%
	48	0.9%	1.0%	1.0%	0.3%	0.2%	0.2%
	72	0.4%	0.2%	0.3%	0.1%	0.3%	0.2%
	96	0.1%	0.1%	0.1%	0.0%	0.0%	0.0%
Cage Wash Subtotal		6.0%	3.6%	4.8%	2.1%	1.7%	1.9%
Cage Wipes Extract	96	0.04%	0.02%	0.03%	0.02%	0.01%	0.01%
Fecal Container Wipe ^A	0-96	0.00%	0.00%	0.00%	0.02%	0.01%	0.01%
Total Sum		94.7%	93.4%	94.0%	93.1%	94.1%	96.1%

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Note:

NA = Not Applicable

A. For homogenization, fecal sample was removed from the original container and transferred to new container due to bigger volume of the resulted fecal homogenate. The original container was cleaned with wipe and radioactivity in the wipe was counted.

Pharmacokinetic drug interactions (only two studies are reviewed below; see the review by the clinical pharmacology team for review of other drug interaction studies)

Human CYP Isozymes that are Responsible for the In Vitro Metabolism of INCB018424

Key Study Finding:

- Study results suggested that CYP3A4 is the predominant CYP isozyme responsible for the metabolism of INCB018424.

Study no: INCYTE-DMB-09.93.1

Volume #, and page #: electronic submission, page 1-8

Conducting laboratory and location: Incyte Corporation

(b) (4)

(b) (4)

Date of study initiation: July 15, 2008

GLP compliance: no

QA report: yes () no (x)

Drug, lot #, radiolabel, and % purity:

INCB018424

Lot SS-IN2-175

Purity: not provided

Formulation/vehicle: not provided

Methods: INCB018424 (1 μ M) was incubated (N=3) with human liver microsomes (2.0 mg/mL of protein), NADPH (2 mM), and 50 mM potassium phosphate buffer (pH 7.4) at 37°C. Parallel incubations using the same conditions included either furafylline (5 μ M), sulfaphenazole (10 μ M), (S)-(+)-N-3 Benzylnirvanol (5 μ M), quindine (5 μ M), or ketoconazole (1 μ M) to selectively inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, respectively. Aliquots were taken at 0, 10, 20 and 30 minutes and deproteinized with acetonitrile, centrifuged and the supernatants analyzed by LC/MS. Incubations without NADPH served as controls.

Results: the following table is excerpted from the Applicant's submission

INCB018424 Incubation Condition	Percent of Initial INCB018424 Remaining after 30 Minute Incubation (N=3)
No inhibitor	35±1
With Furafylline (5 µM, CYP1A2 inhibitor)	38±1
With Sulfaphenazole (10 µM, CYP2C9 inhibitor)	40±1
With Benzylnirvanol (5 µM, CYP2C19 inhibitor)	35±2
With Quinidine (5 µM, CYP2D6 inhibitor)	42±2
With Ketoconazole (1 µM, CYP3A4 inhibitor)	74±1
All Inhibitors Added	86±5

Summary: When ketoconazole, a selective inhibitor of CYP3A4, was co-incubated with INCB018424, 74% of the parent compound remained, whereas co-incubations with selective inhibitors of CYP1A2, CYP2C9, CYP2C19 and CYP2D6, had a minimal effect with 38±1%, 40±1%, 35±2% and 42±2%, respectively of the initial concentration of INCB018424 remaining.

In vitro evaluation of INCB018424 as an inducer of cytochrome P450 expression in cultured human hepatocytes

Key Study Finding:

- INCB018424, at concentrations up to 10 µM did not induce CYP1A2 or CYP2B6 activity in cultured human hepatocytes

Study no: INCYTE-DMB-11.06.1

Volume #, and page #: electronic submission, page 1-31

Conducting laboratory and location: (b) (4)

Date of study initiation: February 11, 2011

GLP compliance: no

QA report: yes () no (x)

Drug, lot #, radiolabel, and % purity: INCB018424
Lot # BPR-07-101-B2-21
Purity: 98%

Formulation/vehicle: DMSO, 0.1% v/v

Methods: Three preparations of cultured human hepatocytes (two cryopreserved and one fresh) from three separate livers were treated once daily for three consecutive days with dimethyl sulfoxide (DMSO, 0.1% v/v, vehicle control), one of three concentrations of INCB018424 (1, 3 or 10 μ M) or one of two known human CYP inducers, namely, omeprazole (100 μ M) and phenobarbital (750 μ M). After treatment, the cells were treated *in situ* with the appropriate marker substrates for the analysis of phenacetin O-dealkylation (marker for CYP1A2) and bupropionhydroxylation (marker for CYP2B6) by LC/MS/MS.

Discussion and Conclusions

The absorption, distribution, metabolism and excretion of ruxolitinib has been studied in mice (CD-1, hairless and transgenic), rats (albino and pigmented), rabbits, dogs, monkeys and minipigs. Summary and conclusion below is mostly based on the study results from rat and dog studies.

Oral pharmacokinetics studies have shown that ruxolitinib was absorbed rapidly with T_{max} values ranging from 0.45 to 2 h; the terminal elimination half-life of ruxolitinib was generally short after oral and IV dosing, ranging from 1.5 h (rat) to 2 h (dog). The absolute oral bioavailability was variable across the nonclinical species, 29% in male rats and 105% in female rats, and approximately 50% in dogs. No accumulation was observed after 1-month repeated daily dosing, while small accumulation was observed after 6-month daily administration of ruxolitinib (the plasma exposures at the end of 6-month treatment were about 2-fold of those observed on study day 1). There were generally no gender differences in the exposure of ruxolitinib and its metabolites in dogs. In rats, the C_{max} and AUC values were several-fold higher in females compared to males, in part due to higher metabolic clearance in male rats. In addition, the human metabolites of ruxolitinib were identified and observed at similar or higher exposures compared to human during the course of nonclinical toxicology studies in mice, rat and dog and in the carcinogenicity study in Tg.rasH2 mouse. The terminal half-life, routes and rate of excretion for ruxolitinib-derived radioactivity and metabolites observed between male and female rats were similar. Following IV administration of ruxolitinib, the total systemic clearance ranged from moderate in dogs to very high in rats. Following IV administration of ruxolitinib, the total systemic clearance and volume of distribution was species-dependent and ranged from moderate in dogs (26% of hepatic blood flow in dogs) to very high in rats (greater than 100% of hepatic blood flow). The apparent steady-state volume of distribution (V_{ss}) of ruxolitinib in male rats, female rats, and dogs was 3.8, 1.6, and 1.1 L/kg, respectively, indicating ruxolitinib is not distributed extensively beyond body water in dog (consistent with humans), and may be distributed to a greater extent in rat. Ruxolitinib is not distributed significantly beyond body water in dog and monkey and may be distributed to a greater extent in rats.

In rats, after a single oral dose of ¹⁴C-ruxolitinib, drug-derived radioactivity was widely distributed with rapid and complete elimination from most tissues. High concentration of ruxolitinib was detected in the GI system, levels in the CNS were below LOQ. Ruxolitinib was eliminated from most tissues rapidly and completely. In pregnant rats administered a single oral dose of ¹⁴C-ruxolitinib, fetal exposure was observed but

was less than maternal exposure with fetus:maternal plasma and fetal tissue:maternal plasma concentration ratios being less than one for all fetal tissues. The plasma protein binding of ruxolitinib is species-dependent 3.3% in human. In rat and dog mass balance studies, elimination of drug-derived radioactivity after oral and IV dosing is similarly rapid and complete with excretion via urine, bile and feces. In rats, ruxolitinib-derived radioactivity preferentially partitions into milk with the qualitative metabolite profile being similar to plasma. Milk concentrations were less than 1% of C_{max} by 24 h. In milk, the qualitative metabolite profile was similar to plasma, with quantitative differences likely due to the higher exposure of ruxolitinib-related radioactivity in milk relative to plasma.

Oxidation was the predominant metabolic pathways in rats and dogs. In vitro studies suggest that CYP3A4 is the predominant CYP isozyme responsible for the metabolism of ruxolitinib. Ruxolitinib is metabolized by isozymes including CYP1A2, CYP2C6 and CYP2D1 found in both male rats and female rats. In rat liver microsomes, ruxolitinib is metabolized to a greater extent in males compared to females, consistent with ruxolitinib being metabolized by the male-rat-specific isozymes CYP2C11, CYP2C13 and CYP3A2. For the major human metabolites (M18 and M27) and most of the measured minor metabolites, they were studied in one or more animal species at the exposure levels exceeding or approaching corresponding human exposure at the highest proposed therapeutic dose (25 mg twice daily).

Tables and figures to include comparative TK summary

The following tables are from the Applicant. Some of the studies summarized in the table (e.g. mouse, minipig, monkey studies) are not reviewed.

2.6.5.3.a. Pharmacokinetics: Absorption After a Single Dose

					Test Article: ruxolitinib		
Study No.	[INCYTE-DMB-08.170.1]		[INCYTE-DMB-06.169.1]		[INCYTE-DMB-06.182.1]	[INCYTE-DMB-07.08.1]	[INCYTE-DMB-08.143.1]
Species	CD-1 Mouse		Rat		Dog	Monkey	Human
Gender (M/F)/Number of animals:	3M ^a	3F ^a	2M	2F	2M	3M	6M
Feeding condition:	Fasted		Fasted		Fasted	Fasted	Fasted
Vehicle/Formulation:	Suspension / 0.5% methylcellulose		Suspension / 0.5% methylcellulose		Solution / 0.5% methylcellulose	Solution/0.2% Tween-20 in 0.5% methylcellulose	Solution / Water
Method of Administration:	Gavage		Gavage		Gavage	Gavage	Oral
Dose (mg/kg):	15 ^b		50		10	10	25 mg
Sample (eg, whole blood, plasma, serum):	Plasma		Plasma		Plasma	Plasma	Plasma
Analyte:	INCB018424		INCB018424		INCB018424	INCB018424	INCB018424
Assay:	HPLC/MS		HPLC/MS		HPLC/MS	HPLC/MS	HPLC/MS
PK parameters:							
T _{max} (hr)	0.5	0.5	0.5	0.5	2.0	1.7	0.63
C _{max} (µM)	2.09	1.76	2.24	30.4	8.71	1.52	1.09
AUC (µM*h) (Time for calculation – hr)	2.64 (0–24)	3.05 (0–24)	5.40 (0–∞)	39.3 (0–∞)	38.9 (0–∞)	8.05 (0–∞)	3.20 (0–∞)
T _½ (hr) (Time for calculation – hr) ^c	0.899 (2-24)	0.821 (2-24)	1.7	1.2	2.2	1.5	2.3 (2-36)
Additional Information:							
A single oral dose was well absorbed in mice, rats, dogs, monkeys and humans. Similarly rapid clearance across species.							
In rats, plasma C _{max} and AUC values were higher in females compared to males, but the terminal elimination half-lives were similar. No gender difference after a single oral dose in mice.							
^a per time point (21M/21F total)							
^b 100 mg/kg in male and female CD-1 also performed in same study, but not shown (C _{max} = 39.8 and 62.5 µM, respectively; AUC = 97.0 and 168 µM*h)							
^c where not indicated, at least three datapoints in the terminal phase were used to calculate half-life							

2.6.5.3.b. Absorption After a Single Intravenous (iv) Dose

						Test Article: ruxolitinib	
Study No.	[INCYTE-DMB-06.169.1]		[INCYTE-DMB-06.182.1]	[INCYTE-DMB-07.10.1]		[INCYTE-DMB-07.08.1]	
Species	Rat		Dog	Minipig		Monkey	
Gender (M/F)/Number of animals:	2M	2F	1M	1M	1F	2M	
Feeding condition:	Fasted		Fasted	Fasted		Fasted	
Vehicle/Formulation:	Solution/2.0 mg/mL in 10% dimethyl acetamide, 30% SBE-beta-cyclodextrin (50% w/v) and 60% saline		Solution/1 mg/mL in saline	Solution/1 mg/mL in 10% dimethyl acetamide, 30% hydroxypropyl betacyclodextrin (45% w/v) and 60% normal saline		Solution/1 mg/mL in 10% dimethyl acetamide, 30% hydroxypropyl betacyclodextrin (45% w/v) and 60% normal saline	
Method of Administration:	iv		iv	iv		iv	
Dose (mg/kg):	10		5	5		5	
Sample (eg, whole blood, plasma, serum):	Plasma		Plasma	Plasma		Plasma	
Analyte:	INCB018424		INCB018424	INCB018424		INCB018424	
Assay:	HPLC/MS		HPLC/MS	HPLC/MS		HPLC/MS	
PK parameters:							
CL (L/h/kg)	9.4	4.8	0.48	9.0	7.7	0.91	
V _{ss} (L/hr)	3.8	1.6	1.1	5.0	7.7	0.81	
AUC (μM*hr) (Time for calculation – hr)	3.75 (0–∞)	7.49 (0–∞)	34.1 (0–∞)	1.82 (0–∞)	2.10 (0–∞)	18.0 (0–∞)	
T _½ (hr) (Time for calculation – hr) ^a	0.41	0.43	2.5	0.42	0.72	0.88	
% dose in urine as unchanged parent	< 1	< 1	< 1	< 1	< 1	< 1	
Additional Information:							
Total systemic clearance and volume of distribution was species-dependent and ranged from moderate (26% of hepatic blood flow in dogs) to very high (450% of hepatic blood flow in minipigs).							
Ruxolitinib not distributed extensively beyond body water in dogs and monkeys; may be distributed to a greater degree in rats and minipigs.							
^a where not indicated, at least three datapoints in the terminal phase were used to calculate half-life							

2.6.5.6.a. In Vitro Plasma Protein Binding

			Test Article: ruxolitinib
Study system: In vitro			
Target entity, Test system and method: Plasma, Equilibrium dialysis			
Species	Conc. Tested	% Unbound	Study No.
CByB6F1-Tg(HRAS)2Jic (Tg.rasH2) mice	11 µM	5.2	[INCYTE-DMB-08.158.1]
CD-1 mouse	1 – 10 µM	2.7 - 3.4	[INCYTE-DMB-08.191.1]
Hairless mouse	0.43 – 4.3 µM	3.8 – 5.2	[INCYTE-DMB-09.62.1]
Rat	1.0 – 3.0 µM	12 - 17	[INCYTE-DMB-07.11.1]
Rabbit (gestating)	0.5 – 5 µM	10.0 – 13.7	[INCYTE-DMB-09.61.1]
Dog	1.0 – 10 µM	11 - 13	[INCYTE-DMB-07.11.1]
Minipig	3.0 µM	26	[INCYTE-DMB-07.11.1]
Human	10 µM	3.3	[INCYTE-DMB-07.11.1]
Additional Information:			
Non-gestating rabbits also determined (11.2% bound).			

2.6.5.6.b. In Vitro Serum Protein Binding

			Test Article: ruxolitinib
Study system: In vitro			
Target entity, Test system and method: Serum, Equilibrium dialysis			
Species	Conc. Tested	% Unbound	Study No.
Rat	3.0 – 10 µM	14 - 15	[INCYTE-DMB-07.11.1]
Dog	3.0 – 10 µM	9.2 - 10	[INCYTE-DMB-07.11.1]
Monkey	3.0 µM	5.6	[INCYTE-DMB-07.11.1]
Minipig	3.0 - 10 µM	25 - 30	[INCYTE-DMB-07.11.1]
Human	3.0 - 10 µM	2.6 – 3.6	[INCYTE-DMB-07.11.1]

2.6.5.6.c. Ex Vivo Plasma Protein Binding

			Test Article: ruxolitinib
Study system: Ex vivo			
Target entity, Test system and method: Plasma, Equilibrium dialysis			
Species	Conc. Tested	% Unbound	Study No.
CByB6F1-Tg(HRAS)2Jic (Tg.rasH2) mice	1.2 – 13.6 µM	4.9 – 5.0	[INCYTE-DMB-08.158.1]
CD-1 mouse	5.7 – 19.5 µM	2.4 - 3.0	[INCYTE-DMB-08.191.1]
Hairless mouse	1.3 – 14 µM	3.0	[INCYTE-DMB-09.62.1]
Rat	4.3 µM	18	[INCYTE-DMB-07.11.1]
Rabbit (gestating)	0.7 – 3.1 µM	11.8 – 13.1	[INCYTE-DMB-09.61.1]
Dog	0.39 – 4.8 µM	7.3 – 12	[INCYTE-DMB-07.11.1]
Minipig	1.1	33	[INCYTE-DMB-07.11.1]

2.6.5.7.b. Excretion into Milk

						Test Article: Ruxolitinib
Excretion into milk						Study No. [INCYTE-DMB-10.50.1]
Species: Rats						
Lactating date/Number of animals: Lactation Day 10/3 animals per time point						
Feeding condition: Not fasted						
Vehicle/Formulation: 0.5% methylcellulose						
Method of Administration: Oral gavage						
Dose (mg/kg): 30						
Analyte: Total radioactivity, ¹⁴ C						
Assay: LSC						
Time (hr)	1	2	4	8	24	AUC _{0-∞} ^b
Concentration/Amount (μg/g) ^a						
Milk:	12.0	14.0	12.7	7.25	0.128	145
Plasma:	3.02	2.09	1.02	0.307	BLQ	10.8
Milk/plasma:	4.02	6.72	12.6	24.8	NA	13.4
Neonates:						
Additional Information:						
Milk:plasma ratio of radioactivity based on AUC _{0-∞} was 13.4, indicating ruxolitinib-derived radioactivity preferentially partitions into milk. Milk concentrations were < 1% of C _{max} by 24 h.						
Metabolite profile in milk and plasma also examined, but not shown. The qualitative metabolite profile in milk was similar to plasma, with quantitative differences likely due to the higher exposure of INCB018424-related radioactivity in milk relative to plasma.						
Blood also examined, but not shown (blood/plasma between 1 and 8 h ranged from 0.96 to 0.99)						
^a μg Equivalent/g values are reported to three significant figures with a maximum of three decimal places.						
^b AUC _{0-∞} reported as μg equivalent*h/g.						
BLQ - Below the limit of quantitation (< 43.2 ng equivalents ¹⁴ C-INCB018424/g for plasma and < 51.1 ng equivalents ¹⁴ C-INCB018424/g for milk).						
NA – Not applicable						

2.6.5.9.a. In Vivo Metabolism in Mice and Rats

													Test Article: ruxolitinib			
Gender (M/F)/Number of animals:			Mice: 21M/21F (3M/3F/timepoint)				Rats: 6M (plasma); 4M (excreta)				Rats: 4F					
Feeding condition:			Not fasted				Fasted				Fasted					
Vehicle/Formulation:			0.5% MC in water				0.5% MC in water				0.5% MC in water					
Method of Administration:			Gavage				Gavage				Gavage					
Dose (mg/kg):			50				25 (plasma); 50 (excreta)				25					
Radionuclide: ¹⁴ C																
Specific Activity:			5.25 x 10 ⁶ Bq/mg				5.25 x 10 ⁶ Bq/mg				5.45 x 10 ⁶ Bq/mg					
Study Number		[INCYTE-DMB-08.154.1]					[INCYTE-DMB-08.169.1] (plasma) [INCYTE-DMB-08.61.1] (excreta)					[INCYTE-DMB-09.84.1]				
			Mice (Male)			Mice (Female)			Rat (Male)				Rat (Female)			
Species		Pl	Ur	Fe	Pl	Ur	Fe	Pl	Ur ^a	Bile ^a	Fe ^a	Pl	Ur	Bile	Fe	
Sampling Time or Period		0.25 hr	4-8 hr	8-24 hr	0.25 hr	4-8 hr	8-24 hr	1 hr	0-96 hr ^b	0-96 hr ^b	0-96 hr ^b	1 hr	0-8 hr	0-8 hr	0-24 hr	
% of Dose in Sample		-	15.4	16.4	-	22.6	10.3	-	52.0	36.7	11.9	-	40.1	36.8	18.6	
% Radioactivity in Sample																
Parent		64.2	ND	2.8	60.1	ND	2.7	6.7	0.3	ND	4.6	34.5	0.1	0.1	1.4	
M1									10.1				2.6	4.3		
M1-B													0.9	1.8		
M2													1.1	2.5		
M2-B													2.5	1.4		

2.6.5.9.a. In Vivo Metabolism in Mice and Rats (cont'd)

											Test Article: ruxolitinib			
Species	Mice (Male)			Mice (Female)			Rat (Male)				Rat (Female)			
	Pl	Ur	Fe	Pl	Ur	Fe	Pl	Ur ^a	Bile ^a	Fe ^a	Pl	Ur	Bile	Fe
M3								3.3				5.2		
M4								4.6				3.5		3.7
M5									7.1					
M6									7.4					
M7	15.3	22.8	11.5	19.9	27.4	14.8	10.0	30.5		33.7	4.2	5.0	3.4	14.2
M8	2.3	6.8	10.1	ND	6.9	10.3	18.9				20.2	17.8		29.4
M9	1.3	2.8	ND	1.3	3.5	ND	14.0	29.0	9.2	8.8	2.3	5.1	1.7	2.6
M11	ND	7.8	3.7	1.6	7.5	2.3	18.2			21.8	11.3	19.1	6.6	5.6
M15									11.6				9.2	
M16	ND	5.9	5.3	0.7	5.1	5.7	6.8	4.1		6.5	3.8		1.3	5.7
M17									31.4				0.7	
M18	5.3	1.8	4.9	4.3	1.9	6.4	1.7	2.4			3.7			1.0
M19												12.1	4.7	4.9
M20								3.8				2.5		
M21								3.2				2.2		
M25													12.7	
M26												0.2	3.7	
M27		3.5	2.8		2.1	2.1					3.4	5.7		12.3
M28												2.9	22.0	
M34													0.5	

2.6.5.9.a. In Vivo Metabolism in Mice and Rats (cont'd)

											Test Article: ruxolitinib			
	Mice (Male)			Mice (Female)			Rat (Male)				Rat (Female)			
Species	Pl	Ur	Fe	Pl	Ur	Fe	Pl	Ur ^a	Bile ^a	Fe ^a	Pl	Ur	Bile	Fe
M37		1.0	8.2		1.5	6.2								
M40		4.6	2.7		3.7	2.3								
M41		ND	9.2		5.9	11.0	7.1							
M42		11.3			5.3									
M43							2.9							
M48		1.5	1.4		1.9	3.4	4.8				4.1	2.2		2.8
M49												0.5		
M50	4.1		0.8	2.8		0.3						0.5	1.9	
M50-B											2.3	2.9		
M52							1.7							
M53							2.7						3.6	
M54											1.1			
Unknown peaks ^c			19.2			15.9					1.6	0.9	4.4	11.9
Others ^d											9.7	1.2	13.4	3.1

Additional Information:

^a In some cases, multiple metabolites co-eluted in male rat urine, bile and feces due to the shorter run time performed for these matrices.

^b ~ 30% of each sample was pooled from each time point such that 90% of the excreted dose from one rat was contained in a single sample.

^c represents metabolite peak(s) where metabolite structure could not be elucidated or those containing an undefined mixture of metabolites.

^d In female rats, multiple mono-, di-, tri- and quad- oxygenated metabolites and in some cases, subsequent conjugation, were also observed, each constituting ≤ 5% of radioactivity in the corresponding matrix.

MC – methylcellulose
 ND – not detected

In male rats, metabolite profiles in excreta after iv dosing were similar to oral dosing.

2.6.5.9.b. In Vivo Metabolism in Dogs and Humans

			Test Article: ruxolitinib						
Gender (M/F)/Number of animals:	Dogs: 2M			Dogs: 2F			Humans: 6M		
Feeding condition:	Not fasted			Not fasted			Fasted		
Vehicle/Formulation:	Solution / 0.5% MC in water			Solution / 0.5% MC in water			Solution / Water		
Method of Administration:	Gavage			Gavage			Oral		
Dose (mg/kg):	3			3			25 mg		
Radionuclide: ¹⁴ C									
Specific Activity:	5.25 x 10 ⁶ Bq/mg						5.45 x 10 ⁶ Bq/mg		
Study Number	[INCYTE-DMB-08.149.1]						[INCYTE-DMB-08.153.1]		
	Dog (Male)			Dog (Female)			Human		
Species	Plasma	Urine	Feces	Plasma	Urine	Feces	Plasma	Urine	Feces
Sampling Time or Period (hr)	1 hr	0-4 hr	0-24 hr	1 hr	0-4 hr	0-24 hr	1 hr	0-8 hr	24-48 hr
% of Dose in Sample	-	10.3	46.8	-	10.8	45.5	-	45.1	9.7
Mean % Radioactivity in Sample									
Parent	27.3	4.6	19.8	31.0	2.6	25.1	74.1	0.5	1.2
M7	1.3	ND	0.8	1.9	ND	1.0	3.8	14.3	9.9
M8	2.5	6.5	4.2	3.4	2.7	6.4	3.6	17.8	22.1
M9	2.7	4.1 ^a	3.3	3.2	2.3 ^a	1.2	ND	ND	ND
M11	1.1	ND	0.9	1.5	ND	1.2	3.7	23.6	ND
M16	2.9	2.9	^b	5.0	5.9	^b	2.3	5.2	4.5
M18	12.5	5.8	2.8	16.3	9.6	4.2	7.3		6.3
M23			3.2			5.2			
M24			2.8			3.2			
M25		5.2			6.4				
M26		2.0			7.1				
M27	^c	8.4	3.6	^c	10.2	3.9		18.9	14.5
M28		2.8			2.5			1.3	

2.6.5.9.b. In Vivo Metabolism in Dogs and Humans (cont'd)

							Test Article: ruxolitinib		
Species	Dog (Male)			Dog (Female)			Human		
	Plasma	Urine	Feces	Plasma	Urine	Feces	Plasma	Urine	Feces
M29			4.5			4.6			
M30		4.3			ND				
M31	2.6	2.0	3.5	3.6	2.9	4.0			4.6
M32	7.3			6.3					
M34	1.9			1.3					
M35		5.5			8.8				
M37	5.9	22.9	14.7 ^d	5.0	22.4	7.2 ^d		1.4	
M38		4.8			3.8		1.6		
M39	22.6			10.6					
M43									6.2
M45									2.3
M49							2.2	11.0	15.6
M51								1.9	
Unknown peak			11.4			10.8			
Additional Information: ^a In dog urine, M14 co-eluted with M9 ^b In dog feces, M16 co-eluted with M11 ^c In dog plasma, M27 co-eluted with stereoisomer, M16 ^d In dog feces, M37 co-eluted with M36 MC - methylcellulose									

26.5.13.a. Excretion in Rats After a Single Oral Dose

													Test Article: ruxolitinib	
Species:	Rat				Rat				Rat					
Gender (M/F)/Number of animals:	4M				4M				4F					
Feeding condition:	Fasted				Fasted				Fasted					
Vehicle/Formulation:	Solution / 0.5% methylcellulose in water				Solution / 10% DMAC, 30% of SBE-beta-cyclodextrin aqueous solution (50% w/v), and 60% saline				Solution / 0.5% methylcellulose in water					
Method of Administration:	Oral				Intravenous				Oral					
Dose (mg/kg):	50				10				25					
Analyte:	TRA ^a				TRA ^a				TRA ^a					
Assay:	LSC				LSC				LSC					
Excretion route:	Urine	Bile	Feces	Total	Urine	Bile	Feces	Total	Urine	Bile	Feces	Total		
Time														
0 – 24 hr	51.6	36.5	12.6	101	48.3	36.3	12.9	97.5	44.8	39.1	18.6	102		
0 – 48 hr	51.9	36.6	13.1	102	48.6	36.5	14.1	99.2	45.2	39.3	19.8	104		
0 – 72 hr	52.0	36.7	13.3	102	48.7	36.5	14.2	99.4	45.3	39.5	20.0	105		
0 – 96 hr	52.0	36.7	13.5	102	48.8	36.5	14.4	99.7	45.4	39.5	20.1	105		
Study number	[INCYTE-DMB-08.61.1]							[INCYTE-DMB-09.82.1]						
Additional Information:														
Cage wash also examined, but not shown														
^a Total radioactivity; percent recovery, ¹⁴ C														

2.6.5.13.b. Excretion in Dogs and Humans After a Single Oral Dose

			Test Article: ruxolitinib						
Species:	Dog			Dog			Human		
Gender (M/F)/Number of animals:	2M			2F			6M		
Feeding condition:	Not fasted			Not fasted			Fasted		
Vehicle/Formulation:	Solution / 0.5% methylcellulose in water			Solution / 0.5% methylcellulose in water			Solution / water		
Method of Administration:	Oral			Oral			Oral		
Dose (mg/kg):	3			3			25 mg		
Analyte:	TRA ^a			TRA ^a			TRA ^a		
Assay:	LSC			LSC			LSC		
Excretion route:	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total
Time									
0 – 24 hr	32.1	46.8	78.9	32.8	45.5	78.3	69.9	0.5	70.4
0 – 48 hr	33.9	53.1	87.0	35.8	51.9	87.7	73.0	9.9	82.9
0 – 72 hr	34.3	54.5	88.8	36.2	57.3	93.5	73.4	16.1	89.5
0 – 96 hr ^b	34.4	54.7	89.1	36.3	57.9	94.2	73.5	18.8	92.3
0 – 192 hr ^b							73.6	21.9	95.5
Study number	[INCYTE-DMB-08.62.2]						[INCYTE-DMB-08.150.1]		
Additional Information:									
^a Total radioactivity; percent recovery, ¹⁴ C									
^b For dogs, samples collected up to 96 hr. Human samples collected up to 144 hr for four subjects, 168 hr for one subject and 192 hr for one subject.									
In cases when there was no sample for a given interval from an individual subject (ie 0-24 h feces), the TRA for the individual sample was assigned a value of 0 for calculations.									
Cage wash for dog also examined, but not shown.									

6 General Toxicology

Overall toxicology summary

General toxicology: Single- and repeat-dose toxicology studies up to 6 months in duration in rats and up to 12 months in duration in dogs were conducted. Single doses of ruxolitinib up to 100 mg/kg in rats and 40 mg/kg in dogs were well tolerated; these were the highest doses tested in these studies. No ruxolitinib-related acute toxicity was determined in the single dose studies. Of note single-dose studies were non-GLP, only limited dose levels were used and minimal toxicity evaluations were performed. Repeated dosing in rats and dogs resulted in toxicities mainly in the hematopoietic system including reduced levels of circulating leukocytes, especially lymphocytes in rats and dogs. Lymphoid depletion was noted in multiple lymph nodes and spleen.

Genetic toxicology: Ruxolitinib was not mutagenic in the bacterial mutagenicity assay or clastogenic in the *in vitro* chromosome aberration assay or in the *in vivo* micronucleus assay in rats.

Carcinogenicity: Ruxolitinib was not carcinogenic in a 26-week study in Tg.rasH2 mice. A 2-year rat carcinogenicity study is ongoing.

Reproductive toxicology: In embryo-fetal developmental studies in the rat and rabbit, ruxolitinib was not teratogenic, but was associated with increased late resorptions (rabbit only) and fetal toxicity (reduced fetal weights in rats and rabbits). The No-Observed-Adverse-Effect-Level (NOAEL) dose for the rat and rabbit study was 30 mg/kg/day. In a pre- and post-natal development study, there were no adverse findings for fertility indices and maternal and embryo-fetal survival, growth, and developmental parameters. A placental transfer and lactation study in rats given ruxolitinib demonstrated that low concentrations of ruxolitinib cross the placenta, and parent compound is eliminated rapidly resulting in limited fetal exposure. In lactating rats, ruxolitinib derived radioactivity was excreted into the milk with a concentration that was 13-fold higher than the corresponding maternal plasma concentration.

Special toxicology: no study conducted

6.1 Single-Dose Toxicity

Some single-dose studies were reviewed by Dr. Babara Hill under IND 77101, the results are not presented here. In conclusion, the toxicities associated with ruxolitinib were similar to those observed in the repeated-dose studies.

6.2 Repeat-Dose Toxicity

Study title: 6-month oral (gavage) toxicity study of INCB018424 in rats with a 6 week recovery period

Study no.: (b) (4)-519048
Sponsor study No.: T07-10-06
Study report location: Electronic submission, M4. pages 1-4625
Conducting laboratory and location: (b) (4)
Date of study initiation: 1 October 2007
GLP compliance: yes
QA statement: yes (X) no ()
Drug, lot #, and % purity: INCB018424, SS-IN3-139, 99.9%

Key Study Findings

- No treatment-related death was observed at doses up to 60 mg/kg/day for 26 weeks;
- Lower body weights were noted in a dose-related manner for treated males and lower food consumption was noted for the 60 mg/kg/day group males;
- Reduced levels of circulating leukocytes were noted at all dose levels along with lower spleen weights in both sexes.
- Lymphoid depletion was noted in most spleen sections and in several mandibular lymph nodes at the 60 mg/kg/day dose level;
- Treatment-related changes were generally reversible.

Methods

Doses: 5,10,30, 60 mg/kg*
 * The dose levels were stated to be based on previous studies; no other specific information was provided

Frequency of dosing: once daily for 182 days, followed by a 42-day recovery period (recovery group)

Route of administration: Oral gavage

Dose volume: 10 mg/mL

Formulation/Vehicle: 0.5% methylcellulose in reverse osmosis-treated water

Species/Strain: Rat/Crl:CD(SD)

:
 Number/Sex/Group: See table below

Age: approximately 35 days old

Weight: ranged from 199 g to 286 g for males and from 139 g to 199 g for females

Satellite groups: 5/sex for control, 11/sex/group for treatment group

Unique study design: none

Deviation from study protocol: none

Number of Animals/sex/group- Rising Dose					
	Vehicle 0 mg/kg/day	5 mg/kg/day	10 mg/kg/day	30 mg/kg/day	60 mg/kg/day
Main	15	15	15	15	15
Recovery	8	8	8	8	8

Observations and Results

OBSERVATIONS AND TIMES:

<u>Mortality</u>	Two times daily
<u>Clinical examinations</u>	Two times daily
<u>Detailed physical examinations</u>	weekly
<u>Body weights</u>	weekly
<u>Food consumption</u>	weekly
<u>Ophthalmoscopy</u>	Weeks -1, 25, 32
<u>Clinical Pathology:</u>	week 12 (hematology and serum chemistry), and prior to sacrifice (week 26 or 32)
<u>Gross pathology:</u>	At death or at scheduled sacrifice
<u>Organ weights:</u>	At sacrifice
<u>Histopathology:</u>	At sacrifice or death Adequate Battery: yes (x), no (), Peer review: yes (x), no ()

<u>Toxicokinetics:</u>	prior to dosing and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours after dose administration on study days 0, 27 and 181.

RESULTS:**Mortality**

Animal	Sex	Dose (mg/kg/day)	Days of death	Type of death	Death cause
8177	M	0	57	Found dead	unknown
8078	M	5	162	Found dead	unknown
8198	M	30	155	Found dead	unknown
8222	M	30	166	Found dead	unknown
8331	F	60	101	Found dead	unknown

Summary: None of the early death are considered as treatment-related deaths.

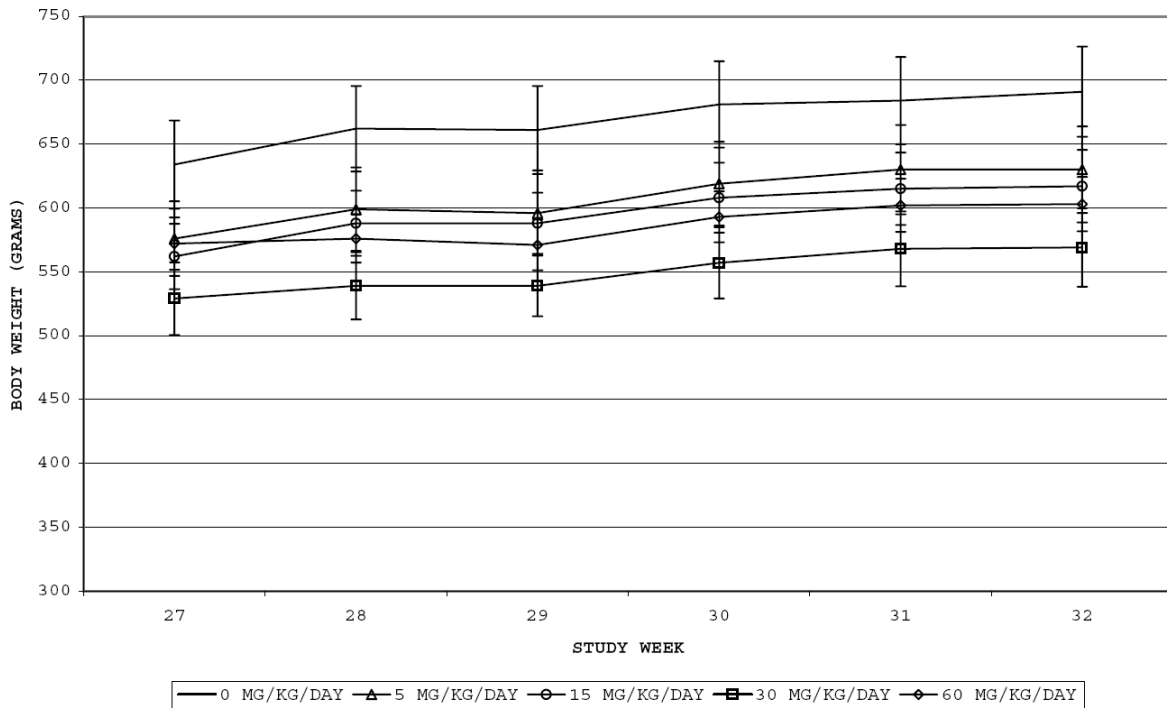
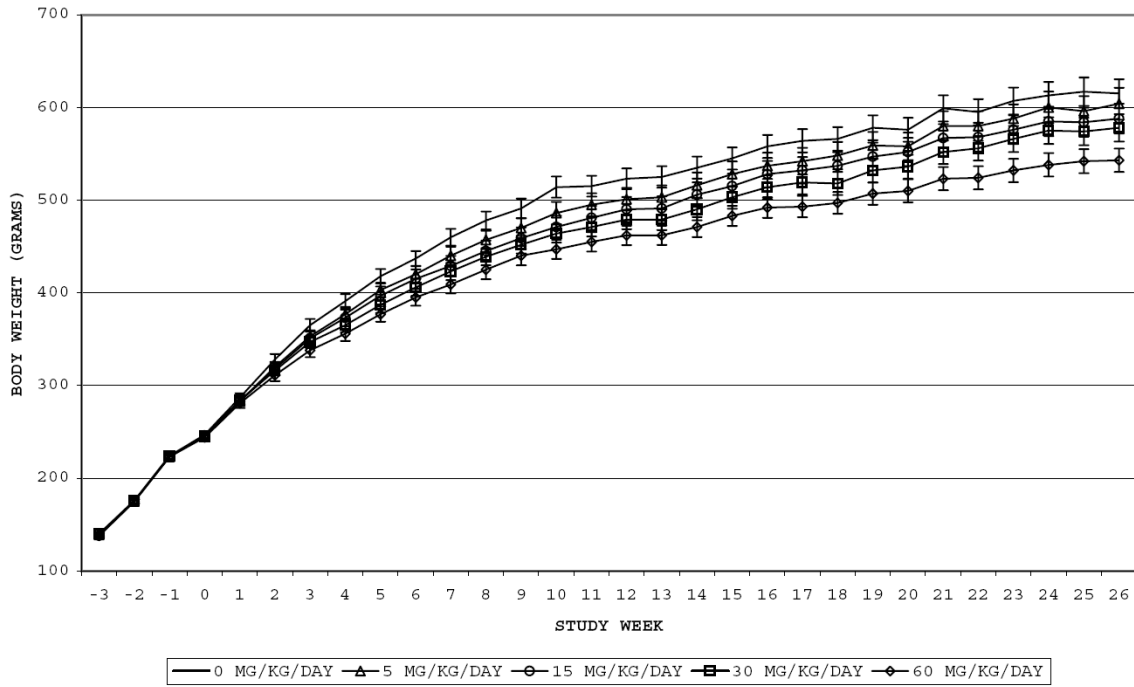
Clinical Signs

Early death animals	• unremarkable
5 mg/kg/day	• unremarkable
10 mg/kg/day	• unremarkable
30 mg/kg/day	• unremarkable
60 mg/kg/day	• wet clear and wet/dry red material around the mouth, male and female

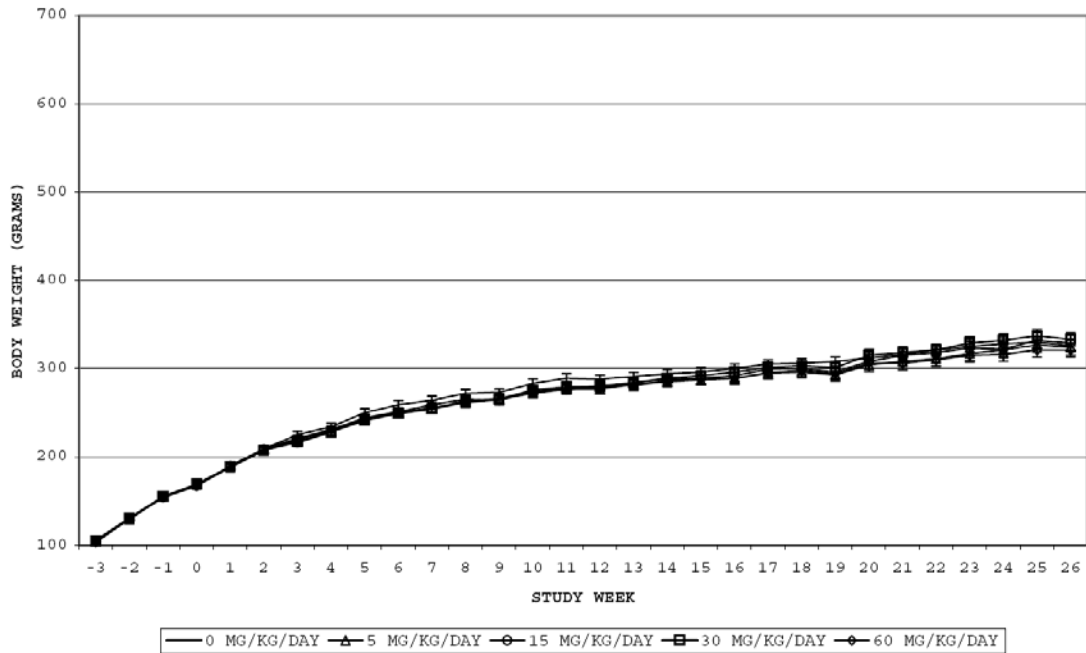
Body Weights

The following figures are excerpted from the Applicant's submission, the data are verified by the reviewer.

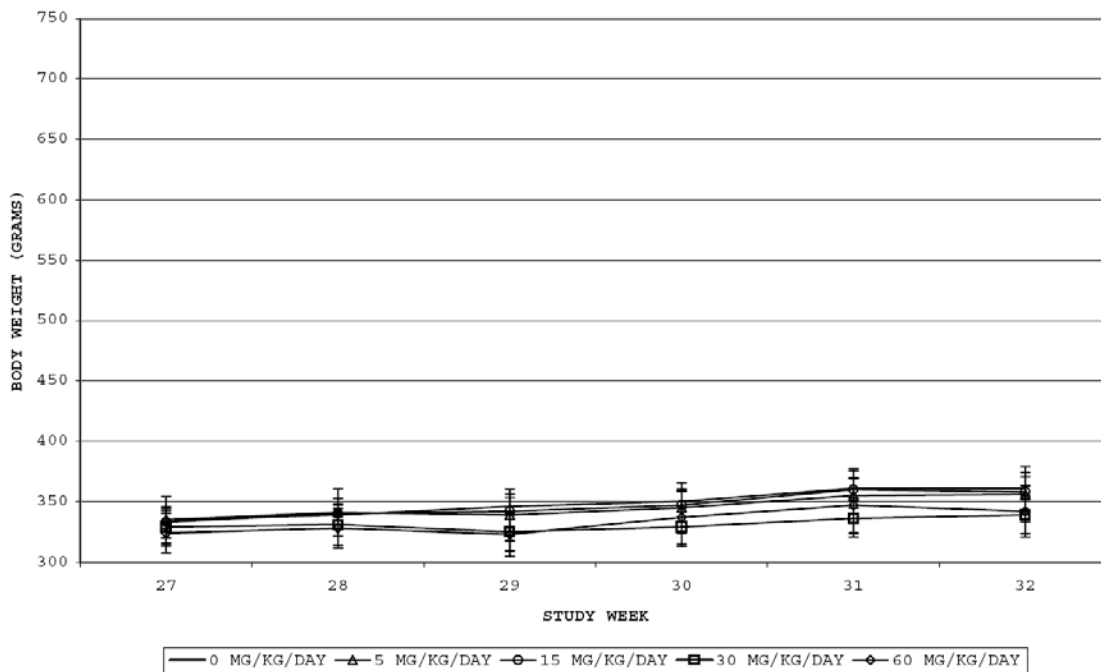
Summary of body weight (g) (dosing period- males)



Summary of body weight (g) (dosing period- Females)



Summary of body weight (g) (dosing period- females)



Summary:

- During the dosing period, decreased body weights were observed in test article-treated group males as early as the second week of dosing. Mean body weights at the end of the dosing period were 1.8%, 4.4%, 6.0% and 11.7% lower than control values for the 5, 15, 30 and 60 mg/kg/day group males, respectively. Lower weight changes were partially recovered by the end of the recovery period.
- No significant body weight changes were observed in females.

Feed Consumption

Lower food consumption (occasionally statistically significant) was noted for the 60 mg/kg/day group males (↓0- 21%). A similar trend was not observed for the 60 mg/kg/day group females.

Ophthalmoscopy

No test-article related changes

Hematology

MALES	Percent Change From Vehicle Control											
Doses (mg/kg/day)	5			15			30			60		
Assessment week	12	26	32	12	26	32	12	26	32	12	26	32
Hemoglobin										↓7	↓4	
hematocrit										↓7	↓3	
WBC	↓12	↓5	↓18	↓30	↓16		↓29	↓24	↓18	↓32	↓32	↓14
Neutrophil (E ³ /μl)	↓9	↓6	↓23	↓8		↑39	↑15		↓12	↑45	↑12	↓6
Lymphocyte (E ³ /μl)	↓13	↓5	↓16	↓33	↓20	↓8	↓36	↓31	↓19	↓45	↓43	↓16
Monocyte (E ³ /μl)	↑10		↓20		↑18	↑10	↓5	↓5	↓23	↑10	↓14	↓13
Eosinophil (E ³ /μl)	↑8		↓21	↓25	↓8	↓7	↓42	↑23		↑25	↓8	↑7
Basophil (E ³ /μl)	↓33		↓50	↓33			↓33	↓57	↓14	↓63	↓57	↓14
LUC (E ³ /μl)	↓12	↓28		↓38	↓14		↓63	↓44		↓25	↓57	↓13
FEMALES	Percent Change From Vehicle Control											
Doses (mg/kg/day)	5			15			30			60		
Assessment week	12	26	32	12	26	32	12	26	32	12	26	32
Hemoglobin										↓4	↓2	
WBC	↓6	↓17	↑8	↓21	↓10		↓19	↓21		↓39	↓38	
Neutrophil (E ³ /μl)	↑21	↓6	↓8		↑30	↓6	↑22	↓8	↓8	↑44		↓8
Lymphocyte (E ³ /μl)	↓9	↓19	↑12	↓24	↓18		↓25	↓23		↓50	↓46	↑10
Monocyte (E ³ /μl)		↓25		↓14	↓10		↑7	↓30	↓15	↓7	↓40	↓20
Eosinophil (E ³ /μl)			↑33		↓11	↑11		↓22		↓43	↓44	
Basophil (E ³ /μl)	↓50		↓50				↓50	↓100		↓50		↓100
LUC (E ³ /μl)	↓20	↓40		↓40	↓40	↑33	↓40	↓60	↑33	↓60	↓60	

Blank cells: unremarkable changes.

Week 32 represents the recovery data.

LUC: large unstained cell.

Summary:

- Lower white blood cell counts and lower counts of absolute, lymphocyte, monocyte, basophil, and large unstained cells (LUC) were noted at study weeks 12 and 26 in male and female animals at all dose levels of INCB018424. Hemoglobin and hematocrit were slightly lower in the male and female groups at 60 mg/kg/day. These changes were reversible.

Clinical Chemistry

No test-article related changes

Urinalysis

No test-article related changes

Gross Pathology

Unremarkable

Organ Weights

The following table is excerpted from the Applicant's application. The data on the table are verified by the reviewer.

Toxicologically Relevant Final Body Weight and Organ Weight Changes At Study Week 26

Dose Group (mg/kg/day):	<u>5</u>	<u>15</u>	<u>30</u>	<u>60</u>
Final Body Weight (male)	↑3.2	↑0.2%	↑0.2%	↓11.2%*
Final Body Weight (female)	↓2.0%	0.0%	↑3.9%	↓1.6%
Adrenal Gland (Male)				
Absolute	↓12.2%**	↓15.0%**	↓23.1%**	↓26.7%**
Relative-to-Body	↓10.0%**	↓10.0%**	↓20.0%**	↓10.0%**
Relative-to-Brain	↓12.1%**	↓14.4%**	↓23.4%**	↓24.8%**
Spleen (Male)				
Absolute	↓11.0%	↓17.1%**	↓23.2%**	↓39.0%**
Relative-to-Body	↓13.9%**	↓16.7%**	↓23.6%**	↓31.3%**
Relative-to-Brain	↓11.4%	↓17.0%**	↓23.3%**	↓37.9%**
Spleen (Female)				
Absolute	↓14.8%*	↓13.0%	↓16.7%**	↓27.8%**
Relative-to-Body	↓13.1%*	↓11.9%*	↓19.9%**	↓26.1%**
Relative-to-Brain	↓14.0%*	↓13.7%*	↓15.1%*	↓26.8%**

* = Significantly different from the control group at p<0.05 using Dunnett's test

** = Significantly different from the control group at p<0.01 using Dunnett's test

Toxicologically Relevant Final Body Weight and Organ Weight Changes At Study Week
32 (recovery)

Dose Group (mg/kg/day):	<u>5</u>	<u>15</u>	<u>30</u>	<u>60</u>
Final Body Weight (male)	↓9%	↓11%	↓18%	↓13%
Final Body Weight (female)			↓5%	↓5%
Adrenal Gland (Male)				
Absolute	↑4%	↓13%	↓2%	↓8%
Relative-to-Body	↑25%		↑25%	↑13%
Relative-to-Brain		↓13%		↓9%
Spleen (Male)				
Absolute	↑6%	↑12%		
Relative-to-Body	↑17%	↑25%**	↑20%	↑17%
Relative-to-Brain		↑13%		
Spleen (Female)				
Absolute		↓7%	↓5%	↓7%
Relative-to-Body		↓5%		
Relative-to-Brain		↓6%		

Note: Blank: unremarkable change

Summary:

- Test article-related changes include decreased weights of the spleen in both males and females, and decreased weights of adrenal gland in males. Organ weight changes were reversible.

Histopathology

At the study week 26, test article-related histologic changes were restricted to the 60 mg/kg/day group where minimal to mild lymphoid depletion was observed in the spleen and mandibular lymph nodes of both genders. Additionally, minimal cortical atrophy was observed in the adrenal glands of the 60 mg/kg/day group males. The incidence and severity of microscopic findings in the spleen, mandibular lymph nodes, and adrenal glands are summarized in the following table (from the submission). At the study week 32 (recovery necropsy), microscopic changes were not observed that were attributed to the test article, suggesting full recovery.

**Incidence Of Selected Histopathologic Findings At The
Study Week 26 Primary Necropsy**

Dosage (mg/kg/day):	Males					Females				
	0	5	15	30	60	0	5	15	30	60
Adrenal Cortex ^a	15	15	15	15	15	15	0	0	1	15
Atrophy	0	0	0	0	7	0	0	0	0	0
Minimal	-	-	-	-	7	-	-	-	-	-
Mandibular lymph node ^a	15	15	15	15	14	15	15	15	15	15
Depletion, lymphoid	0	0	0	0	3	0	0	0	0	3
Minimal	-	-	-	-	2	-	-	-	-	2
Mild	-	-	-	-	1	-	-	-	-	1
Spleen ^a	15	15	15	15	15	15	15	15	14	15
Depletion, lymphoid	1	0	1	1	15	0	0	0	0	11
Minimal	0	-	0	1	6	-	-	-	-	9
Mild	1	-	1	0	9	-	-	-	-	2

^a = Number of tissues examined from each group.

Toxicokinetics: refer to PK section.

STUDY SUMMARY:

INCB018424 administered by oral gavage to Sprague Dawley rats at doses of 5, 15, 30 and 60 mg/kg/day for 26 weeks was well tolerated, with no test article-related deaths, ophthalmic findings or alterations in coagulation and urinalysis parameters. Test article-related clinical observations were limited to findings of clear and red material around the mouth noted for the 60 mg/kg/day group males and females. Lower body weights were noted in a dose-related manner for treated males and lower food consumption was noted for the 60 mg/kg/day group males. The mean body weight for the 60 mg/kg/day males was approximately 12% lower than the mean control value by the end of the dosing period and did not fully recover by the end of the 42-day recovery period. Reduced levels of circulating WBCs and lymphocytes were noted at all dose levels along with lower spleen weights in both sexes. Lymphoid depletion was documented in most spleen sections and in several mandibular lymph nodes at the 60 mg/kg/day dose level. Adrenal atrophy observed in histopathology correlated with reduced absolute and relative weight of adrenal glands. Clinical and anatomical pathology findings at the study week 32 recovery necropsy indicated that partial to full recovery was in progress in both genders administered all dose levels of INCB018424.

Study title: A 6-month oral (gavage) toxicity study with INCB018424 in beagle dogs with 6-week recovery period

Study no.: (b) (4)-519049

Sponsor study number: T07-10-07

Study report location: M4.2.3.2.8, ncl-124-report.pdf, , page 1-779

Conducting laboratory and location: (b) (4)

Date of study initiation: 26 September 2007

GLP compliance: yes

QA statement: yes (X) no ()

Drug, lot #, and % purity: INCB018424, SS-IN3-139, 99.9%

Key study findings:

- Unscheduled deaths were observed at 10 mg/kg;
- The causes of death were attributed to inflammatory lesions in the lung/thoracic cavity;
- All early death animals were also observed with bacterial infections of the lungs and/or the paws;
- Demodectic mange associated bacterial infections of the skin were observed in animals at 5 and 10 mg/kg groups;
- lower red blood cells, hematocrit and hemoglobin were observed in the 5 mg/kg/day group males and 10 mg/kg/day group males and females; higher absolute neutrophil and monocyte counts and lower absolute lymphocyte and eosinophil counts, was most prominent in the 10 mg/kg/day group males;
- Histopathology changes included lymph node depletion within follicular centers, granulomatous inflammation with parasitic mites in the regional lymph nodes, inflammatory cell infiltrates in the lymph nodes, and acute and/or subacute inflammation of the lung tissues at doses ≥ 5 mg/kg/day.

METHODS:

Doses:	0.5, 2.5, 5 and 10 mg/kg/day
Dose Justification:	Dosage levels were selected based on results from a previous 28-day dog study (Burns, 2007) in which 10 mg/kg/day was defined as the NOAEL dose
Controls:	0.5% methylcellulose in reverse osmosis-treated water
Species/strain:	Beagle dog

Number/sex/group:					
Number of Animals/sex/group					
	Vehicle Control	0.5 mg/kg/d	2.5 mg/kg/d	5.0 mg/kg/d	10mg/kg/d
Main	5	5	3	3	5
Recovery	1-2	1-2	1-2	1 -2	1-2
Route, formulation, volume			Oral gavage. diluted in 0.5% methylcellulose in reverse osmosis-treated water, 10 mg/mL		
Satellite groups used for toxicokinetics:			12/sex/group		
Study design:			Male and female dogs were dosed daily via oral gavage for a total 6 months, followed by a 43 days recovery period (recovery groups)		

OBSERVATIONS AND TIMES:

<u>Mortality</u>	Two times daily
<u>Clinical examinations</u>	daily
<u>Detailed physical examinations</u>	weekly
<u>Body weights</u>	weekly
<u>Food consumption</u>	Recorded daily, reported weekly
<u>Hematology and coagulation</u>	prior to randomization (study day -5) and on study days 27, 49, 86, 135 (hematology only), 174 and 224
<u>Serum chemistry</u>	prior to randomization (study day -5) and on study days 27, 49, 86, 174 and 224
<u>Urinalysis</u>	prior to randomization (study day -5) and on study days 27, 49, 86, 174 and 224
<u>Urine metabolite profiling</u>	on study days -8, 0 and 176
<u>Ophthalmoscopy</u>	during study weeks -2, 25 and 32
<u>EKG</u>	weeks -2, 25 and 31
<u>Gross pathology:</u>	All animals sacrifice
<u>Organ weights:</u>	All animals at sacrifice
<u>Histopathology:</u>	animals found dead or euthanized in extremis as well as all animals in the control (0 mg/kg/day) and high dose (10 mg/kg/day) groups. Adequate Battery: yes (x), no (), Peer review: yes (x), no ()
<u>Toxicokinetics:</u>	prior to dosing and at 0.5, 1, 2, 4, 8, 12 and 24 hours after dose administration on study days 0, 40 and 175

RESULTS:

Mortality: Three early deaths at 10 mg/kg/day.

1 female (# 4454): died on study day 126,

2 males: # 4411 was found dead on study day 179,

4430 was euthanized in extremis on study day 156.

Clinical signs:**Early death:**

Male #4411: reddened facial area, clear to colored discharge from the eyes, soft feces and/or diarrhea were observed prior to death.

Male #4430: hypoactivity, prostration with labored respiration and swelling in the left hindlimb were noted. Other clinical observations noted prior to euthanasia included soft feces, diarrhea and clear and/or colored discharge from the eyes and warts on the left hindlimb.

Female #4454: Clinical observations prior to death included hypoactivity, increased respiration rate, labored respiration, diarrhea, swelling of the left and right forelimbs and hindlimbs and impaired use of the left and right hindlimbs.

Terminal death:

Test article-related clinical observations consisting of clear to colored discharge from the eyes, soft feces and/or diarrhea (females), reddened areas, swelling and hair loss on the limbs (which correlated to demodectic mange), were noted for the 5 and 10 mg/kg/day group males and females

Several animals in the 10 mg/kg/day group were also observed with interdigital cysts. Additionally, four animals at this dose had warts on the limbs and/or facial area.

Bodyweight: With the exception of the early death animals in the 10 mg/kg/day group which had some notable body weight changes (male #4430 lost 0.7 kg total; female #4454 lost 0.7 kg total), there were no obvious test article-related changes in mean body weights in any treated group when compared to the control group.

Food Consumption:

< week 19: unremarkable

19-26 weeks:

male: lower at 10 mg/kg, ↓8%-28% comparing to control group

female: dose-dependently reduced in all treatment groups

0.5 mg/kg-↓11%-22% comparing to control group

2.5 mg/kg- ↓4%-18% comparing to control group

5 mg/kg- ↓11%-17% comparing to control group

10 mg/kg--↓11%-28% comparing to control group

26-32 weeks:

male: lower at 10 mg/kg, ↓31%-51% comparing to control group

female: 0.5 mg/kg-↓10%-42% comparing to control group

2.5 mg/kg- ↓41%-↑9% comparing to control group

5 mg/kg- ↓12%-37% comparing to control group

10 mg/kg--↓42%-↑17% comparing to control group

Hematology:

MALES		Percent Change From Vehicle Control					
5 mg/kg/day							
Assessment Day	27	49	86	135	174	224	
RBC	↓8	↓4	↓10	↓9	↓14		
Hemoglobin	↓6		↓10	↓9	↓16		
Hematocrit	↓7		↓10	↓9	↓15		
Reticulocyte	↓27	↓29	↓25	↓29	↑15	↓10	
Neutrophils	↑29	↑23	↓6	↑5	↑9	↓5	
Lymphocytes	↓13	↓11	↓11		↓14		
Monocytes	↑49	↑32	↓17	↑15	↑31	↑43	
Eosinophils	↓17	↓18	↓59	↓35	↓36		
Basophils	↓50		↓50			↑50	
10 mg/kg							
RBC	↓11	↓13	↓16	↓20	↓27	↓9	
Hemoglobin	↓10	↓13	↓18	↓22	↓33	↓17	
Hematocrit	↓11	↓14	↓17	↓21	↓30	↓16	
Reticulocyte	↓32	↓17	↓30	↓12	↑22	↑11	
Neutrophils	↑22	↑16	↑30	↑71	↑64	↓23	
Lymphocytes	↓21	↓29	↓23	↓13	↑28	↓33	
Monocytes	↑37	↑21	↑46	↑70	↑102	↑60	
Eosinophils	↓48	↓53	↓64	↓30	↓59	↓29	
Basophils	↓25	↓33	↓50	↑8		↑38	
LUC			↑20	↑100	↑50	↓63	
FEMALES		Percent Change From Vehicle Control					
5 mg/kg/day							
Assessment Day	27	49	86	135	174	224	
RBC					↓8		
Hemoglobin				↓6	↓9		
Hematocrit				↓5	↓9		
Reticulocyte	↓18		↓18	↓30	↑47	↓21	
Monocytes			↓10	↑12	↑20	↓26	
Eosinophils	↓41	↓68	↓57	↓49	↓80	↑74	
Basophils		↑67	↑67	↑100	↑50	↑100	
LUC	↑85	↑71	↑63	↑113	↑83		
10 mg/kg/day							
RBC			↓6	↓7	↓14	↑8	
Hemoglobin	↓5	↓8	↓11	↓11	↓19		
Hematocrit		↓6	↓9	↓10	↓17		
Reticulocyte	↑5	↓15	↓12	↓12	↑32	↑226	
Neutrophil			↓10	↑11	↑10	↓15	
Monocytes	↑16	↑23	↑17	↑42	↑76	↓27	

Eosinophils	↓59	↓65	↓57	↓55	↓73	↑79
Basophils		↑33	↑33	↑33	↑50	
LUC	↑114	↑171	↑50	↑137	↑117	↓33

Day 224 represents the recovery data

Summary:

- Test article-related effects included lower red blood cell counts, hemoglobin and hematocrit in the 5 mg/kg/day group males and the 10 mg/kg/day group males and females. Absolute reticulocyte counts were also lower in spite of lower red cell mass, which suggested a nonregenerative anemia and appeared to be reflective of a test article-related suppression of erythropoiesis. The study results showed a trend over time toward higher absolute neutrophil and monocyte counts (suggesting inflammation) and lower absolute lymphocyte and eosinophil counts, most prominent in the 10 mg/kg/day group males. Full or partial recovery was evident in hematologic parameters on study day 224.

Clinical Chemistry: unremarkable

Urinalysis: unremarkable

Ophthalmoscopy: unremarkable

EKG: unremarkable

Organ Weight: unremarkable

Gross Pathology:

Early deaths:

Male #4411: Reddened areas of the gastrointestinal tract, thickened heart and over 300 mL of red fluid in the thoracic cavity were observed macroscopically.

Male #4430: Reddened areas in the gastrointestinal tract, dark red and white discolorations on the lungs, lungs not fully collapsed and enlarged thyroid glands were noted.

Female #4454: Reddened areas in the gastrointestinal tract, dark red and white discolorations on the lungs, small and pale spleen, pale thyroid glands and approximately 100 mL of red fluid in the thoracic cavity were noted

Terminal deaths: The following summary table was excerpted from the submission

Toxicologically Relevant Gross Necropsy Observations

<u>Organ</u>	<u>Observation</u>	<u>Dosage Level(s)</u> <u>(mg/kg/day)</u>	<u>Sex</u>	<u>Interval(s)</u>
Skin or Ears	Parasitic mite-related	5.0, 10	M	PN, RN
	Scabbing/Discoloration or Swelling	10	F	PN, RN
Skin or Ears	Papilloma-related Nodule(s)	10	M/F	PN
Lungs	Acute to subacute inflammation-related Discolorations	5.0, 10	M	PN
		5.0	F	
Prostate	Small	10	M	PN
Female Reproductive Organs	Diestrus-related gross findings or comments	5.0, 10	F	PN

M = Males, F = Females, PN = Primary Necropsy, RN = Recovery Necropsy

Histopathology:**Early death animals:**

Male #4411: Variable lymphoid depletion in lymphoid organs and parasitic mite-related changes in the skin and mandibular lymph node were noted microscopically. Acute inflammation within the thoracic cavity was considered to be the cause of death.

Male #4430: moderate acute inflammation in the lungs morphologically consistent with a bacterial bronchopneumonia, which was considered to be the cause of death, and variable lymphoid depletion in the lymphoid organs were noted.

Female #4454: lymphoid depletion was evident in most sections of lymphoid tissue. Moderate bone marrow hypocellularity was noted. The cause of death was attributed to multifocal necrosis (with acute inflammation and bacteria) in the lung. Acute inflammation, necrosis and hemorrhage were noted in all 4 paws. There was also evidence of bacterial colonization of areas of skin with inflammation.

Terminal animals: Minimal-to-moderate acute or subacute inflammation was noted in the lungs of occasional dogs administered ≥ 2.5 mg/kg/day. Parasitic mites without inflammation were noted in one 2.5 mg/kg/day female. Lymphoid depletion within follicular centers and/or more generalized lymphoid depletion, and granulomatous inflammation with parasitic mites in regional lymph nodes were noted in animals at 5 and 10 mg/kg groups. Areas of inflammation occasionally included the

presence of bacterial colonization. Squamous cell papilloma with basophilic intranuclear inclusion bodies in the skin was noted in 2 dogs (1 male and 1 female) administered 10 mg/kg/day of the drug.

In the reproductive organs, prostate hypoplasia/atrophy was noted in 1 dog administered 5 mg/kg/day and 2 dogs administered 10 mg/kg/day. In the female dogs, the diestrus stage of the estrous cycle was noted in 1, 1, and 3 females administered 0.5, 5 and 10 mg/kg/day, respectively. Estrus was noted in 1 female administered 0.5 mg/kg/day and in 1 female administered 5 mg/kg/day. All control group females were in either anestrus or proestrus. A lack of regressing/residual corpora lutea and minimal mammary gland development in most females suggested that these dogs were either sexually immature or in their first estrous cycle.

At the recovery examination, pyogranulomatous inflammation in the skin, typically associated with mite and/or bacterial infestation, was noted in males and females that had been administered 5 or 10 mg/kg/day, with extension of inflammation into the mandibular lymph node. One control group female and 5 of 7 females administered INCB018424 were in diestrus.

Toxicokinetics: refer to PK section

STUDY SUMMARY:

INCB018424 was administered to male and female dogs via oral gavage at doses of 0, 0.5, 2.5, 5, and 10 mg/kg/day daily for 6 months, followed by a 6-week recovery period. Systemic toxicity was observed at dosage levels of 5 and 10 mg/kg/day. Test article-related effects included 3 unscheduled deaths in the 10 mg/kg/day group animals with clinical findings of reddened areas, swelling and hair loss on the limbs, diarrhea and/or soft feces and clear and/or colored discharge from the eyes. The causes of death in all 3 dogs were attributed to inflammatory lesions in the lung/thoracic cavity (acute inflammation in both males and lung necrosis in the female). Generalized lymphoid depletion, granulomatous inflammation with parasitic mites, inflammatory cell infiltrates in the lymph nodes and acute and/or subacute inflammation of the lungs were noted microscopically in the ≥ 5 mg/kg/day group animals. Microscopic findings consisted of demodectic mange in one 2.5 mg/kg/day group animal.

Study title: 52-week oral gavage chronic toxicity and toxicokinetic study with INCB018424 in dogs with a 6-week recovery period

Study no.: 7456-271

Sponsor study number: T08-07-03

Study report location: Electronic submission, page 1-1106

Conducting laboratory and location: (b) (4)

Date of study initiation: 02 July 2008

GLP compliance: yes

QA statement: yes (X) no ()

Drug, lot #, and % purity: INCB018424, BPR-07-101-B2-21, 97.8%

Key study findings:

- Unscheduled deaths were observed at 6 mg/kg;
- Dogs died of clinical demodicosis;
- Treatment with INCB018424 resulted in reduced mean absolute lymphocytes, eosinophils, and red cell mass parameters;
- Histopathology changes included decreased lymphocytes in the gut-associated lymphoid tissue (GALT) of the ileum, in the cortex of the mandibular and mesenteric lymph nodes, and in the white pulp of the spleen;
- Treatment-related changes were reversible.

METHODS:

Doses:	0.75, 1.5, 3, and 6 mg/kg/day				
Dose Justification:	Dosage levels were selected based on results from a previous 28-day dog study (Burns, 2007) in which 10 mg/kg/day was defined as the NOAEL dose				
Controls:	0.5% methylcellulose in reverse osmosis-treated water				
Species/strain:	Beagle dog				
Number/sex/group:					
Number of Animals/sex/group					
	Vehicle Control	0.75 mg/kg/d	1.5 mg/kg/d	3 mg/kg/d	6 mg/kg/d
Main	5	5	5	5	5
Recovery	2	2	2	2	2
Route, formulation, volume	Oral gavage. diluted in 0.5% methylcellulose in reverse osmosis-treated water, 10 mg/mL				
Satellite groups used for toxicokinetics:	none				

Study design:	Male and female dogs were dosed daily via oral gavage for a total 52 weeks, followed by a 6-week recovery period (recovery groups). Note: male group at 6 mg/kg were terminated early (dosing phase week 29, dosing phase day 197)

OBSERVATIONS AND TIMES:

<u>Mortality</u>	Two times daily
<u>Clinical examinations</u>	daily
<u>Detailed physical examinations</u>	weekly
<u>Body weights</u>	predose phase, weekly during the dosing phase, on the first day of recovery phase, and weekly thereafter during the recovery phase.
<u>Food consumption</u>	1-week interval during the predose phase, weekly during the dosing phase, on the first day of recovery phase, and weekly thereafter during the recovery phase
<u>Hematology and coagulation</u>	prior to randomization (study day -5) and on study days 27, 49, 86, 135 (hematology only), 174 and 224
<u>Serum chemistry</u>	during the predose phase and once during dosing phase weeks 4, 12, 26, 39, and 52 (excluding Group 5 males) of the dosing phase additionally, a hematology sample was collected from Group 5 Male No. H49124 on dosing phase day 169 approximately 24 hours postdose (based on dosing time from dosing phase day 168) Blood and urine samples were collected prior to the early sacrifice of the surviving group 5 males on dosing phase day 197
<u>Urinalysis</u>	once during the predose phase and once during dosing phase weeks 4, 12, 26, 39, and 52 (excluding Group 5 males) Blood and urine samples were collected prior to the early sacrifice of the surviving Group 5 males on Dosing Phase Day 197
<u>Urine metabolite profiling</u>	Urine samples were collected once prior to dosing, on day 1, and during dosing phase weeks 4, 26, and 52 (excluding Group 5 males) of the dosing phase
<u>Ophthalmoscopy</u>	during the predose phase, during week 52 of the dosing phase (excluding Group 5 males),

	and during week 6 of the recovery phase (excluding Group 5 males)
<u>EKG</u>	Recorded once during the predose phase, during Week 52 of the dosing phase (excluding Group 5 males), and during week 6 of the recovery phase (excluding Group 5 males)
<u>Gross pathology:</u>	All animals at sacrifice
<u>Organ weights:</u>	All animals at sacrifice
<u>Immunophenotype</u>	all animals during Week 26 (in conjunction with the clinical pathology samples).
<u>Histopathology:</u>	All animals at sacrifice Adequate Battery: yes (x), no () Peer review: yes (x), no ()
<u>Toxicokinetics:</u>	day 1 and during weeks 4, 13, 26, and 52 (excluding Group 5 males) of the dosing phase within 1 hour of dosing and approximately 0.5, 1, 2, 4, 8, 12, and 24 hour postdose. Additionally, a sample was collected from Group 5 Male No. H49124 on Dosing Phase Day 169 approximately 24 hours postdose (based on dosing time from Dosing Phase Day 168). Surviving Group 5 males were bled on Dosing Phase Day 196 (Week 28) within 1 hour of dosing and approximately 0.5, 1, 2, 4, 8, 12, and 24 hours postdose. The 12 and 24 hour samples were collected from fasted dogs.

RESULTS:

Mortality: four early deaths at 6 mg/kg/day.

1 female: on study day 197; moribund sacrifice

3 males: on study day 197; moribund sacrifice

The moribund condition was attributed to inflammation of the skin/subcutis and footpad

Clinical signs:

Early death: cage sores, alopecia, black skin, broken skin, dry skin, red skin, scabs, interdigital cysts, interdigital furunculosis, papillomatosis, and pododermatitis

Male #4411: reddened facial area, clear to colored discharge from the eyes, soft feces and or diarrhea were observed prior to death.

Male #4430: hypoactivity, prostration with labored respiration and swelling in the left hindlimb were noted. Other clinical observations noted prior to

euthanasia included soft feces, diarrhea and clear and/or colored discharge from the eyes and warts on the left hindlimb.

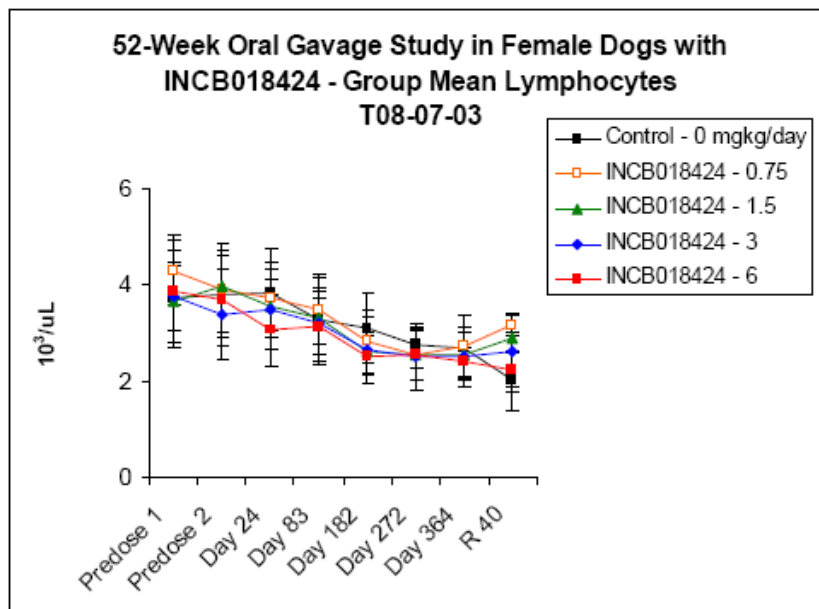
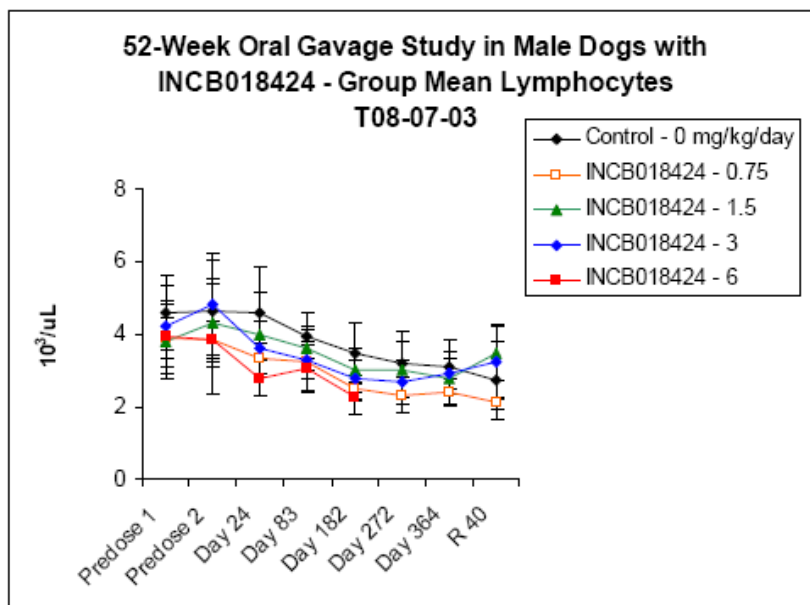
Female #4454: Clinical observations prior to death included hypoactivity, increased respiration rate, labored respiration, diarrhea, swelling of the left and right forelimbs and hindlimbs and impaired use of the left and right hindlimbs.

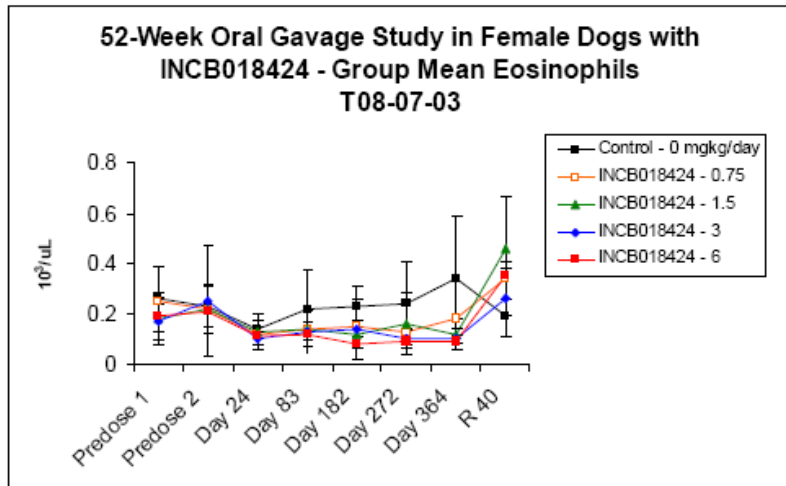
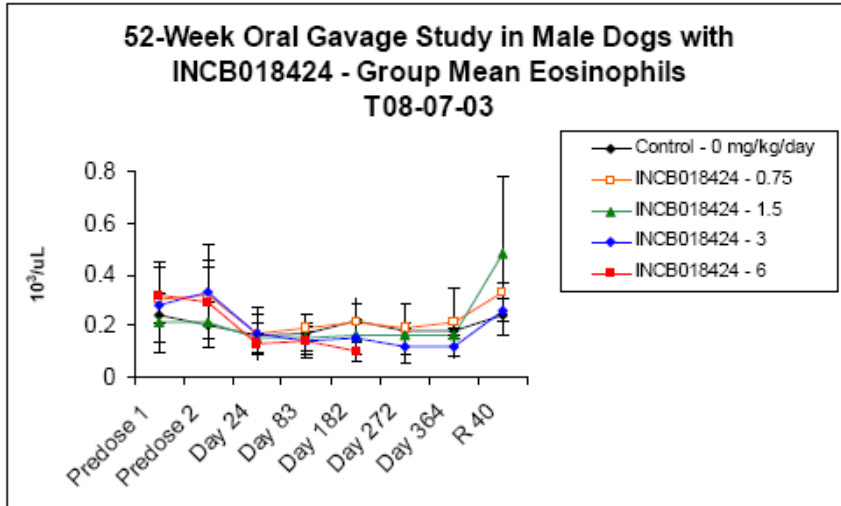
Terminal sacrifices: unremarkable

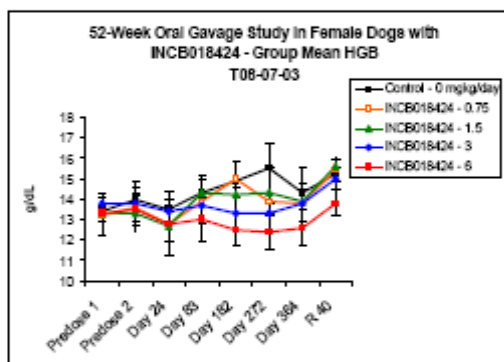
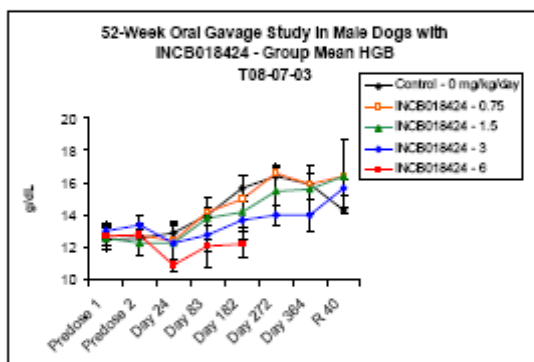
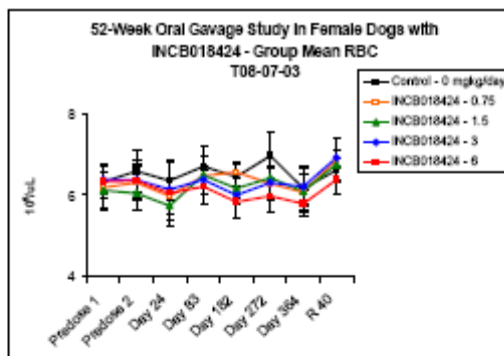
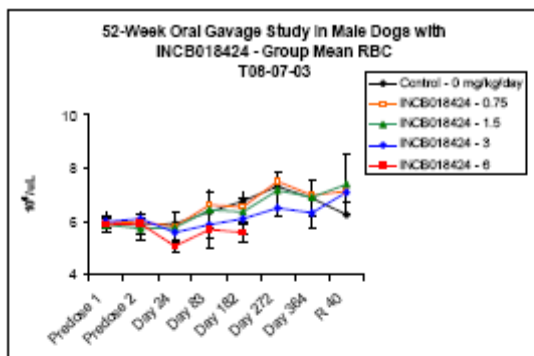
Bodyweight: unremarkable

Food Consumption: unremarkable

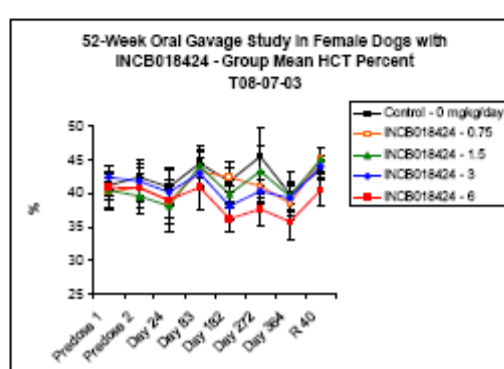
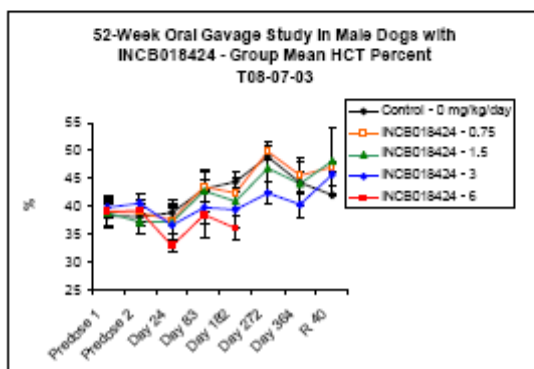
Hematology:







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Summary:

- Decreased red cell parameters including decreased red cell count ($\downarrow$ up to 17%), hemoglobin concentration ($\downarrow$ up to 22%), and/or hematocrit percentage ($\downarrow$ up to 18%) was observed in both males and females, which was generally present in males from Day 24 through Day 197 of the dosing phase, and in females starting from Day 24 throughout the dosing phase. There was recovering trends in females, but not fully recovered by the end of the recovery period (day 40 of recovery phase);
- Decreased eosinophil counts were observed in female dogs at all dose levels from Day 83 ($\downarrow$ up to 45%), and males at doses of ≥ 3 mg/kg/day from Day 182 ($\downarrow$ up to 55%). These changes in eosinophil counts were reversed by Day 40 of the recovery phase;
- Lymphocyte counts of males given 6 mg/kg/day were decreased from Day 24 through Day 197 of the dosing phase (up to $\downarrow$ 35%);

- Other hematologic changes included an increase of neutrophil and monocyte counts (↑up to 40%) from Days 182 through 197 in males at 6 mg/kg/day, suggesting inflammation.

Notes:

- 1) Compensatory increase in reticulocytes was not observed;
- 2) Decreases in lymphocytes correlated with the microscopic observations of decreased lymphocytes in gut-associated lymphoid tissue, mandibular and mesenteric lymph nodes. Decreased lymphocyte counts also correlated with decreases in total T cells, CD4+ cells and CD8+ cells in males;
- 3) Increased neutrophil and monocyte counts of males from Days 182 through 197 correlated with the microscopic observation of cutaneous pyogranulomatous inflammation associated with demodex mange mites.

Clinical Chemistry: unremarkable

Urinalysis: unremarkable

Ophthalmoscopy: unremarkable

EKG: unremarkable

Organ Weight: unremarkable

Gross Pathology: Abrasion, discoloration, scaling, thickening, and/or alopecia of the skin/subcutis and footpad were observed in animals and females at doses ≥ 3 mg/kg, including early deaths. Lymph node enlargement (mandibular and other) was observed in two males given 6 mg/kg/day. Footpad abrasions were present at the end of the recovery phase, other findings were recovered.

Histopathology:

Early death animals: The microscopic findings in the four moribund animals were similar to those in the other animals given 6 mg/kg/day (see below), except minimal acute inflammation of the liver (Animal No. H49124), minimal hypocellularity (decreased neutrophil storage pool) of sternal bone marrow (Animal No. H49125), minimal acute inflammation of the mandibular lymph node (Animal No. H49128), and moderate acute fibrinous inflammation of the mesenteric lymph node (Animal No. H49162).

Note: Special histologic staining procedures for microorganisms (Periodic acid-Schiff and the Gram stains, Brown and Brenn and Brown and Hopps) did not reveal a cause for the inflammation in the mesenteric lymph node. Above findings in early death animals were considered secondary to the marked inflammation of the skin/subcutis and/or footpad present in these animals, which in the case of Animal Nos. H49124 and H49162 may have been accompanied by the systemic spread of opportunistic pathogens.

All animals including early death animals and scheduled sacrificed animals:
The following table is excerpted from the submission, the data have been verified by the reviewer.

Text Table 1: Significant Microscopic Findings, Dosing Phase (Including Unscheduled Deaths)
Incidence (Mean Severity)

Sex	Males					Females				
Number Examined	5	5	5	5	7	5	5	5	5	5
Dose Level (mg/kg/day)	0	0.75	1.5	3	6	0	0.75	1.5	3	6
Organ										
Ileum- Decreased Lymphocytes, Gut-Associated Lymphoid Tissue	-	-	-	5(1.0)	7(1.0)	-	-	-	1(0.2)	4(1.6)
Lymph node, Mandibular- Decreased Lymphocytes, Cortex	-	-	-	-	-	-	-	-	-	1(0.2)
Inflammation, Pyogranulomatous	-	-	-	-	2(0.9)	-	-	-	-	-
Lymph node, Other ^a - Inflammation, Pyogranulomatous	ne	ne	ne	ne	1(2.0)	ne	ne	ne	ne	ne
Spleen- Decreased Lymphocytes, White Pulp	-	-	-	-	-	-	-	-	-	1(0.2)
Lymph node, Mesenteric- Decreased Lymphocytes, Cortex	-	-	-	-	2(0.3)	-	-	-	-	1(0.2)
Skin/Subcutis- Inflammation, Pyogranulomatous	-	-	-	2(1.0)	6(2.7)	-	-	-	-	4(2.0)
Mites, Intrafollicular	-	-	-	1(P)	5(P)	-	-	-	-	4(P)
Hyperkeratosis	-	-	-	2(1.2)	-	-	-	-	1(1.6)	-
Foot/Footpad ^a - Inflammation, Pyogranulomatous	ne	ne	ne	1(3.0)	3(4.0)	ne	ne	-	3(3.3)	-
Mites, Intrafollicular	ne	ne	ne	1(P)	3(P)	ne	ne	-	1(P)	-
Rectum, Perianal Skin- Inflammation, Pyogranulomatous	-	-	-	-	2(0.6)	-	-	-	1(0.4)	3(1.2)
Mites, Intrafollicular	-	-	-	-	2(P)	-	-	-	-	-

a = Not required by protocol (the number examined ranged from 1-3)

- = Not present

ne = Not examined

() = Grading scale: 1 = minimal; 2 = slight; 3 = moderate, 4 = marked, 5 = severe, P = Present

Recovery animals:

The following table from the submission, the data have been verified by the reviewer.

Text Table 2: Significant Microscopic Findings, Recovery Phase (Including Unscheduled Deaths)
Incidence (Mean Severity)

Sex	Males					Females				
Number Examined	2	2	2	2	0	2	2	2	2	2
Dose Level (mg/kg/day)	0	0.75	1.5	3	6	0	0.75	1.5	3	6
Organ										
Ileum- Decreased Lymphocytes, Gut-Associated Lymphoid Tissue	-	-	-	1(0.5)	ne	-	-	-	1(0.5)	1(0.5)
Lymph node, Mandibular- Decreased Lymphocytes, Cortex	-	-	-	-	ne	-	-	-	-	-
Inflammation, Pyogranulomatous	-	-	-	-	-	-	-	-	-	-
Lymph node, Other ^a - Inflammation, Pyogranulomatous	ne	ne	ne	ne	ne	ne	ne	ne	ne	ne
Spleen- Decreased Lymphocytes, White Pulp	-	-	-	-	ne	-	-	-	-	-
Lymph node, Mesenteric- Decreased Lymphocytes, Cortex	-	-	-	-	ne	-	-	-	-	1(0.5)
Skin/Subcutis- Inflammation, Pyogranulomatous	-	-	-	-	ne	-	-	-	-	-
Mites, Intrafollicular	-	-	-	-	ne	-	-	-	-	-
Hyperkeratosis	-	-	-	-	ne	-	-	-	-	-
Foot/Footpad ^a - Inflammation, Pyogranulomatous	ne	ne	ne	1(4.0)	ne	-	-	1(3.0)	1(3.0)	2(3.5)
Mites, Intrafollicular	ne	ne	ne	-	ne	-	-	-	1(P)	1(P)
Rectum, Perianal Skin- Inflammation, Pyogranulomatous	-	-	-	-	ne	-	-	-	1(1.0)	1(1.0)
Mites, Intrafollicular	-	-	-	-	ne	-	-	-	-	-

a = Not required by protocol (the number examined ranged from 1-3)

- = Not present

ne = Not examined

() = Grading scale: 1 = minimal; 2 = slight; 3 = moderate, 4 = marked, 5 = severe, P = Present

Summary:

- A test article-related decrease in lymphocytes was noted microscopically in some organs of males and females given >3 mg/kg/day. The decrease in lymphocytes was most consistently evident in the gut-associated lymphoid tissue (GALT) of the ileum. Pyogranulomatous inflammation of the skin/subcutis (including the perianal skin present with the section of rectum) and footpad affected most of the animals given 6 mg/kg/day and some of those given 3 mg/kg/day. Decreased lymphocytes and pyogranulomatous inflammation of the skin/subcutis were reversible, but not fully recovered at the end of recovery phase.

Toxicokinetics: refer to PK section

STUDY SUMMARY:

INCB018424 caused death when it was given to dogs daily at the dose of 6 mg/kg. Treatment lowered mean absolute lymphocytes, reduced eosinophil counts and decreased red cell parameters. Histopathology changes included decrease of lymphocytes in the gut-associated lymphoid tissue (GALT) of the ileum, in the cortex of the mandibular and mesenteric lymph nodes, and in the white pulp of the spleen. The development of generalized demodicosis, a secondary effect based of INCB018424, was considered adverse at dose levels of 3 and 6 mg/kg/day.

Histopathology inventory

Study	(b) (4) -519048	(b) (4) -519049	7456-271
Species	Rat	Dog	Dog
Adrenals	x*	x*	x*
Aorta	x	x	x
Bone Marrow smear	x	x	x
Bone (femur)	x	x	x
Brain	x*	x*	x*
Cecum	x	x	x
Cervix	x	x	x
Colon	x	x	x
Duodenum	x	x	x
Epididymis	x	x	x
Esophagus	x	x	x
Eye	x	x	x
Fallopian tube			
Gall bladder			
Gross lesions	x	x	x
Harderian gland	x	x	x
Heart	x*	x*	x*
Ileum	x	x	x
Injection site	x		
Jejunum	x	x	x
Kidneys	x*	x*	x*
Lachrymal gland	x	x	x
Larynx		x	x
Liver	x*	x*	x*
Lungs	x*	x*	x*
Lymph nodes, cervical			
Lymph nodes mandibular	x	x	x
Lymph nodes, mesenteric	x	x	x
Mammary Gland			
Nasal cavity			
Optic nerves	x		
Ovaries	x	x	x
oviducts	x	x	x
Pancreas	x	x	x
Parathyroid	x		
Peripheral nerve			
Peyer's patches	x		

Pharynx		X	X
Pituitary	X*	X*	X*
Prostate	X	X	X
Rectum	X	X	X
Salivary gland	X	X	X
Sciatic nerve	X	X	X
Seminal vesicles	X	X	X
Skeletal muscle	X	X	X
Skin	X	X	X
Spinal cord	X	X	X
Spleen	X*	X*	X*
Sternum		X	X
Stomach	X	X	X
Teeth			
Testes	X	X	X
Thymus	X*	X*	X*
Thyroid	X*	X*	X*
Tongue	X	X	X
Trachea	X	X	X
Urinary bladder	X	X	X
Uterus	X	X	X
Vagina	X	X	X
Zymbal gland			

X, histopathology performed

*, organ weight obtained

7 Genetic Toxicology

***In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)**

Study title: INCB018424: *Salmonella* plate incorporation mutagenicity assay
- reviewed by Dr. Barbara Hill under IND 77,455

Key findings: INCB01824 (free base) was not mutagenic in the *Salmonella* plate incorporation assay, under the conditions of this experiment.

Study no.: AB22ZU.501.BTL

Sponsor study no.: T06-01-electronic submission

Conducting laboratory: (b) (4)

Date of study initiation: 1-16-06

GLP compliance: No

QA reports: No

Drug, lot #, and % purity: INCB01824 (free base), Lot# 003

Vehicle: DMSO

Methods

Strains/species/cell line: *Salmonella typhimurium* strains TA98 and TA100

Concentrations used in definitive study: 1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg/plate (±S9; S9 derived from Aroclor 1254 induced rat liver homogenate); 2 plates/dose

Basis of concentration selection: No range finding study was performed. No appreciable toxicity or precipitate were noted at concentrations used in the definitive study.

Negative controls: DMSO

Positive controls:

1) TA 98 strain – 2-Nitrofluorene (-S9, 1 µg/plate) and 2-aminoanthracene (+S9, 1 µg/plate)

2) TA 100 strain – Sodium azide (-S9, 1 µg/plate) and 2-aminoanthracene (+S9, 1 µg/plate)

Incubation and sampling times: Plates were incubated at 37 ± 2°C for 2 days (*S. typhimurium*) after treatment. Plates were counted for colony formation by hand after completion of the incubation period.

Results

Study validity:

A test article was considered to be positive if it produced at least a 2-fold increase in the mean revertants per plate for tester strains TA98 or TA100 and this increase in the mean number of revertants per plate had to be accompanied by a dose response to increasing concentrations of the test article.

Solvent control mean reversion frequencies fell within established ranges. Positive control results were appropriate showing a mean reversion frequency that was three times or more greater than the mean reversion frequency of the solvent control

plates. The dose range selected for the definitive study was appropriate according to ICH guidelines.

Study outcome:

The test article produced a negative response in the presence and absence of S-9 activation. All of the tester strains treated with the test article exhibited a mean reversion frequency that was similar to the corresponding solvent control.

Study title *Salmonella-Escherichia coli* mammalian-microsome reverse mutation assay with a confirmatory assay

- reviewed by Dr. Barbara Hill under IND 77,455

Key findings: INCB01824 phosphate was not mutagenic in the Ames test, under the conditions of this experiment.

Study no.: 7456-188

Sponsor study no.: T06-08-01

Volume #, and page #: electronic submission

Conducting laboratory: (b) (4)

Date of study initiation: 7-24-06

GLP compliance: Yes

QA reports: Yes

Drug, lot #, and % purity: INCB01824 phosphate, Lot# 009

Vehicle: DMSO

Methods

Strains/species/cell line: *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537; *Escherichia coli* strain WP2 *uvrA*

Concentrations used in definitive study: 33.3, 100, 333, 1000, 2500 and 5000 µg/plate (±S9; S9 derived from Aroclor 1254 induced rat liver homogenate) in all tester strains; 3 plates/dose. A confirmatory assay was conducted using the same doses used in the definitive study.

Basis of concentration selection: The range finding study conducted with 6.67, 10.0, 33.3, 66.7, 100, 333, 337, 1000, 3330 and 5000 µg/plate for tester strains TA98 and WP2 *uvrA* (±S9; S9 derived from Aroclor 1254 induced rat liver homogenate); 1 plate/dose. No precipitate was noted at any concentration. Very slight toxicity was noted at 5000 µg/plate in TA98 and no toxicity was noted at 5000 µg/plate in WP2 *uvrA*. The maximum concentration used in the definitive study was 5000 µg/plate for tester strains based on the results of the range finding study.

Negative controls: DMSO

Positive controls: Provided in following table

Test strain	S9 mix	Positive control	Dose ($\mu\text{g}/\text{plate}$)
TA 98	+	Benzo[a]pyrene	2.5
TA 98	-	2-nitrofluorene	1.0
TA 100	+	2-aminoanthracene	2.5
TA 100	-	Sodium azide	2.0
TA 1535	+	2-aminoanthracene	2.5
TA 1535	-	Sodium azide	2.0
TA 1537	+	2-aminoanthracene	2.5
TA 1537	-	ICR-191	2.0
WP2 $uvrA$	+	2-aminoanthracene	25
WP2 $uvrA$	-	4-nitroquinoline-N-oxide	1.0

Incubation and sampling times: Plates were incubated at $37 \pm 2^\circ\text{C}$ for 2 days (*S. typhimurinum*) or 3 days (*E. coli*) after treatment. Plates were counted for colony formation by automated colony counter and/or by hand after completion of the incubation period.

Results

Study validity:

A test article was considered to be positive if it produced at least a 2-fold increase in the mean revertants per plate for tester strains TA98, TA100 or WP2 $uvrA$ or if it produced at least a 3-fold increase in mean revertants per plate for tester strains TA1535 or TA1537. This increase in the mean number of revertants per plate had to be accompanied by a concentration-response to increasing concentrations of the test article. Solvent control mean reversion frequencies fell within established ranges. Positive control results were appropriate showing a mean reversion frequency that was three times or more than the mean reversion frequency of the solvent control plates. The c range selected for the definitive study was appropriate according to ICH guidelines.

Study outcome:

The test article produced a negative response in the presence or absence of S-9 activation. All tester strains treated with the test article exhibited a mean reversion frequency that was similar to the corresponding solvent control.

***In Vitro* Assays in Mammalian Cells**

Study title INCB018424: Chromosomal aberrations in cultured human peripheral blood lymphocytes

reviewed by Dr. Barbara Hill under IND 77,455

Key findings: INCB01824 was negative in the human blood peripheral lymphocyte assay with or without S9 activation, under the conditions of this assay.

Study no.: 7456-187

Sponsor study no.: T06-08-02

Volume #, and page #: electronic submission

Conducting laboratory: (b) (4)

Date of study initiation: 7-24-06

GLP compliance: Yes

QA reports: Yes

Drug, lot #, and % purity: INCB01824 phosphate, Lot# 009

Vehicle: DMSO

Methods

Strains/species/cell line: Human peripheral blood lymphocytes

Doses used in definitive study:

In the initial chromosomal assay, concentrations of 5.43, 7.75, 11.1, 15.8, 22.6, 32.3, 46.1, 65.9, 94.1, 134, 192, 274, 392, 560 and 800 µg/ml INCB01824 phosphate were used for a 3-hr incubation ($\pm$ S9); 2/concentration. Cultures treated with concentrations of 22.6, 32.3, 46.1 and 65.9 µg/ml INCB01824 phosphate without metabolic activation and 15.8, 22.6, 32.3 and 94.1 µg/ml INCB01824 phosphate with metabolic activation were analyzed for chromosomal aberrations.

In the confirmatory chromosomal assay, concentrations of 1.25, 2.50, 5.00, 10.0, 20.0, 40.0, 65.0, 80.0, 95.0 and 110 µg/ml INCB01824 phosphate were used for a 22-hr incubation (-S9) and concentrations of 5.0, 10.0, 20.0, 30.0, 40.0, 50.0, 65.0, 80.0, 95.0, 110, 125 and 150 µg/ml INCB01824 phosphate were used for a 3 hr incubation (+S9); 2/concentration. Cultures treated with concentrations of 10.0, 20.0, 50.0 and 65.0 µg/ml INCB01824 phosphate without metabolic activation and 10.0, 20.0, 50.0 and 95.0 µg/ml INCB01824 phosphate with metabolic activation were analyzed for chromosomal aberrations.

Basis of concentration selection:

The concentrations selected for analysis of chromosomal aberrations was based on the level of toxicity noted for the incubations. The high concentration was selected so that at least 50% reduction in the mitotic index relative to the solvent control was noted. For the initial chromosomal assay, the 65.9 µg/ml INCB01824 phosphate concentration exhibited a 56% mitotic index reduction for the 3-hour incubation (-S9) and the 94.1 µg/ml INCB01824 phosphate concentration exhibited a 51% mitotic index reduction for the 3-hour incubation (+S9). For the confirmatory chromosomal assay, the 65.0 µg/ml INCB01824 phosphate concentration exhibited a 55% mitotic index reduction for the 22-hour incubation (-S9) and the 95.0 µg/ml INCB01824 phosphate concentration exhibited a 54% mitotic index reduction for the 3-hour incubation (+S9).

Negative controls: DMSO

Positive controls: Mitomycin C (-S9): 0.75, 1.0 and 1.5 µg/ml for 3 hour exposure, 0.2, 0.3, and 0.4 µg/ml for 22 hour exposure.

Cyclophosphamide (+S9): 20, 25 and 40 µg/ml for 3 hour exposure

Incubation and sampling times:

Cell cultures were incubated with test article $\pm$ S9 for 3 hours and harvested 22 hours after treatment initiation. Cell cultures were incubated with test article -S9 for 22

hours and then harvested for analysis. Slides were prepared from the harvested cultures and stained with 5% Giemsa solution for the analysis of mitotic index and chromosomal aberrations.

Results

Study validity:

A test article was considered to be positive for inducing chromosomal aberrations if a significant increase (the difference was considered significant when $p \leq 0.05$) in the number of cells with chromosomal aberrations is observed at one or more concentrations and a linear trend test demonstrates a concentration-response relationship. Solvent control mean reversion frequencies fell within established ranges. Positive control results were appropriate for this assay. The range of concentrations selected for the initial and confirmatory assays were appropriate according to ICH guidelines.

Study outcome:

No significant increase in cells with chromosomal aberrations was noted in the analyzed cultures.

***In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)**

Study title INCB018424: In vivo rat bone marrow micronucleus assay

reviewed by Dr. Barbara Hill under IND 77,455

Key findings: INCB01824 was negative in the in vivo rat micronucleus assay, under the conditions of this experiment.

Study no.: 7456-209

Sponsor study no.: T06-10-02

Volume #, and page #: electronic submission

Conducting laboratory: (b) (4)

Date of study initiation: 9-27-06

GLP compliance: Yes

QA reports: Yes

Drug, lot #, and % purity: INCB01824 phosphate, Lot# SS-IN2-175

Vehicle: 0.5% methylcellulose

Methods

Strains/species/cell line: Sprague-Dawley rats; 9 weeks; males: 266-304 g;
females: 196-233 g

Doses used in definitive study:

Single oral (gavage) doses of 0 (vehicle), 62.5, 125, 250 mg/kg INCB01824 phosphate; 10 ml/kg; 5/sex/dose/timepoint (an additional 3 high-dose males and 12 high-dose females were dosed as potential replacements)

Basis of dose selection: Preliminary toxicity study was conducted with single oral (gavage) doses of 250, 300 and 350 mg/kg INCB01824 phosphate, 10 ml/kg, 3/sex/dose. Mortality was noted in the mid- (1 male, 2 females) and high-dose groups (1 male, 2 females). Clinical signs of toxicity were noted in low-, mid- and high-dose groups which included squinted eyes, hypoactivity, ataxia, labored, irregular or audible respiration, lacrimation, body cold to touch, flattened posture, pale appearance and hunched posture. The high-dose was selected as 250 mg/kg based on the results of the preliminary toxicity study.

Negative controls: 0.5% methylcellulose

Positive controls: Cyclophosphamide (60 mg/kg), oral (gavage)

Incubation and sampling times: Single oral (gavage) doses of INCB01824 phosphate or cyclophosphamide were administered to rats. Bone marrow for analysis of nucleated cells was obtained from control and high-dose INCB01824 phosphate treated rats at 24 and 48 hours (5/sex/group/timepoint) after dose administration and at 24 hr after dose administration in low-dose, mid-dose, and positive control animals (5/sex/group).

Stained bone marrow slides were scored for micronucleus and the PCE (polychromatic erythrocytes) to NCE (normal chromatic erythrocytes) cell ratio. The micronucleus frequency (expressed as percent micronucleated cells) was determined by analyzing the number of micronucleated PCEs from at least 2000 PCEs per animal. The PCE:NCE ratio was determined by scoring the number of PCEs and NCEs observed while scoring at least 500 erythrocytes per animal.

Results

Study validity:

A test article was considered to be positive if a statistically significant increase in micronucleated PCEs for at least one dose level, and a statistically significant dose-related response were observed.

Solvent control mutant frequencies fell within established ranges. Positive control results were appropriate. Dose range selected for the definitive study was appropriate according to ICH guidelines.

Study outcome:

INCB01824 phosphate did not induce any statistically significant increases in micronucleated PCEs at any of the doses tested in this study. A high level of mortality was noted in high-dose females (16/25). No mortality was noted in low- or mid-dose animals or high-dose males. No clinical signs of toxicity were noted in low-dose animals. Clinical signs of toxicity noted in mid-dose animals included squinted eyes, ataxia, hypoactivity and/or reddened skin on the paws, ears and/or nose. Clinical signs of toxicity noted in high-dose animals included squinted eyes, ataxia, hypoactivity, reddened skin on the paws, ears, and/or nose, irregular or labored respiration, lacrimation, hyperactivity, convulsions, body that was cold to touch, and/or lateral recumbency. In addition, bone marrow toxicity was noted in the high dose group (20%

decrease in PCE/NCE ratio compared to concurrent vehicle control). Due to the unexpected mortality in the high dose females, no slides were prepared for this group for the 48 hour timepoint.

8 Carcinogenicity

The carcinogenicity study was reviewed by Dr. Miyun Tsai-Turton.

Study title: INCB018424: 26 week repeated dose oral carcinogenicity study in Tg.rasH2 mice

Adequacy of the carcinogenicity study and appropriateness of the test model: Yes. The Applicant followed eCAC recommendations.

Key study findings:

- Ruxolitinib was given to mice once daily at 0, 15, 45, and 125 mg/kg for 26 weeks via oral gavage. TK group was included in this study. Urethane (1000 mg/kg; three i.p. injection on Week 1) was used as positive control whereas 0.5% methylcellulose was used as vehicle control.
- In main study animals, there were deaths in low-dose (1 M and 1 F) and mid-dose (3 M and 4 F) groups but not in high-dose group. In TK study animals, there was one death in high-dose (1 F) group.
- No ruxolitinib related clinical sign was noted.
- There was a decrease in body weight gain in high-dose animals (11 % in male and 15% in female) but there were no signs of toxicity associated with ruxolitinib. Food consumption was decreased in treated males (all dose groups) and females (mid-dose/high-dose groups).
- Decreased absolute and/or relative organ weights were noted (*male*: brain/kidneys/liver/testes and *female*: brain/kidneys/liver/heart/spleen). These were probably attributed to decreased body weights and no correlation to gross histological findings.
- Neoplastic findings: ruxolitinib did not increase the incidence of neoplastic lesions. There were lesions/tumors in lungs (i.e. multiple adenomas and/or carcinoma in control/treated animals) and in spleen (i.e. hemangiosarcomas in treated animals), or in multiple organs such as skin/skeletal muscle (i.e. hemangiosarcomas/hemangiomas in control/treated animals, sarcoma in treated animals). Other tumors observed in control/treated animals included Harderian gland adenoma, liver adenoma, thyroid follicular adenoma, nasal adenocarcinoma, stomach papilloma, and thymus thymoma. All findings, however, either had low incidence rates or fell within historical control ranges established by (b) (4).
- Non-neoplastic findings: ruxolitinib increased the incidence/severity of non-neoplastic inflammatory lesions of the nasal cavity (i.e. minimal to moderate exudative inflammation).

Study no.: T09-02-03

Volume #, and page #: eCTD 4.2.3.4

Conducting laboratory and location: (b) (4)**Date of study initiation:** Feb 17th (male) and Feb 19 (female) 2009**GLP compliance:** Yes**QA report:** Yes**Drug, lot #, and % purity:** INCB018424, Lot No. BPR-07-101-B2-21, 99.6% purity**CAC concurrence:** Yes on SPA (special protocol assessment for dose selection and test model)**Methods**

- **Doses:** 0, 15, 45, and 125 mg/kg/day INCB018424

Group	Dose levels (mg/kg/day)	Dose Concentration (mg/mL)	Number of Animals			
			Main Study (Tg.rasH2)		TK Study (CByB6F1)**	
			Male	Female	Male	Female
Group 1 (Vehicle)	0	0	25	25	10	10
Group 2 (Positive Control)	1000 (urethane)*	100	25	27 ¹	-	-
Group 3	15	1.5	25	25	44	44
Group 4	45	4.5	25	25	44	44
Group 5	125	12.5	25	25	44	44
Total			125	127	142	142

*The Positive Control animals were administered a total of 3 intraperitoneal (i.p.) injections on Study Days (SD) 1, 3, and 5.

**Extra TK animals (4/sex for Group 1 and 2/sex for Groups 3-5) were used to reasonably ensure adequate animals for TK bleeding. Extra TK animals in Group 1 remaining after the Day 1 TK bleed remained on study for use during urine collection.

¹ = Two additional animals were added as replacement.

- **Basis of dose selection:** MTD
- **Species/strain:** hemizygous Tg.rasH2 mice
- **Number/sex/group (main study):** 25/sex/group
- **Route, formulation, volume:** oral gavage
- **Frequency of dosing:** daily for 182 to 183 consecutive days
- **Satellite groups used for toxicokinetics or special groups:** TK (44/sex/group) with CByB6F1 mice
- **Age:** 8 weeks
- **Animal housing:** environmentally controlled room with temp of 69-75 °F and a relative humidity of 30-70% with a 12 hr light/12 hr D cycle
- **Restriction paradigm for dietary restriction studies:** *ad libitum* access to drinking water and diet
- **Drug stability/homogeneity:** stability (prepared in 0.5% methylcellulose at 0.005 to 1000 mg/ml was confirmed for 24 hrs at RT and 14 days under refrigerated conditions. Homogeneity was confirmed with the means of each location (top,

middle, bottom) were within 7% of the overall mean and all replicates were within 5% of their respective mean. The mean concentration results were within 10% of the theoretical concentration and all replicates were within 5% of their respective means.

- *Dual controls employed:* Yes, vehicle control was 0.5% methylcellulose and the positive control was 1000 mg/kg urethane (via i.p. injection on Days 1, 3, and 5).
- *Interim sacrifices:*
- *Deviations from original study protocol:* Yes but these were not expected to affect the outcome of the study.

Observation times

- *Mortality:* twice daily
- *Clinical signs:* twice daily
- *Body weights:* once weekly from Day 1 to Week 13 and biweekly thereafter
- *Food consumption:* weekly
- *Organ weight:* organs (i.e. adrenal glands, brain, heart, kidneys, liver, spleen, and testes/ovaries) were collected and weighted on scheduled necropsy
- *Histopathology: Peer review:* yes, organ tissues (see below) were collected on scheduled necropsy for microscopic evaluation.

Adrenal glands	Ovaries
Aorta	Pancreas
Bone (femur and sternum)	Parathyroid glands
Bone marrow (femur and sternum)	Pituitary gland
Brain	Prostate gland
Epididymides	Salivary gland
Esophagus	Sciatic nerve
Eyes	Seminal vesicles
Gall bladder	Skeletal muscle (thigh)
Gross lesions	Small intestine duodenum, jejunum, and ileum)
Harderian gland	Spinal cord (cervical, thoracic, and lumbar)
Heart	Spleen
Kidneys	Stomach
Large intestine (cecum, colon, rectum)	Testes
Liver	Thymus
Lungs and bronchi	Thyroid glands
Lymph nodes (mesenteric, mediastinal, and mandibular)	Trachea
Mammary gland with adjacent skin	Urinary bladder
Nasal cavity	Uterus
	Vagina

- *Toxicokinetics:* blood samples were collected from 3 animals/sex/dose/timepoint on Days 1-2 and 176-177 (predose, 0.5, 1, 2, 4, 8, and 24 hr post-dose for ruxolitinib-treated TK animals). Urine samples of designated TK animals (3 animals/cage) were collected during week 26 for metabolite identification.
- *Serum antibody analysis:* blood collection from designated animals (10 M/10F predose, 10M/10F Group1 and surviving M/F Group 5 on Day 183) were collected via retroorbital sinus for possible future analysis (non-GLP).

Results

Mortality: mortalities (main study) were seen in 1 low-dose (LD) and 3 mid-dose (MD) male rats, 1 LD and 4 MD female rats (compared to 12 males and 12 females with urethane-treated animals). Mortality (TK study) was seen in 1 high-dose (HD) female.

Clinical signs: there were no treatment-related effects on clinical observations. Clinical signs were either transient, with no dose-response, or appeared in a small number in treated animals (compared to clinical signs such as ataxia, decreased motor activity, labored breathing, hunched posture, hyperactivity, and hypothermia in urethane-treated animals).

Body weights: there were decreases (but no dose-related effects) on body weights or body weight gains in LD and MD males. There was also 11% (males) and 15% (females) decreases in absolute body weight gain from Day 1 to Day 183 in HD group.

Food consumption: There was a decrease in total food consumption from Day 1 to Day 183 in all treated males when compared to the vehicle control. There was also a significant decrease in total food consumption in MD and HD females when compared to the vehicle control.

Organ weights: There were decreases in several absolute and relative organ weights (i.e. male: brain/kidneys/liver/testes and female: brain/kidneys/liver/heart/spleen). Such decreases (with no histological correlates) were considered to be secondary to decreased body weight.

[Absolute Male Organ Weights] Group 3-5 Vs. Group 1

Parameter	Group No.	Significant Difference compared to Control (Group 1) ↑ or ↓
Brain	5	↓ DR
Kidneys	4 & 5	↓ DR
Liver	3, 4 & 5	↓ DR
Testes	5	↓

↑ = Statistically significantly ($p < 0.05$) increased compared to Group 1.

↓ = Statistically significantly ($p < 0.05$) decreased compared to Group 1.

DR = Dose Related

Nominal Dose: Group 1 – 0 mg/kg/day Group 3 – 15 mg/kg/day
 Group 4 – 45 mg/kg/day Group 5 – 125 mg/kg/day

[Relative Male Organ Weights] Group 3-5 Vs. Group 1

Parameter	Group No.	Significant Difference compared to Control (Group 1) ↑ or ↓
Kidneys	5	↓ DR
Liver	3, 4 & 5	↓

[Absolute Female Organ Weights] Group 3-5 Vs. Group 1

Parameter	Group No.	Significant Difference compared to Control (Group 1) ↑ or ↓
Brain	4 & 5	↓ DR
Heart	3, 4 & 5	↓
Kidneys	4 & 5	↓ DR
Liver	3, 4 & 5	↓ DR
Spleen	4 & 5	↓ DR

[Relative Female Organ Weights] Group 3-5 Vs. Group 1

Parameter	Group No.	Significant Difference compared to Control (Group 1) ↑ or ↓
Heart	3 & 4	↓
Kidneys	5	↓
Liver	3, 4 & 5	↓ DR
Spleen	4 & 5	↓ DR

↑ = Statistically significantly (p < 0.05) increased compared to Group 1.
 ↓ = Statistically significantly (p < 0.05) decreased compared to Group 1.
 DR = Dose Related

Nominal Dose: Group 1 – 0 mg/kg/day Group 3 – 15 mg/kg/day
 Group 4 – 45 mg/kg/day Group 5 – 125 mg/kg/day

Gross pathology: There was no treatment-related effect on macroscopic findings in either sex (compared to the pulmonary and splenic lesions noted in urethane-treated animals)

Histopathology: see appendix for detailed microscopic findings provided by the sponsor.

- Non-neoplastic: Minimal to moderate exudative inflammation of the nasal cavity was observed.

Nasal cavity

Mostly minimal to mild inflammation of the submucosa of the nasal cavities was considered a background lesion. These were characterized by infiltration of mostly neutrophils and fewer lymphocytes in the submucosal glands and the interglandular spaces. The incidence of such lesion was increased slightly in the ruxolitinib treated mice in both sexes.

Exudative inflammations of the nasal cavities were noted. These were characterized by accumulation of degenerate neutrophils, rare lymphocytes and macrophages, fibrin, and sloughed cells. This was only occasionally noted in the vehicle control mice. However, this incidence and severity of this inflammation were higher in the HD group but comparable in the LD and MD groups when compared to vehicle control in both sexes.

Additional changes present in both lesion and inflammation include dilation of glands, presence of eosinophilic droplets, and hyperplasia of submucosal glands or lining epithelium (mostly minimal intensity). These changes were considered to be part of the inflammatory process.

Adenocarcinoma of the nasal cavity was seen in 1 Group 3 male and 2 Group 3 females. This appeared to arise from the deep submucosal glands. The incidence of this nasal adenocarcinoma was low (with no dose relationship) and comparable with historical control range established by the (b) (4)

Male				
	Group 1	Group 3	Group 4	Group 5
Inflammation, submucosa				
Minimal	16	21	21	24
Mild	3	0	0	1
Inflammation, exudative				
Minimal	2	1	6	16
Mild	0	1	3	7
Moderate	0	0	1	2
Adenocarcinoma	0	1	0	0
Female				
	Group 1	Group 3	Group 4	Group 5
Inflammation, submucosa				
Minimal	12	19	21	25
Mild	1	0	0	0
Inflammation, exudative				
Minimal	4	1	3	6
Mild	0	1	2	11
Moderate	0	0	0	5
Adenocarcinoma	1	2	0	0

Nominal Dose: Group 1 – 0 mg/kg/day Group 3 – 15 mg/kg/day
Group 4 – 45 mg/kg/day Group 5 – 125 mg/kg/day

Others

A variety of other non-neoplastic lesions (i.e. minimal brain inflammation, mild aorta proliferation, minimal heart periarteritis, and minimal liver necrosis) were noted but all were considered to be background/spontaneous, incidental, and/or their incidences were comparable across the dose groups.

Based on these findings, the nasal cavity was considered to be a target organ for non-neoplastic inflammatory changes.

- ***Neoplastic:*** There was no significant increase in the incidence of neoplasia (i.e. lesions in lung, spleen, hemangiomas/hemangiosarcomas in spleen/other organs, sarcomas in multiple organs, non-vascular/sarcomas/pulmonary tumors in multiple organs).

Neoplastic lesions in lungs

The incidence of single or multiple adenomas, carcinomas, and that of combined incidence of all pulmonary tumors in vehicle and ruxolitinib treated mice was comparable and fell within the historical control range established by (b) (4)

There was significant increase in the incidence of pulmonary tumors in urethane-treated mice when compared to control mice, proving the validity of the test system.

MALE						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR
Adenoma, single	1	0	2	3	2	0-6
Adenoma, multiple	1	25	0	0	0	0-1
Carcinoma	0	8	0	0	0	0-2
All Lung Tumor	2	25*	2	3	2	0-6
FEMALE						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR
Adenoma, single	3	0	3	1	1	0-6
Adenoma, multiple	0	25	0	0	0	0-1
Carcinoma	0	18	1	0	0	0-1
All Lung Tumor	3	25*	4	1	1	0-6

Nominal Dose: Group 1 – 0 mg/kg/day

Group 2 – Positive Control

Group 3 – 15 mg/kg/day

Group 4 – 45 mg/kg/day

Group 5 – 125 mg/kg/day

HCR: Historical Control Range (See Appendix I).

*: Multiple adenomas and/or carcinomas were present in the same animal in Urethane treated mice

Neoplastic lesions in spleen

The incidence of splenic hemangiosarcomas was low and comparable between ruxolitinib treated dose groups and fell within the historical control range. There were no splenic hemangiosarcomas seen in the vehicle control mice of both sexes.

There was significant increase in the incidence of splenic hemangiosarcomas in urethane-treated mice when compared to control mice, proving the validity of the test system.

MALE						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR
Hemangiosarcoma	0	24	0	1	1	0-4
FEMALE						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR
Hemangiosarcoma	0	24	2	2	0	0-4

Nominal Dose: Group 1 – 0 mg/kg/day Group 2 – Positive Control Group 3 – 15 mg/kg/day
 Group 4 – 45 mg/kg/day Group 5 – 125 mg/kg/day
 HCR: Historical Control Range (See [Appendix I](#))

Hemangiomas and hemangiosarcomas in multiple organs including spleen (under the general category of mesenchymal tumors)

There was a non significant increase in the incidence of hemangiomas and hemangiosarcomas in multiple organs of Groups 4/5 males (i.e. spleen, skin, and skeletal muscle) and Groups 3/4 females (i.e. spleen and skin). However such increase was not dose-dependent. The incidence of all hemangiomas and hemangiosarcomas in multiple organs in vehicle as well as ruxolitinib treated dose groups fell within the historical control range established at (b) (4)

MALE					
	Group 1	Group 3	Group 4	Group 5	HCR
Hemangiosarcomas					
Spleen	0	0	1	1	0-4
Testes	1	0	0	0	0-1
Skin	0	0	1	0	NR
Hemangiomas					
Skeletal muscle	0	0	0	1	NR
Combined incidence	1	0	2	2	0-4
FEMALE					
	Group 1	Group 3	Group 4	Group 5	HCR
Hemangiosarcomas					
Spleen	0	2	2	0	0-4
Skin	0	1	0	0	0-1
Combined incidence	0	3	2	0	0-4

Nominal Dose: Group 1 – 0 mg/kg/day Group 3 – 15 mg/kg/day
 Group 4 – 45 mg/kg/day Group 5 – 125 mg/kg/day

HCR: Historical Control Range (See [Appendix I](#))

NR: Not recorded in our historical control data base since no findings were found.

Sarcomas in multiple organs (under the general category of mesenchymal tumors)

The incidence of these sarcomas was low and involved random organs and these were not present in control Group 1.

Male					
	Group 1	Group 3	Group 4	Group 5	HCR
Skin, sarcoma	0	0	1	0	0-1
Skeletal muscle, sarcoma	0	1	0	0	NR
Female					
	Group 1	Group 3	Group 4	Group 5	HCR
Multicentric, sarcoma	0	0	1	0	NR

Nominal Dose: Group 1 – 0 mg/kg/day Group 3 – 15 mg/kg/day
 Group 4 – 45 mg/kg/day Group 5 – 125 mg/kg/day

HCR: Historical Control Range (See [Appendix I](#))

NR: Not recorded in our historical control data base since no findings were found.

Other tumors (non vascular, non-sarcomas, and non pulmonary) in multiple organs

There was a non-dose dependent increase in the incidence of thymomas in Group 4 females. However, they were not seen in vehicle control and were not recorded in the historical control ranges.

The incidence of all remaining tumors involved isolated organs and/or fell within the historical control ranges.

Male					
	Group 1	Group 3	Group 4	Group 5	HCR
Harderian gland, adenoma	2	0	0	1	0-1
Thyroid, follicular adenoma	0	1	0	0	NR
Nasal, Adenocarcinoma	0	1	0	0	0-2*
Liver, adenoma	0	0	1	0	NR
Female					
	Group 1	Group 3	Group 4	Group 5	HCR
Harderian gland, adenoma	2	0	0	2	0-4
Stomach, papilloma	1	0	0	0	0-1
Thymus, thymoma	0	0	3	0	NR
Nasal, adenocarcinoma	1	2	0	0	0-1

Nominal Dose: Group 1 – 0 mg/kg/day Group 3 – 15 mg/kg/day
 Group 4 – 45 mg/kg/day Group 5 – 125 mg/kg/day

HCR: Historical Control Range in vehicle control mice (See [Appendix I](#))

*: Nasal cavity adenomas are reported in the HCR but no adenocarcinomas.

NR: Not recorded in our historical control data base since no findings were found.

Based on these findings, the lung, spleen, skin, skeletal muscle were apparent to be target organs for neoplastic changes/lesions. However, ruxolitinib did not increase the incidence of these lesions. Most changes identified occurred with low incidences and with no dose-response, or fell within historical control ranges established by (b) (4)

Toxicokinetics: TK analysis showed that there was minimal gender difference in CByB6F1 hybrid mice. The C_{max} values did not always increase proportionally with dose and were similar between Day 1 and Day 176 in males, but decreased slightly (30-

50%) in females on Day 176. The AUC values increased in a greater than dose proportionally and were generally similar between Day 1 and Day 176, except a slight decrease (39%) in HD females on Day 176. The $t_{1/2}$ values were higher in HD groups when compared to LD and MD groups.

Summary of Toxicokinetics in a 26-Week Carcinogenicity Study in Tg.rasH2 Mice [T09-02-03]

Gender	Day	Parameter	15 mg/kg	45 mg/kg	125 mg/kg
Male	1	C_{max} (μ M)	4.51	12.3	28.6
		T_{max} (h)	0.500	0.500	0.500
		AUC ₀₋₂₄ (μ M*h)	3.83	16.4	69.3
		$t_{1/2}$ (h)	0.487	1.01	2.33
	176	C_{max} (μ M)	4.02	13.9	24.4
		T_{max} (h)	0.500	0.500	0.500
		AUC ₀₋₂₄ (μ M*h)	4.55	18.5	67.8
		$t_{1/2}$ (h)	0.787	1.07	1.39
Female	1	C_{max} (μ M)	4.73	13.0	26.6
		T_{max} (h)	0.500	0.500	0.500
		AUC ₀₋₂₄ (μ M*h)	5.76	23.1	127
		$t_{1/2}$ (h)	1.19	1.01	3.62
	176	C_{max} (μ M)	3.30	7.68	13.1
		T_{max} (h)	0.500	0.500	0.500
		AUC ₀₋₂₄ (μ M*h)	5.14	22.5	78.0
		$t_{1/2}$ (h)	1.08	1.20	3.91

9 Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title: Oral gavage study of fertility and early embryonic development to implantation with INCB018424 in rats

Study no.: 8212204

Study report location: (b) (4)

Conducting laboratory and location: (b) (4)

Date of study initiation: 6/22/2009

GLP compliance: yes

QA statement: yes

Drug, lot #, and % purity: INCB018424, lot#BPR-07-101-B2-21, 97.8%

Key Study Findings

Males

- Reduction in body weight was observed at ≥ 30 mg/kg of the drug; NOAEL is 10 mg/kg
- Doses up to 60 mg/kg did not affect male reproductive function (no effects on sperm count, concentration, or motility)

Females

- Doses up to 60 mg/kg did not result in toxicities in females; a NOAEL was not identified
- At doses up to 60 mg/kg, there were no treatment-related effects on the estrous cycling, number of pregnancies or copulation rates
- A treatment-related increase in post-implantation loss was noted in the 60 and 30 mg/kg/day groups. In the 60 mg/kg/day group, this increase was significant and was attributed to an increase in the number of late resorptions

Conclusions:

- Reproductive function and fertility were not affected in males or females at doses up to 60 mg/kg;
- Embryo-fetal viability was reduced at ≥ 30 mg/kg (not affected at 10 mg/kg).
- The dose of 30 mg/kg/day and 60 mg/kg/day result in an AUC_{0-24} approximately 34% and 2-fold the human AUC_{0-24} , respectively, at the maximum human dose of 25 mg twice daily (the human AUC_{0-24} being 8.8 $\mu\text{M}\cdot\text{h}$).

Methods

Doses: 0, 10, 30, 60 mg/kg at dose volume of
Frequency of dosing:
Dose volume: 10 mL/kg
Route of administration: oral gavage
Formulation/Vehicle: 0.5% (w/v) methylcellulose (400 cps), in reverse osmosis/deionized water
Species/Strain: Crl:CD(SD) rats
Number/Sex/Group: 22/sex/dose
Satellite groups: None
Study design: All males were dosed for at least 10 weeks and included at least 28 days prior to mating and throughout the mating phase. Females were dosed for at least 14 days prior to mating (pre-mating phase), throughout the mating phase, and through Gestation Day 7 (GD 7). Treated males were paired with treated females during the mating phase. On GD 13, females were necropsied and the uterus of each was examined for the number of live and dead fetuses and resorptions. Ovaries were examined for the number of corpora lutea. All males were necropsied and evaluated for reproductive capacity.

Deviation from study protocol: none

Observations and Results

Parameters and endpoints evaluated: mortality, clinical observations, body weight and food consumption data, necropsy findings, cesarean section data, and reproductive organ weight data, estrous cycle, and sperm evaluations

Statistical evaluations: Levene's test was done to test for variance homogeneity. One-way analysis of variance [ANOVA] was used to analyze data. If the ANOVA was significant ($p < 0.05$), Dunnett's t-test was used for control versus treated group comparisons. The sperm motility and total count was compared using the Kruskal-Wallis nonparametric ANOVA test. If a significant result was obtained at the 5% probability level, the Wilcoxon (Mann-Whitney U) test served as the post-hoc group comparison test (at the 5% one-tailed probability level).

Mortality

Two females were sacrificed moribund (10 mg/kg on day 34 and 60 mg/kg on day 30). Note: As the moribundity of these animals did not display a dose-dependency, no clinical signs were noted with the exception of moribundity (pale appearance) and resorptions (red vaginal discharge), and there were no treatment related necropsy findings, these unscheduled deaths were not considered treatment-related.

Clinical Signs

Early death: Prior to death, both of these animals were noted with clinical signs of a pale appearance to the entire body, red vaginal discharge, red fluid in the pan, and/or both eyes pale.

Scheduled death (males and females): unremarkable

Body Weight

Early death: unremarkable

Scheduled death:

Male: Treatment-related decreases in mean body weight were observed in all treatment groups.

10 mg/kg: ↓3 to 5%, compared to control from Day 35 to the end of study, which also correlated with a decrease in mean body weight gain from Day 35 to the end of study.

30 mg/kg: ↓4-9%, beginning on Day 17, lasting to the end of study on Day 71, statistically significant compared to control from Day 38 until the end of the study.

60 mg/kg/day: ↓3-11%, beginning on Day 24, lasting to the end of study on Day 71; statistically significant compared to control from Day 38 until the end of the study.

Female: unremarkable

Feed Consumption

Male: 9% increase compared to control in mean food consumption was noted in the 60 mg/kg/day males from Days 0 to 28.

Female: unremarkable

Necropsy

Male: There were no treatment-related effects on average organ weights or relative organ weights, sperm count, sample, concentration and motility.

Female: There were no treatment-related effects on the estrous cycling of females.

There were no treatment-related effects on pregnancy or copulation rates.

Preimplantation loss was slightly increased in the 60 mg/kg/day group. This was mainly due to litter effects (Animal Nos. B55161 and B55163), and as the remaining 18 litters in the 60 mg/kg/day group were similar to controls. A treatment-related increase in postimplantation loss was noted in the 60 and 30 mg/kg/day groups. In the 60 mg/kg/day group, this increase was significant and was attributed to a 100% litter involvement in resorptions and an increase in the number of late resorptions compared to control.

Overall reproductive function data are presented in the following table (excerpted from the application, data have been verified by the reviewer).

	0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	60 mg/kg/day
No. of males paired	22	22	22	22
No. of animals mated (Male/Female Copulation Index)	22	21	21	21
Male/Female Copulation Index (%)	100	95	95	95
No. of Females Pregnant	22	20	21	21
Male/Female Fertility Index (%)	100	91	95	95

Toxicokinetics

TK: not conducted in this study. The Applicant used data from study T07-10-14 (GLP study, Oral Administration of INCB018424 via Gavage: Dose Range Study for Effects on Embryo-Fetal Development in Sprague Dawley Rats) to compare the plasma exposure (AUCs) in rats and humans.

The following table is from the Applicant's submission (Study# T07-10-14).

Summary of INCB018424 Toxicokinetics in Pregnant Sprague-Dawley Rats on Gestation Day 13 Given Daily Oral Doses of 15, 30, 60 or 120 mg/kg INCB018424

Parameter	Dose			
	15 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg
C _{max} (μM)	0.375	1.02	3.35	9.56
T _{max} (h)	1.00	1.00	1.00	1.00
AUC _{0-t} (μM*h)	0.712	2.59	18.3	57.6
AUC ₀₋₂₄ (μM*h)	0.750	2.98	19.0	57.6
t _{1/2} (h)	2.42	3.98	2.17	2.09

Embryo-fetal Development

Study title: Oral Administration of INCB018424 via Gavage: Definitive Study for Effects on embryo-fetal Development in Sprague Dawley rats

Study no.: (b) (4) study # 1603-07595

Incyte Study# T07-12-04

Study report location: Module 4

Conducting laboratory and location: (b) (4)

Date of study initiation: December 3, 2007

GLP compliance: Yes

QA statement: yes (x) no ()

Drug, lot #, and % purity: INCB018424, Lot #: BPR-07-101-B2-21, Purity: 98.9%

Key Study Findings

- Maternal mortality was observed at 60 mg/kg;
- Statistically significant decreased fetal weights (up to 9%) were observed at 60 mg/kg, the dose that resulted in mortality in 2 dams.
- No maternal or embryo-fetal developmental effect was seen at 30 mg/kg/day dose (NOAEL=30 mg/kg/day)
- The dose of 60 mg/kg results in an AUC₀₋₂₄ of 19 µM.hr which is 2 times the human AUC₀₋₂₄ at the highest dose of 25 mg, twice daily (50 mg/day).

Methods

Doses:	15*, 30, 60 mg/kg/day
	*Due to a typographical error, the actual dose level was 14 mg/kg/day
	Dose justification: Dose selection was based on results from previous developmental dose-range finding toxicity study.
Frequency of dosing:	once daily
Dose volume:	10 mL/kg
Route of administration:	oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Female CrI:CD®(SD)IGS BR rats 201-236 g and 8-10 weeks at mating
Number/Sex/Group:	25 animals/group
Study design:	daily dosing from gestation days (GD) 7-20*, Necropsy/cesarean on gestation day 22 *the day of confirmation of mating was considered GD1
Deviation from study protocol:	none

Observations and Results

Parameters and endpoints evaluated:

Procedure	Frequency of Testing
Cageside Observations	≥ 2 Daily
Clinical Observations	GD 7, 10, 13, 16, 20, and 22
Postdose Observations	30 minutes (± 5 minutes) after each dose
Body Weight	GD 7, 10, 13, 16, 20, and 22
Food Consumption	GD 7-10, 10-13, 13-16, 16-20, and 20-22

Reproductive parameters: the number and placement of uterine implantation sites, the number of live and dead fetuses, the number of early or late resorptions, any abnormalities of the

placenta or embryonic sac, and the number of corpora lutea on each ovary.

Fetal examination: Each fetus (live or dead) was sexed, weighed, examined for external malformations/variations, visceral/skeletal malformations/variations).

Statistical evaluations:

Quantitative data (body weights, body weight changes, food consumption, uterine weights, and uterine data) were analyzed using the Kolmogorov-Smirnov test for normality, the Levene Median test for equal variance, and by one-way Analysis of Variance (ANOVA). If either the normality or equal variance test failed, then the analysis was continued using the non-parametric Kruskal-Wallis ANOVA on rank transformed data. For parametric data, if the ANOVA indicated statistical significance among experimental groups then the Dunnett's t-test was used to delineate which groups (if any) differed from the control. For non-parametric data, if the ANOVA indicated statistical significance among experimental groups then the Dunn's test was used to delineate which groups (if any) differed from the control. The probability value of less than 0.05 (two-tailed) was used as the critical level of significance for all tests. The litter was used as the experimental unit.

TK: not conducted in this study. The Applicant used data from study T07-10-14 (GLP study, Oral Administration of INCB018424 via Gavage: Dose Range Study for Effects on Embryo-Fetal Development in Sprague Dawley Rats) to compare the plasma exposure (AUCs) in rats and humans.

The following table is from the Applicant's submission (Study# T07-10-14).

Summary of INCB018424 Toxicokinetics in Pregnant Sprague-Dawley Rats on Gestation Day 13 Given Daily Oral Doses of 15, 30, 60 or 120 mg/kg INCB018424

Parameter	Dose			
	15 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg
C _{max} (μM)	0.375	1.02	3.35	9.56
T _{max} (h)	1.00	1.00	1.00	1.00
AUC _{0-t} (μM*h)	0.712	2.59	18.3	57.6
AUC ₀₋₂₄ (μM*h)	0.750	2.98	19.0	57.6
t _{1/2} (h)	2.42	3.98	2.17	2.09

In life observations:

Mortality: 2 early deaths at 60 mg/kg. DG18, GD22 (prior to the scheduled necropsy).

Clinical signs:

Early death

1 death at GD18: there were no abnormal observations prior to death.

1 death at GD22: brown vaginal discharge was noted starting on GD 20.

Scheduled death: unremarkable

Body weight: Body weights and body weight changes for treated animals were comparable to those of controls throughout the study.

Food consumption: Overall, there were no differences between the groups in the total amount of food consumed (GD 7-22).

Terminal and necropsy evaluations:**Dams:***Necropsy evaluation:*

Early death:

1 death on GD 18: a discolored uterus with brown amniotic fluid was noted at necropsy.

1 death on GD22: unremarkable

Scheduled death: unremarkable

Uterine and Ovarian parameters

Changes in uterine weight: unremarkable

Embryo-fetal data:*Changes of mean fetal body weight*

Index	Fetal weight (g)				Percentage deviation from control			
	0	15	30	60	0	15	30	60
Group (mg/kg)								
Male	5.6	5.8	5.6	5.3**	-	-	-	-5**
Female	5.5	5.5	5.3	5.0**	-	-	-4	-9**
Male+ female	5.7	5.6	5.4	5.2**	-	-	-5	-9**

** p≤0.01

Fetal morphological data: unremarkable

Conclusion: Under the conditions of this study, INCB018424 was not teratogenic in rats; the maternal no-observed-adverse-effect level (NOAEL) and the fetal NOAEL are 30 mg/kg.

Study title: Oral Administration of INCB018424 via Gavage: Definitive Study for Effects on Embryo-Fetal Development in New Zealand White Rabbits

Study no.: (b) (4) study # 1603-07597
Incyte Study# T07-12-05

Study report location:
Conducting laboratory and location:

(b) (4)

Date of study initiation: December 10, 2007
GLP compliance: yes
QA statement: yes (x) no ()
Drug, lot #, and % purity: INCB018424
Lot #: BPR-07-101-B2-21
Purity: 98.9%

Key Study Findings

- Two unscheduled mortalities were observed at 60 mg/kg;
- The following were noted in one unscheduled death: moderate appetite loss, low posture, limping, hypersensitivity to touch, languid behavior, and decreases in body weight and food consumption were noted
- Treatment with INCB018424 resulted in a significantly higher number of late resorptions at 60 mg/kg/day, a dose that resulted in mortalities in does. Increased late resorption contributed to increased total post-implantation loss at 60 mg/kg/day dose
- INCB018424 at 60 mg/kg caused lower fetal weights;
- No maternal or embryo-fetal developmental effect was seen at 30 mg/kg/day dose (NOAEL=30 mg/kg/day)
- The dose of 60 mg/kg results in an AUC₀₋₂₄ of 606 nM.hr of which is 7% the human AUC₀₋₂₄ at the highest dose of 25 mg twice daily (50 mg/day), the human AUC₀₋₂₄ being 8.8 µM.h.

Methods

Doses:	10, 30, 60 mg/kg/day
Dose justification:	Dose selection was based on results from previous developmental dose-range finding toxicity study.
Frequency of dosing:	once daily
Dose volume:	10 mL/kg
Route of administration:	oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Female New Zealand white rabbits 3000-3873 g and 5-6 weeks at mating
Number/Sex/Group:	20 animals/group
Satellite groups:	3 animals/group
Study design:	daily dosing from gestation days (GD) 8-21*, Necropsy/cesarean on gestation day 30 *the day of confirmation of mating was considered GD1.
Deviation from study protocol:	None

Observations and Results

Parameters and endpoints evaluated:

Procedure	Frequency of Testing	
	Main Phase Animals	Toxicokinetic Animals
Cageside Observations	≥ 2 Daily	≥ 2 Daily
Clinical Observations	GD 8, 11, 14, 17, 21, 24, 27, and 30	GD 8, 11, 14, 17, and 21 ^a
Body Weight	Daily	GD 8, 11, 14, 17, and 21 ^b
Food Consumption	Daily	Not required

Reproductive parameters: the number and placement of uterine implantation sites, the number of live and dead fetuses, the number of early or late resorptions, any abnormalities of the placenta or embryonic sac, and the number of corpora lutea on each ovary.

Fetal examination: Each fetus (live or dead) was sexed, weighed, examined for external malformations/variations, visceral/skeletal malformations/variations).

Statistical evaluations:

Quantitative data (body weights, body weight changes, food consumption, uterine weights, and uterine data) were analyzed using the Kolmogorov-Smirnov test for normality, the Levene Median test for equal variance, and by one-way Analysis of Variance (ANOVA). If either the normality or equal variance test failed, then the analysis was continued using the non-parametric Kruskal-Wallis ANOVA on ranktransformed

data. For parametric data, if the ANOVA indicated statistical significance among experimental groups then the Dunnett's t-test was used to delineate which groups (if any) differed from the control. For non-parametric data, if the ANOVA indicated statistical significance among experimental groups then the Dunn's test was used to delineate which groups (if any) differed from the control. The probability value of less than 0.05 (two-tailed) was used as the critical level of significance for all tests. The litter was used as the experimental unit.

TK: prior to dosing, and 0.5, 1, 2, 4, 8, and 24 hours after dosing on GD 8-9 and 21-22

Results

In life observations:

Mortality: one death at 60 mg/kg on GD21, and one became moribund on GD21.

Clinical signs:

Early death

1 death at GD21: there were no abnormal observations prior to death.

1 moribund at GD21 (animal#4359): moderate appetite loss, low posture, limping, hypersensitivity to touch, and moderate languid behavior were noted

Scheduled death: unremarkable

Body weight: Body weights and body weight changes for treated animals were comparable to those of controls throughout the study, except for the 1 moribund (animal #4359) which had notable weight loss from GD19.

Food consumption: Treatment with INCB018424 did not affect food consumption, except animal No. 4359 had reduced food consumption from GD 9 onwards until becoming moribund on GD 21.

Terminal and necroscopic evaluations

Doe:

Necropsy evaluation:

Early death:

1 death on GD 21: failure of the lung to collapse.

1 moribund at GD21: red vaginal fluid was noted

Scheduled death: unremarkable

Uterine and Ovarian parameters

Changes of uterine weight: unremarkable

Other uterine or ovarian parameters:

Doses (mg/kg/day)	0	10	30	60
Corpora lutea/rabbit	9.8	10.7	10.6	10.2
Implantation sites/rabbit	9.3	9.8	9.9	9.8
% pre-implantation loss/group (mean%)	5.5	7.9	6.7	4.8
Total post-implantation loss/group (mean%)	12 (6.8)	25 (11.7)	12 (6.9)	27 (15)
Total resorptions/rabbit	0.6	1.3	0.6	1.3
Late resorptions/rabbit	0.3	0.5	0.5	1.1*
Early resorptions/rabbit	0.3	0.8	0.2	0.3

* p < 0.05

Note: Calculated values do not include animals which were not pregnant or did not survive to the scheduled termination.

Summary: Treatment with INCB018424 at 60 mg/kg/day resulted in a significantly higher number of late resorptions (1.1 per dam at 60 mg/kg/day vs. 0.3 per control dam).

Embryo-fetal data:*Mean fetal body weight*

Index	Fetal weight (g)				Percentage deviation from control			
	0	10	30	60	0	10	30	60
Group (mg/kg)								
Male	40	40	39	36*	-	-	-	-10*
Female	39	40	39	35	-	-	-	-10
Male+ female	39	40	38	36*	-	-	-	-8

** p≤0.01

Summary: Treatment with INCB018424 resulted in lower fetal weights at 60 mg/kg.

Fetal morphological data: unremarkable

Toxicokinetics: The following tables are excerpted from the study report. Toxicokinetic parameters for 10 mg/kg were not calculated as plasma concentrations were below the quantitation limit (0.01 µM) in all but three samples.

Summary of INCB018424 toxicokinetics in pregnant rabbits given daily oral dose of 30 or 60 mg/kg INCB018424

GD	Parameter	Mean ± SD	
		30 mg/kg	60 mg/kg
8	C _{max} (μM)	0.0984 ± 0.029	0.336 ± 0.042
	T _{max} (h)	0.833 ± 0.29	0.667 ± 0.29
	AUC ₀₋₄ (μM*h)	0.0891 ± 0.066	0.440 ± 0.20
	AUC ₀₋₂₄ (μM*h)	0.122 ± 0.066	0.479 ± 0.19
	t _{1/2} (h)	NC	0.474 ^b
21	C _{max} (μM)	0.0872 ± 0.054	0.380 ± 0.34
	T _{max} (h)	0.500 ± 0.0	0.500 ± 0.0
	AUC ₀₋₄ (μM*h)	0.0572 ± 0.040	0.556 ± 0.44
	AUC ₀₋₂₄ (μM*h)	0.0684 ± 0.043	0.606 ± 0.48
	t _{1/2} (h)	NC	1.33 ± 0.38

GD: Gestation Day; GD 8 was the first day of dosing
 NC: Not calculated due to insufficient time points to define the terminal phase
 a: Toxicokinetic parameters for 10 mg/kg not calculated as plasma concentrations were below the quantitation limit of 0.010 μM in all but three samples
 b: N=2; not calculated for one rabbit due to insufficient time points to define the terminal phase

Summary:

- The mean plasma C_{max} and AUC values for INCB018424 on GD 8 and 21 increased in a greater than dose proportional manner;
- C_{max} and AUC values on GD 21 were similar to those on GD 8;
- Absorption and elimination were rapid
- The AUC₀₋₂₄ at 60 mg/kg dose (606 nM.hr) is 7% the human AUC at the human dose of 50 mg/day

Conclusion: Under the conditions of this study, INCB018424 was not teratogenic in rabbits; the maternal no-observed-adverse-effect level (NOAEL) and the fetal NOAEL are 30 mg/kg.

Prenatal and Postnatal Development

Study title: Oral Gavage Study for Effects on Pre- and Post-natal Development, Including Maternal Function with INCB018424 in Rats

Study no.: 1001237

Study report location: electronic submission

Conducting laboratory and location: (b) (4)

Date of study initiation: 02/18/2010

GLP compliance: yes

QA statement: yes

Drug, lot #, and % purity: INCB018424, lot# BPR-09-134-B1-12, 98.9%

Key Study Findings

- Adverse effects included a slightly prolonged gestation period, reduced number of implantation sites, and reduced number of pups delivered in the 30 mg/kg/day F0 females;
- Reduced body weights were observed in the F1 pups at the highest maternal dose of 30 mg/kg/day. However, this effect seemed to be due to reduced initial weights on LD0 and lower early weight gain.
- The AUCs₀₋₂₄ at dose of 30 mg/kg/day were 4 $\mu\text{M}\cdot\text{h}$ on GD13, and 2.7 $\mu\text{M}\cdot\text{h}$ on lactation day 10 (LD10).
- Overall, no toxicologically significant drug-related effects were observed in F1 or F2. The highest dose tested (30 mg/kg/day) results in an AUC₀₋₂₄ that is approximately 34% the human AUC₀₋₂₄ at the maximum human dose of 25 mg twice daily (the human AUC₀₋₂₄ being 8.8 $\mu\text{M}\cdot\text{h}$).

Methods

Doses: 0, 5, 15, 30 mg/kg/day
Frequency of dosing: Once daily
Dose volume: 10 mg/mL
Route of administration: oral gavage
Formulation/Vehicle: 0.5% (w/v) methylcellulose (400 cps) in reverse osmosis/deionized water
Species/Strain: Female Crl:CD(SD) rats
Number/Sex/Group: 25 F0 females/group
Satellite groups: 6/group (3/group for control)
Study design: F0 in main study were dosed once daily beginning on GD 6 and continuing through LD 20
F0 in TK study were dosed once daily beginning on GD 6 and continuing through LD 10
Deviation from study protocol: none

Parameters and endpoints evaluated:

- F0: Mortality, clinical signs, body weight during gestation and lactation, food consumption during gestation, natural delivery and litter data and necropsy data
- F1: Maturation phases based on mortality, clinical signs, body weights, sexual development, locomotor activity, learning ability, and estrous cycle data during the postweaning;
Mortality, clinical signs, body weights, natural delivery and litter data and necropsy data on F1 females during the mating and gestation phases;
Mortality, clinical signs, body weight, breeding behavior, and necropsy data on F1 males
- F2: Survival and body weight on lactation day 1 (LD 1).

Toxicokinetics: from F0 females via a jugular vein on GD 13 and LD 10 prior to dosing and 1, 2, 4, 8, and 24 hours postdose as follows: Three animals in Group 5 (control) were bled prior to dosing and at 1 hour postdose. The first three animals in Groups 6, 7, and 8 were bled prior to dosing and at 2 and 8 hours postdose. The second three animals in Groups 6, 7, and 8 were bled at 1, 4, and 24 hours postdose.

Results:**F0 dams**In-life observations:*Gestation*

Mortality: Three F0 animals died at an unscheduled interval: one control female (B61091) was sacrificed on LD 1 after total litter death, one 5 mg/kg/day female (B61116) was sacrificed on GD 27 and was determined to be not pregnant, and one 30 mg/kg/day female (B61185) died as a result of a dosing-related accident on LD 8.

Note: The Applicant stated that above deaths are not considered treatment-related, the treatment is not considered to have adverse effect on survival. The reviewer agrees.

Clinical signs: unremarkable

Body weight: unremarkable

Food consumption: unremarkable

Natural Delivery, Litter, and Lactation

- No INCB018424-related effects on maternal survival, F1 survival, clinical signs, or maternal body weights were observed.
- Although the effect was slight, the mean gestation duration of 30 mg/kg/day animals was statistically significantly longer compared to control (22.1 versus 21.7 days, respectively) and greater than that seen in historical data (21.6 to 21.9 days: (b) (4), 2005-2009).
- While not significant, the mean number of implantation sites and mean number of pups delivered at 30 mg/kg/day were also less than those found in historical data (11.76 versus 11.83-14.44 and 11.52 versus 11.62-13.21, respectively).

- The mean number of live pups/litter with live pups at 30 mg/kg/day was also lower than control on LD 0 and precull LD 4 (11.12 versus 11.48 and 10.52 versus 11.38, respectively).

Toxicokinetics: report INCYTE DMB-08.25.1

Summary of INCB018424 Toxicokinetics in Female Sprague-Dawley Rats Given Daily Oral Doses of INCB018424 from Gestation Day 6 through Lactation Day 20

Day ^a	Parameter	5 mg/kg	15 mg/kg	30 mg/kg
GD13	C _{max} (μM)	0.0888	0.474	1.04
	T _{max} (h)	1.00	1.00	1.00
	AUC ₀₋₄ (μM*h)	0.207	0.911	3.25
	AUC ₀₋₂₄ (μM*h)	0.241	1.14	4.01
	t _{1/2} (h)	1.21	1.52	2.09
LD10	C _{max} (μM)	0.0695	0.312	0.863
	T _{max} (h)	1.00	1.00	1.00
	AUC ₀₋₄ (μM*h)	0.0920	0.848	2.28
	AUC ₀₋₂₄ (μM*h)	0.137	0.928	2.68
	t _{1/2} (h)	NC	1.41	1.78

a: GD = Gestation day; LD = Lactation day

NC: Not calculated due to insufficient timepoints

Note: the above summary table is excerpted from the application

Summary:

- The plasma C_{max} and AUC values generally increased in a greater than dose proportional manner;
- The plasma C_{max} and AUC values on GD 13 were generally comparable to those on LD 10;
- T_{max} and T_{1/2} are similar between DG13 and LD10;
- AUC₀₋₂₄ (μM*h) at 30 mg/kg: GD 13 = 4; LD 10 = 2.7.

Terminal and necropsy evaluations: unremarkable

F1 offspring

In-life observations: including the evaluation for F1 Postweaning (Maturation) and F1 Breeding, Gestation, Resting Phase

Mortality: none

Clinical signs: unremarkable

Body weight: With the exception of males on LD 7, the mean covariate-adjusted body weight of 30 mg/kg/day F1 pups was statistically lower, compared to control, on LDs 0, 4 (pre and postcull), 7, 14, and 21. The lower mean covariate body weights for both males and females on LD 7, 14, and 21 reflect the low body weight on LD 0 and lower early body weight gains rather than a continuing body weight effect.

The table below is excerpted from the application
Select F1 Pup Body Weight Data

MALES	Dose Level (mg/kg/day)				
	0	5	15	30	
	<u>Mean Covariate Body Weight</u>				
LD 0	6.70	6.52	6.57	6.24	**
LD 4, precul	10.01	9.61	9.65	8.98	**
LD 4, postcul	10.02	9.67	9.65	9.02	*
LD 7	16.02	15.28	15.33	14.45	
LD 14	33.22	32.07	31.33	29.98	**
LD 21	53.44	53.49	51.71	49.05	*
	<u>Percentage Mean Covariate Body Weight Gain</u>				
LD 7 to 14	107.4	109.9	104.4	107.5	
LD 14 to 21	60.9	66.8	65.0	63.6	
FEMALES	Dose Level (mg/kg/day)				
	0	5	15	30	
	<u>Mean Covariate Body Weight</u>				
LD 0	6.27	6.17	6.26	5.88	**
LD 4, precul	9.39	9.07	9.20	8.49	*
LD 4, postcul	9.46	9.10	9.27	8.62	*
LD 7	15.41	14.73	14.59	13.64	**
LD 14	31.97	31.02	30.21	28.61	**
LD 21	51.40	51.11	49.49	47.03	*
	<u>Percentage Mean Covariate Body Weight Gain</u>				
LD 7 to 14	107.5	110.6	107.1	109.8	
LD 14 to 21	60.8	64.8	63.8	64.4	
* = P<0.05 ** = P<0.01					
LD = lactation day					

Food consumption: unremarkable

Terminal and necropsy evaluations: unremarkable

F2 Pups

No treatment-related changes

10 Special Toxicology Studies none

11 Other toxicology studies

Genotoxic potential for identified impurities

The ^(b)₍₄₎ actual and potential impurities, together with the ^(b)₍₄₎ starting materials and ^(b)₍₄₎ intermediates (a total of ^(b)₍₄₎) were evaluated using in silico platforms designed to predict mutagenic liability potential. The in silico systems utilized included ToxCheck (v. 4.0), DEREK (v. 12.0.0), and MCASE (v. 2.1.0.18). Of the ^(b)₍₄₎ impurities evaluated, ^(b)₍₄₎ were identified to have structure alert for potential mutagenicity. The potential mutagenicity of the ^(b)₍₄₎ was further assessed using an in vitro Ames test, and the study reports for the conducted Ames assays were submitted with this application. Of note, the Ames assays were not conducted in compliance with GLP. Under the testing conditions used and applying standard mutagenicity criteria, none of the six impurities demonstrated evidence of

mutagenicity. [REDACTED] ^{(b) (4)} was present in the 6-month Tg.rasH2 carcinogenicity study at 0.17%.

Refer to Appendix/Attachments section for the review of the submitted study reports.

12 Integrated Summary and Safety Evaluation

TOXICOLOGY TABULATED SUMMARY

<i>Repeat Dose Toxicity Studies</i>		
Title	6-month GLP Rat	6-month GLP Dog
Species	Rat	Dog
Test System	Oral by gavage	Oral by gavage
Schedule Dose (mg/kg)	Daily 5,10,30,60 mg/kg/day	Daily 0.5, 2.5, 5, 10 mg/kg/day
Dose (mg/m ²)	30, 60, 180, 360 mg/m ²	10, 50, 100, 200 mg/m ²
Mortality	No treatment-related death	At HD, 2/7 males, 1/7 females
Clinical sign	wet clear and wet/dry red material around the mouth, male and female at HD	<u>Early deaths:</u> reddened facial area, clear to colored discharge from the eyes, soft feces and or diarrhea, hypoactivity, prostration with labored respiration, increased respiration rate. <u>Schedule deaths:</u> clear to colored discharge from the eyes, soft feces and/or diarrhea (females), reddened areas, swelling and hair loss on the limbs at MH, and HD
Body weight	During treatment period, ↓ in males, dose dependent During the recovery period, the mean body weights for the test article-treated males remained low compared to control values, the mean body weight gain were similar between the treatment groups and control group	<u>Early deaths:</u> ↓ <u>Schedule deaths:</u> unremarkable
Food consumption	↓ in males at HD (↓0- 21%)	< week 19: unremarkable 19-26 weeks: male: ↓ HD(↓8%-28%); female: ↓dose-dependent, LD-HD(↓4%-28%);

			26-32 weeks: ↓ HD(↓31%-51%); female: ↓LD-HD(↓10%-42%); ↑at some timepoints and some animals	
Ophthalmoscopy	unremarkable		unremarkable	
EKG	unremarkable		unremarkable	
Hematology	Male: ↓ Hbg: (↓4-7%), HD ↓hematocrit(↓3-7%), HD ↓WBC (↓5-32%), LD-HD Neut: -↓LD, LM(↓6-23%), ↑MH, HD(↑12-45%) ↓Lymphocyte (↓5-45%), LD-HD ↑Monocyte (↑10-20%), LD-HD except on week26 at HD ↓eosinophil (↓7-42%), LD-HD Except on week 26 at HD ↑ at HD ↓basophil (↓14-57%), LD-HD ↓LUC (↓12-63%), LD-HD All reversible	Female: ↓ Hbg: (↓2-4%), HD ↓WBC (↓6-39%), all doses ↑Neutrophil: (↑21-44%)all doses Except week 26, LD, MH (↓6-8%) ↓Lymphocyte: (↓9-50%), LD-HD ↑Monocyte (↑10-20%), LD-HD at HD except on week26 ↓eosinophil (↓11-44%), LMD-HD ↓basophil (↓50-100%), LMD-HD ↓LUC (↓20-60%), LD-HD All reversible	Male: ↓ RBC: (↓4-27%), MHD, HD ↓Hgb:(↓6-33%), MHD, HD ↓hematocrit: (↓7-30%), MHD, HD reticulocyte: ≤day135, ↓17-32%, MHD, HD, ↑15-22%, MHD, HD ↑NEUT(↑45-71%), MHD, HD Day 174, ↓LYM(↓11-33%), MHD, HD ↑MONO(↑15-102%), MHD, HD ↓eosinophil (↓17-64%), MHD, HD ↓basophil (↓25-50%), MHD, HD ↑LUC(↑20-100%), HD All reversible	Female: ↓ RBC: (↓6-14%), MHD, HD ↓Hgb:(↓6-19%), MHD, HD ↓hematocrit: (↓5-17%), MHD, HD reticulocyte: ≤day135, ↓5-30%, MHD, HD, ↑10-47%, MHD, HD ↑NEUT(↑10-11%), HD Day 174, ↑MONO(↑12-76%), MHD, HD ↓eosinophil (↓41-80%), MHD, HD ↑basophil (↑33-100%), MHD, HD ↑LUC(↑50-171%), MHD, HD All reversible, except for baso at MHD
Clinical chemistry	unremarkable		unremarkable	

Urilysis	unremarkable	unremarkable
Organ weight	↓spleen, male and female, ↓adrenal gland, male reversible	unremarkable
Gross Pathology	<i>unremarkable</i>	<i>Early death:</i> hemorrhage, necrosis, ulceration, bacterial colonies in tonsil (cause of death), aorta, GI, hemorrhage in heart, esophagus, thymus, diaphragm, decreased cellularity in lymph nodes, spleen, bone marrow, atrophy in testes, degenerate spermatogenic cells in epididymides <i>Schedule death:</i> MDH, HD, parasitic mite-related scabbing/discoloration or swelling, papilloma-related nodule in skin or ears, acute or subacute inflammation-related discoloration in lungs in male and female, small prostate in male, diestrus-related findings in female reproductive organs <i>Recovery:</i> , parasitic mite-related scabbing/discoloration or swelling, papilloma-related nodule in skin or ears, all others recovered
Histopathology	HD, minimal to mild lymphoid depletion in the spleen and mandibular lymph nodes, male and female; HD, minimal cortical atrophy in the adrenal glands, male	<i>Early death:</i> Variable lymphoid depletion in lymphoid organs, bone marrow hypocellularity, parasitic mite-related changes in the skin and mandibular lymph node, parasitic mite-related , Acute inflammation within the thoracic cavity, prostate hypoplasia/atrophy (death cause) <i>Schedule death:</i> MDH, HD, scabbing/discoloration or swelling, papilloma-related nodule in skin or ears, acute or subacute inflammation-related discoloration in lungs in male and female, small prostate in male, diestrus-related findings in female reproductive organs <i>Recovery:</i> pyogranulomatous inflammation in the skin, all others recovered

Genetic Toxicology Studies

Strains/Species/Cell line	Route	Treatment Duration	Dose	Significant Findings
TA98, TA100,	<i>In vitro</i>	2 days	TA98, TA100: 1.5, 5.0, 15, 50, 150, 500, 1500 and	“-“

TA1535, TA1537; <i>Escherichia coli</i> strain WP2 <i>uvrA</i>	incubation		5000 µg/plate late TA1535, TA1537; <i>Escherichia coli</i> strain WP2 <i>uvrA</i> : 33.3, 100, 333, 1000, 2500 and 5000 µg/plate	
Human peripheral blood lymphocytes	<i>In vitro</i> incubation	With S-9: 3 hrs Without S-9: 22 hrs	1.25, 2.50, 5.00, 10.0, 20.0, 40.0, 65.0, 80.0, 95.0 and 110 µg/ml	"_"
rat	oral	Single dose	62.5, 125, 250 mg/kg (375, 750, 1500 mg/m ²)	"_"
Carcinogenicity studies				
Tg.rasH2 mice	oral	Once daily for 26 weeks	15, 45, and 125 mg/kg (45, 135, 375 mg/m ²)	"_"
Reproductive and Developmental Toxicology Studies				
Rat	oral	Daily for at least 14 days(prior to mating to GD7)	10, 30, 60 mg/kg (60, 180, 360 mg/m ²)	fertility and early embryonic development • Male NOAEL= 10 mg/kg, Female NOEL for maternal toxicity = 60 mg/kg; • Male and female NOEL for reproductive and fertility = 60 mg/kg; • NOEL for embryo/fetal viability = 10mg/kg
Rat	oral	Daily (7-20)	15, 30, 60 mg/kg (90, 180, 360 mg/m ²)	Embryofetal development • Mortality was observed at 60 mg/kg; • A transient increase in food

				consumption was observed at 60 mg/kg during GD 7-13. • Decreased fetal weights were observed at 60 mg/kg;
Rabbit	oral	Daily (G8-21)	10, 30, 60 mg/kg (120, 360, 720 mg/m ²)	Embryofetal development • Mortality at 60 mg/kg; • Moderate appetite loss, low posture, limping, hypersensitivity to touch, languid behavior, and decreases in body weight and food consumption were noted • higher number of late resorptions at 60 mg/kg/day; • lower fetal weights at 60 mg/kg
rat	oral	Daily (GD 6-LD 20)	5, 15, 30 mg/kg (30, 90, 180 mg/m ²)	Prenatal and postnatal development • slightly prolonged gestation period,

				reduced number of implantation sites, and reduced number of pups delivered at 30 mg/kg/day F0 females; • decreased mean initial body weights, mean body weight gain at 30 mg/kg/day F1 pups; • The NOAEL for fertility indices and all maternal and embryofetal survival, growth, and development parameters is 30 mg/kg/day

13 Appendix/Attachments**Study title:** AMES test**Key findings:** Under the study condition, (b) (4) is not mutagenic to test strains TA98, TA100, TA1535, TA97a and TA102 in the Ames reverse-mutation assay.**Study no.:** 1012574**Volume #, and page #:** electronic submission, page 1-20**Conducting laboratory and location:** (b) (4)**Date of study initiation:** May 28, 2010**GLP compliance:** no, following SOP**QA reports:** yes (x) no ()**Drug, lot #, and % purity:** (b) (4)

Lot # 5035-197-2

Purity 99.9%

Methods: plate incorporation**Strains:** TA98, TA 100, TA1535, TA97a, and TA102**Concentrations used in definitive study:**

TA98 and TA100: 15, 50, 150, 500, 1500, and 5000 µg/plate

TA1535, TA97a and TA102, ±S9: 15, 50, 150, 500, 1500, and 5000 µg/plate

Bacteriotoxicity was evident at 5000 µg/plate using strains TA97a –S9 and TA102 +/- S9.

Basis of concentration selection: bacteriotoxicity or ICH S2 criteria for the highest concentration of 5000 µg/plate**Metabolic activation system:** Liver S9 mix from male rats, Aroclor 1254-pretreated, 25 µl/plate**Negative controls:** DMSO 100 µl/plate**Positive controls:**

Tester Strain	Positive controls
TA97a	2-aminoanthracene 9-Aminoacridine
TA98	2-aminoanthracene Benzo(a)pyrene 2-nitrofluorene
TA100	2-aminoanthracene sodium azide
TA102	2-aminoanthracene Mitomycin C
TA1535	2-aminoanthracene sodium azide

Incubation and sampling times: 3 days

Results

Study validity:

No. of replicates: 3

Counting method: not provided

Criteria for positive results: The positive controls induced a response equal to twice (or more) the negative control incidence, which is formally the criterion for a mutagenic activity of a compound. Exception is strain TA102 for which a factor of 1.5 over the concurrent negative control value is considered as positive result.

Selection of bacteria tester strains was adequate based upon Guideline for Industry: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (ICH S2A). Positive controls produced expected responses. Drug concentration selection was adequate based upon observed bacteriotoxicity or ICH S2 criteria.

Study outcome:

Mean revertant counts in the presence of metabolic activation

Test article	Conc. (µg/plate)	Bacteria strain and number of revertant colonies per plate				
		TA98	TA100	TA1535	TA97a	TA102
(b) (4)	15	32	136	15	255	447
	50	34	127	18	249	596
	150	32	132	22	210	586
	500	31	125	13	174	458
	1500	27	136	12	288	410
	5000	31	133	17	243	*
Positive control	2-aminoanthracene Benzo(a)pyrene 2-nitrofluorene	1324 324	2073	228	3811	2176
DMSO	-	46	170	16	244	465

Mean revertant counts in the absence of metabolic activation

Test article	Conc. (µg/plate)	Bacteria strain and number of revertant colonies per plate				
		TA98	TA100	TA1535	TA97a	TA102
(b) (4)	15	18	114	13	256	495
	50	24	96	19	234	527
	150	24	102	21	308	539
	500	30	104	17	334	315
	1500	38	126	23	200	348
	5000	21	123	18	182*	*
Positive control	2-nitrofluorene sodium azide 2aminoanthracene Mitomycin C	118	850	1261	4027	2520
DMSO	-	25	114	20	318	463

* Bacteriotoxicity was evident at 5000 µg/plate using strains TA97a –S9 and TA102 +/- S9

- The mean mutant numbers of negative control plates lay within the range of acceptable negative control values
- The positive controls induced a response equal to twice (or more) the negative control incidence, which is formally the criterion for a mutagenic activity of a compound
- Treatment with the test item did not increase the number of revertants above the corresponding negative control values

Comments and conclusions: The study was valid under the conditions of this study. (b) (4) is not mutagenic to test strains TA98, TA100, TA1535, TA97a and TA102 in the Ames reverse-mutation assay

Study title: AMES test

Key findings: Under the testing condition, (b) (4) is not mutagenic to test strains TA98, TA100, TA1535, TA97a and TA102 in the Ames reverse-mutation assay.

Study no.: 1012575

Volume #, and page #: electronic submission, page 1-23

Conducting laboratory and location: (b) (4)

Date of study initiation: May 28, 2010

GLP compliance: no, following SOP

QA reports: yes (x) no ()

Drug, lot #, and % purity: (b) (4)

Lot # 5035-194-4

Purity 99.9%

Methods: plate incorporation

Strains: TA98, TA 100, TA1535, TA97a, and TA102

Concentrations used in definitive study:

TA98 and TA100: 15, 50, 150, 500, 1500, and 5000 µg/plate

TA1535, TA97a and TA102, ±S9: 15, 50, 150, 500, 1500, and 5000 µg/plate

Bacteriotoxicity was evident at 5000 µg/plate using strain TA102 –S9 and at ≥ 1500 µg/plate using strain TA102 +S9

Basis of concentration selection: bacteriotoxicity or ICH S2 criteria for the highest concentration of 5000 µg/plate

Metabolic activation system: Liver S9 mix from male rats, Aroclor 1254-pretreated, 25 µl/plate

Negative controls: DMSO 100 µl/plate

Positive controls:

Tester Strain	Positive controls
TA97a	2-aminoanthracene 9-Aminoacridine
TA98	2-aminoanthracene Benzo(a)pyrene 2-nitrofluorene
TA100	2-aminoanthracene sodium azide
TA102	2-aminoanthracene Mitomycin C
TA1535	2-aminoanthracene sodium azide

Incubation and sampling times: 3 days

Results

Study validity:

No. of replicates: 3

Counting method: not provided

Criteria for positive results: The positive controls induced a response equal to twice (or more) the negative control incidence, which is formally the criterion for a mutagenic activity of a compound. Exception is strain TA102 for which a factor of 1.5 over the concurrent negative control value is considered as positive result.

Selection of bacteria tester strains was adequate based upon Guideline for Industry: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (ICH S2A). Positive controls produced expected responses. Drug concentration selection was adequate based upon observed bacteriotoxicity or ICH S2 criteria.

Study outcome:

Mean revertant counts in the presence of metabolic activation

Test article	Conc. (µg/plate)	Bacteria strain and number of revertant colonies per plate				
		TA98	TA100	TA1535	TA97a	TA102
(b) (4)	15	46	142	20	293	610
	50	38	138	20	287	714
	150	40	140	17	266	576
	500	44	141	16	244	423
	1500	36	127	13	242	*
	5000	30	121	16	252	*
Positive control	2-aminoanthracene Benzo(a)pyrene 2-nitrofluorene	1324 324	2073	228	3811	2176
DMSO	-	46	170	16	244	465

Mean revertant counts in the absence of metabolic activation

Test article	Conc. (µg/plate)	Bacteria strain and number of revertant colonies per plate				
		TA98	TA100	TA1535	TA97a	TA102
(b) (4)	15	17	109	20	197	513
	50	22	104	19	206	521
	150	26	86	23	204	490
	500	25	118	18	315	411
	1500	29	98	19	312	461
	5000	26	94	31	310	*
Positive control	2-nitrofluorene sodium azide 2-aminoanthracene Mitomycin C	118	850	1261	4027	2520
DMSO	-	25	114	20	463	463

* Bacteriotoxicity was evident at 5000 µg/plate using strain TA102 –S9 and at ≥ 1500 µg/plate using strain TA102 +S9

- The mean mutant numbers of negative control plates lay within the range of acceptable negative control values;
- The positive controls induced a response equal to twice (or more) the negative control incidence, which is formally the criterion for a mutagenic activity of a compound;
- There were no relevant increases in the number of revertants above the corresponding negative control values under any of the test conditions used after treatment with the test item.

Comments and conclusions: The study was valid under the conditions of this study. (b) (4) is not mutagenic to test strains TA98, TA100, TA1535, TA97a and TA102 in the Ames reverse-mutation assay.

Study title: AMES test

Key findings: Under the testing condition, (b) (4) is not mutagenic to test strains TA98, TA100, TA1535, TA97a and TA102 in the Ames reverse-mutation assay.

Study no.: 1012576

Volume #, and page #: electronic submission, page 1-23

Conducting laboratory and location: (b) (4)

Date of study initiation: May 28, 2010

GLP compliance: no, following SOP

QA reports: yes (x) no ()

Drug, lot #, and % purity (b) (4)
 Lot # 5035-197-2
 Purity 86.1%

Methods: plate incorporation

Strains: TA98, TA 100, TA1535, TA97a, and TA102

Concentrations used in definitive study:

TA98 and TA100, $\pm$ S9: 15, 50, 150, 500, 1500, and 5000 μ g/plate

TA1535, TA97a and TA102, $\pm$ S9: 15, 50, 150, 500, 1500, and 5000 μ g/plate

Bacteriotoxicity was evident at 5000 μ g/plate using strains TA98 +/- S9, TA100 +/- S9, TA1535 +/- S9, TA97a -S9 and TA102 - S9 and at $\geq$ 1500 μ g/plate using strains TA97a +S9 and TA102 +S9

Basis of concentration selection: bacteriotoxicity

Metabolic activation system: Liver S9 mix from male rats, Aroclor 1254-pretreated, 25 μ l/plate

Negative controls: DMSO 100 μ l/plate

Positive controls:

Tester Strain	Positive controls
TA97a	2-aminoanthracene 9-Aminoacridine
TA98	2-aminoanthracene Benzo(a)pyrene 2-nitrofluorene
TA100	2-aminoanthracene sodium azide

TA102	2-aminoanthracene Mitomycin C
TA1535	2-aminoanthracene sodium azide

Incubation and sampling times: 3 days

Results

Study validity:

No. of replicates: 3

Counting method: not provided

Criteria for positive results: The positive controls induced a response equal to twice (or more) the negative control incidence, which is formally the criterion for a mutagenic activity of a compound. Exception is strain TA102 for which a factor of 1.5 over the concurrent negative control value is considered as positive result.

Selection of bacteria tester strains was adequate based upon Guideline for Industry: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (ICH S2A). Positive controls produced expected responses. Drug concentration selection was adequate based upon observed bacteriotoxicity.

Study outcome:

Mean revertant counts in the presence of metabolic activation

Test article	Conc. (µg/plate)	Bacteria strain and number of revertant colonies per plate				
		TA98	TA100	TA1535	TA97a	TA102
(b) (4)	15	35	130	12	240	552
	50	31	122	20	243	640
	150	35	160	9	226	595
	500	30	151	20	303	458
	1500	43	131	20	*	*
	5000	*	*	*	*	*
Positive control	2-aminoanthracene Benzo(a)pyrene 2-nitrofluorene	1324 324	2073	228	3811	2176
DMSO	-	46	170	16	244	465

Mean revertant counts in the absence of metabolic activation

Test article	Conc. (µg/plate)	Bacteria strain and number of revertant colonies per plate				
		TA98	TA100	TA1535	TA97a	TA102
(b) (4)	15	27	131	22	233	555
	50	27	126	29	236	546
	150	22	102	28	301	620
	500	25	129	17	244	543

	1500	32	122	28	236	680
	5000	*	*	*	182*	*
Positive control	2-nitrofluorene sodium azide 2aminoanthracene Mitomycin C	118	850	1261	4027	2520
DMSO	-	25	114	20	318	463

* Bacteriotoxicity was evident at 5000 µg/plate using strains TA98 +/- S9, TA100 +/- S9, TA1535 +/- S9, TA97a -S9 and TA102 - S9 and at ≥ 1500 µg/plate using strains TA97a +S9 and TA102 +S9

- The mean mutant numbers of negative control plates lay within the range of acceptable negative control values;
- The positive controls induced a response equal to twice (or more) the negative control incidence, which is formally the criterion for a mutagenic activity of a compound;
- There were no relevant increases in the number of revertants above the corresponding negative control values under any of the test conditions used after treatment with the test item.

Comments and conclusions: The study was valid under the conditions of this study. (b) (4) is not mutagenic to test strains TA98, TA100, TA1535, TA97a and TA102 in the Ames reverse-mutation assay

Study title: AMES test

Key findings: Under the testing condition, (b) (4) is not mutagenic to test strains TA98, TA100, TA1535, TA97a and TA102 in the Ames reverse-mutation assay.

Study no.: 1012577

Volume #, and page #: electronic submission, page 1-20

Conducting laboratory and location: (b) (4)

Date of study initiation: May 28, 2010

GLP compliance: no, following SOP

QA reports: yes (x) no ()

Drug, lot #, and % purity: (b) (4)

Lot # 10022-192-Lot2

Purity 95.7%

Methods: plate incorporation

Strains: TA98, TA 100, TA1535, TA97a, and TA102

Concentrations used in definitive study:

TA98 and TA100, $\pm$ S9: 15, 50, 150, 500, 1500, and 5000 μ g/plate

TA1535, TA97a and TA102, $\pm$ S9: 15, 50, 150, 500, 1500, and 5000 μ g/plate

The test article precipitated at 5000 μ g/plate under all test conditions. In strain TA102 +S9 precipitation was also seen at 1500 μ g/plate. Bacteriotoxicity was not evident in this study; however, precipitation prevented colony counting.

Basis of concentration selection: solubility

Metabolic activation system: Liver S9 mix from male rats, Aroclor 1254-pretreated, 25 μ l/plate

Negative controls: DMSO 100 μ l/plate

Positive controls:

Tester Strain	Positive controls
TA97a	2-aminoanthracene 9-Aminoacridine
TA98	2-aminoanthracene Benzo(a)pyrene 2-nitrofluorene
TA100	2-aminoanthracene sodium azide
TA102	2-aminoanthracene Mitomycin C
TA1535	2-aminoanthracene sodium azide

Incubation and sampling times: 3 days

ResultsStudy validity:

No. of replicates: 3

Counting method: not provided

Criteria for positive results: The positive controls induced a response equal to twice (or more) the negative control incidence, which is formally the criterion for a mutagenic activity of a compound. Exception is strain TA102 for which a factor of 1.5 over the concurrent negative control value is considered as positive result.

Selection of bacteria tester strains was adequate based upon Guideline for Industry: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (ICH S2A). Positive controls produced expected responses. Drug concentration selection was adequate based upon observed solubility.

Study outcome:

Mean revertant counts in the presence of metabolic activation

Test article	Conc. (µg/plate)	Bacteria strain and number of revertant colonies per plate				
		TA98	TA100	TA1535	TA97a	TA102
(b) (4)	15	30	156	12	177	559
	50	20	144	16	189	549
	150	29	163	15	212	547
	500	27	139	14	239	464
	1500	34	141	23	247	410*
	5000	*	*	*	*	*
Positive control	2-aminoanthracene	1324	2073	228	3811	2176
	Benzo(a)pyrene	324				
	2-nitrofluorene					
DMSO	-	46	170	16	244	465

Mean revertant counts in the absence of metabolic activation

Test article	Conc. (µg/plate)	Bacteria strain and number of revertant colonies per plate				
		TA98	TA100	TA1535	TA97a	TA102
(b) (4)	15	40	138	24	189	532
	50	37	145	21	319	513
	150	38	135	21	213	517
	500	40	142	23	237	441
	1500	35	149	33	253	512
	5000	37*	169*	34*	*	*
Positive control	2-nitrofluorene	118				
	sodium azide		850	1261		
	2-aminoanthracene				4027	
	Mitomycin C					2520
DMSO	-	25	114	20	318	463

* The test article precipitated at 5000 µg/plate under all test conditions. In strain TA102 +S9 precipitation was also seen at 1500 µg/plate. Bacteriotoxicity was not evident in this study; however, precipitation prevented colony counting.

- The mean mutant numbers of negative control plates lay within the range of acceptable negative control values;
- The positive controls induced a response equal to twice (or more) the negative control incidence, which is formally the criterion for a mutagenic activity of a compound;
- Treatment with the test item did not increase the number of revertants above the corresponding negative control values under any of the test conditions used.

Comments and conclusions: The study was valid under the conditions of this study. (b) (4) is not mutagenic to test strains TA98, TA100, TA1535, TA97a and TA102 in the Ames reverse-mutation assay.

Study title: AMES test

Key findings: Under the testing condition, (b) (4) is not mutagenic to test strains TA98, TA100, TA1535, TA97a and TA102 in the Ames reverse-mutation assay.

Study no.: 1012578

Volume #, and page #: electronic submission, page 1-27

Conducting laboratory and location: (b) (4) Glowienke, PhD,
Basel/Switzerland site

Date of study initiation: May 28, 2010

GLP compliance: no, following SOP

QA reports: yes (x) no ()

Drug, lot #, and % purity: (b) (4)
Lot # 10026-120-2 Lot 3
Purity 99.1%

Methods: plate incorporation

Strains: TA98, TA 100, TA1535, TA97a, and TA102

Concentrations used in definitive study:

TA98 and TA100, $\pm$ S9: 15, 50, 150, 500, 1500, and 5000 μ g/plate

TA1535, TA97a and TA102, $\pm$ S9: 15, 50, 150, 500, 1500, and 5000 μ g/plate

Basis of concentration selection: ICH S2 criteria for the highest concentration of 5000 μ g/plate

Metabolic activation system: Liver S9 mix from male rats, Aroclor 1254-pretreated, 25 μ l/plate

Negative controls: DMSO 100 μ l/plate

Positive controls:

Tester Strain	Positive controls
TA97a	2-aminoanthracene 9-Aminoacridine
TA98	2-aminoanthracene Benzo(a)pyrene 2-nitrofluorene
TA100	2-aminoanthracene sodium azide
TA102	2-aminoanthracene

	Mitomycin C
TA1535	2-aminoanthracene sodium azide

Incubation and sampling times: 3 days

Results

Study validity:

No. of replicates: 3

Counting method: not provided

Criteria for positive results: The positive controls induced a response equal to twice (or more) the negative control incidence, which is formally the criterion for a mutagenic activity of a compound. Exception is strain TA102 for which a factor of 1.5 over the concurrent negative control value is considered as positive result.

Selection of bacteria tester strains was adequate based upon Guideline for Industry: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (ICH S2A). Positive controls produced expected responses. Drug concentration selection was adequate based upon ICH S2 criteria.

Study outcome:

Mean revertant counts in the presence of metabolic activation

Test article	Conc. (µg/plate)	Bacteria strain and number of revertant colonies per plate				
		TA98	TA100	TA1535	TA97a	TA102
(b) (4)	15	77	135	30	2437	501
	50	64	130	19	3511	529
	150	77	180	17	3706	516
	500	75	143	17	2340	492
	1500	77	134	20	2701	463
	5000	37	130	20	1892	363
Positive control	2-aminoanthracene Benzo(a)pyrene 2-nitrofluorene	1324 324	2073	228	3811	2176
DMSO	-	46	170	16	244	465

Mean revertant counts in the absence of metabolic activation

Test article	Conc. (µg/plate)	Bacteria strain and number of revertant colonies per plate				
		TA98	TA100	TA1535	TA97a	TA102
(b) (4)	15	29	120	22	769	356
	50	28	125	23	986	418
	150	22	116	14	1541	471
	500	27	139	21	1041	440
	1500	31	151	17	1269	450

	5000	26	157	13	440	396
Positive control	2-nitrofluorene sodium azide 2aminoanthracene Mitomycin C	118	850	1261	4027	2520
DMSO	-	25	114	20	318	463

Repeat experiment on TA97a

(b) (4)	Bacteria strain and number of revertant colonies per plate							
Dose (µg/plate)	39	78	156	313	625	1250	2500	5000
+S9								
No, colonies	242	268	264	232	240	contaminated	248	232
Positive cont	2aminoanthracene		3007					
Negative cont	DMSO		222					
-S9								
No, colonies	208	229	232	217	182	235	267	240
Positive cont	2aminoanthracene		3046					
Negative cont	DMSO		218					

Note: increased mean mutant numbers on TA97a were not concentration-dependent. In addition, they could not be confirmed in the repeated experiment. Thus, the test item was not considered to be mutagenic on TA97a.

- The mean mutant numbers of negative control plates lay within the range of acceptable negative control values
- The positive controls induced a response equal to twice (or more) the negative control incidence, which is formally the criterion for a mutagenic activity of a compound
- Treatment with the test item did not increase the number of revertants above the corresponding negative control values.

Comments and conclusions: The study was valid under the conditions of this study. (b) (4) is not mutagenic to test strains TA98, TA100, TA1535, TA97a and TA102 in the Ames reverse-mutation assay

Study title: AMES test

Key findings: Under the testing condition, (b) (4) is not mutagenic to test strains TA98, TA100, TA1535, TA97a and TA102 in the Ames reverse-mutation assay.

Study no.: 1012579

Volume #, and page #: electronic submission, page 1-20

Conducting laboratory and location: (b) (4)

Date of study initiation: May 28, 2010

GLP compliance: no, following SOP

QA reports: yes (x) no ()

Drug, lot #, and % purity: (b) (4)

Lot # 10026-120-1 Lot3

Purity: "not given"-stated in the study report

Methods: plate incorporation

Strains: TA98, TA 100, TA1535, TA97a, and TA102

Concentrations used in definitive study:

TA98 and TA100: 15, 50, 150, 500, 1500, and 5000 µg/plate

TA1535, TA97a and TA102, ±S9: 15, 50, 150, 500, 1500, and 5000 µg/plate

Bacteriotoxicity was evident at 5000 µg/plate using strain TA102 +/- S9.

Basis of concentration selection: Bacteriotoxicity or ICH S2 criteria for the highest concentration of 5000 µg/plate

Metabolic activation system: Liver S9 mix from male rats, Aroclor 1254-pretreated, 25 µl/plate

Negative controls: DMSO 100 µl/plate

Positive controls:

Tester Strain	Positive controls
TA97a	2-aminoanthracene 9-Aminoacridine
TA98	2-aminoanthracene Benzo(a)pyrene 2-nitrofluorene
TA100	2-aminoanthracene sodium azide
TA102	2-aminoanthracene Mitomycin C
TA1535	2-aminoanthracene sodium azide

Incubation and sampling times: 3 days

Results

Study validity:

No. of replicates: 3

Counting method: not provided

Criteria for positive results: The positive controls induced a response equal to twice (or more) the negative control incidence, which is formally the criterion for a mutagenic activity of a compound. Exception is strain

TA102 for which a factor of 1.5 over the concurrent negative control value is considered as positive result.

Selection of bacteria tester strains was adequate based upon Guideline for Industry: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (ICH S2A). Positive controls produced expected responses. Drug concentration selection was adequate based upon bacteriotoxicity or ICH S2 criteria.

Study outcome:

Mean revertant counts in the presence of metabolic activation

Test article	Conc. (µg/plate)	Bacteria strain and number of revertant colonies per plate				
		TA98	TA100	TA1535	TA97a	TA102
(b) (4)	15	21	128	13	172	543
	50	22	154	16	209	578
	150	23	153	17	211	582
	500	27	157	21	246	441
	1500	33	144	15	243	598
	5000	26	143	17	313	616*
Positive control	2-aminoanthracene Benzo(a)pyrene 2-nitrofluorene	1324 324	2073	228	3811	2176
DMSO	-	46	170	16	244	465

Mean revertant counts in the absence of metabolic activation

Test article	Conc. (µg/plate)	Bacteria strain and number of revertant colonies per plate				
		TA98	TA100	TA1535	TA97a	TA102
(b) (4)	15	22	122	9	204	529
	50	19	127	14	243	633
	150	28	130	19	244	628
	500	28	122	17	308	551
	1500	27	130	19	301	607
	5000	27	123	21	307	*
Positive control	2-nitrofluorene sodium azide 2-aminoanthracene Mitomycin C	118	850	1261	4027	2520
DMSO	-	25	114	20	318	463

* Bacteriotoxicity was evident at 5000 µg/plate using strain TA102 +/- S9.

- The mean mutant numbers of negative control plates lay within the range of acceptable negative control values;
- The positive controls induced a response equal to twice (or more) the negative control incidence, which is formally the criterion for a mutagenic activity of a compound;

- Treatment with the test item did not increase the number of revertants above the corresponding negative control values under any of the test conditions used.

Comments and conclusions: The study was valid under the conditions of this study. (b) (4) is not mutagenic to test strains TA98, TA100, TA1535, TA97a and TA102 in the Ames reverse-mutation assay.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The non-clinical studies adequately support the safety of ruxolitinib phosphate by oral route in myelofibrosis. See the EXECUTVE SUMMARY, Page 4, for an overall summary of nonclinical findings.

Signatures:

Reviewer Signature _____

Supervisor Signature _____

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/s/

WEI CHEN
10/26/2011

HALEH SABER
10/27/2011

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202192

Applicant: Incyte

Stamp Date: June 3, 2011,

Drug Name: ruxolitinib phosphate

NDA/BLA Type: new commercial

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		*Appears acceptable.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		*Appears acceptable
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	n/a		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	x		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	x		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	n/a		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	*x		
11	Has the applicant addressed any abuse potential issues in the submission?	n/a		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	n/a		

* Issues generally identified during review.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___yes___

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

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

Wei Chen, Ph.D 06/12/2012

 Reviewing Pharmacologist Date

Saber Haleh, Ph.D

 Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

WEI CHEN
06/14/2011

HALEH SABER
06/14/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202192Orig1s000

STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: 212192/001

Drug Name: Ruxolitinib

Indication(s): Myelofibrosis

Applicant: Incyte Corp.

Date(s): Submitted on 6/3/2011, PDUFA date 12/3/2011

Review Priority: Priority

Biometrics Division: Division of Biometrics V (HFD-711)

Statistical Reviewer: Dr. Laura Lu, Ph.D

Concurring Reviewers: Dr. Mark Rothmann, Ph.D, Team Leader
Dr. Rajeshwari Sridhara, Ph.D, Division Director

Medical Division: Division of Hematology Drug Products (HFD-107)

Clinical Team: Dr. Al Deisseroth, MD, Medical Reviewer
Dr. Ann Farrell, MD, Division Director

Project Manager: Ms. Amy Baird

Keywords:

Response rate, missing data

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1. EXECUTIVE SUMMARY

NDA202192 was submitted to support the approval of ruxolitinib on the treatment of myelofibrosis. Two randomized, controlled studies (Study 351 and Study 352) were conducted. The control arms were placebo and best available therapy (BAT) in Study 351 and Study 352, respectively. The results of these two studies demonstrated that, compared with those in the control arm, patients in the ruxolitinib arm were more likely to achieved at least a 35% reduction in spleen volume from baseline at Week 24 in Study 351 (42% vs. 1%) and Week 48 in Study 352 (28% vs. 0%).

Across subgroups, response rate of the primary endpoint is consistently higher in the ruxolitinib group than those in the placebo group. However, the response rate in female group is much higher than that in the male group within the ruxolitinib arm in both studies (25% vs. 59% respectively in Study 351; 25% vs. 33% respectively in Study 351). And the response rate in V617F positive group is much higher than that in the V617F negative group within the ruxolitinib arm in both studies (48% vs. 28% respectively in Study 351; 33% vs. 14% respectively in Study 351).

2. INTRODUCTION

2.1 Overview

Two randomized, controlled studies (Study 351 and Study 352) have been conducted for ruxolitinib on the treatment of patients with high or intermediate-2 risk myelofibrosis (including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis). The majority of the patients in Study 351 were from US (76%) and all patients in Study 352 were from Europe.

Study 351 is a randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ruxolitinib to placebo in subjects with Primary Myelofibrosis (PMF), Post Polycythemia-myelofibrosis (PPV-MF) or Post Essential Thrombocythemia myelofibrosis (PET-MF). Subjects were randomized with a 1:1 ratio to receive ruxolitinib or matching placebo tablets. The primary endpoint of Study 351 was the proportion of subjects achieving >35% reduction in spleen volume from baseline to Week 24 as measured by MRI (or by CT for applicable). Secondary endpoints include the proportion of subjects who have a 50% reduction from baseline to Week 24 in the total symptom score, change from baseline to Week 24 in the total symptom score and overall survival. The trial was originally planned with a sample size of 240 subjects, which provided a 97% power to detect a treatment difference in the primary endpoint at two-sided alpha level of 0.05 using the chi-square test.

Study 352 is an open-label, randomized study comparing the efficacy and safety of ruxolitinib tablets versus investigator-selected BAT in subjects with MF with splenomegaly of at least 5 cm below the costal margin by manual palpation, and either 2 (Intermediate-2 risk category) or 3 or

more (High risk category) prognostic factors according to the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT). A total of 219 patients were randomized with a ratio of 2:1 to ruxolitinib and BAT. The primary endpoint of Study 352 was the proportion of subjects achieving >35% reduction in spleen volume from baseline to Week 48 as measured by MRI (or by CT for applicable). The key secondary endpoint for this study was the proportion of subjects achieving a $\geq 35\%$ reduction of spleen volume as measured by MRI or CT from baseline at Week 24.

2.2 Data Sources

The study reports and data for this NDA are located at <\\Cdsub1\evsprod\NDA202192\0000\m5\datasets>. Efficacy evaluation in this NDA was mainly based on the following electronic datasets:

1. Aseff3.xpt at <\\Cdsub1\evsprod\NDA202192\0000\m5\datasets\incb-18424-351\listings>; and
2. Aseff3.xpt at <\\Cdsub1\evsprod\NDA202192\0000\m5\datasets\incb-18424-351\listings>.

Note that these two analysis datasets were submitted to the wrong folders. They should be included in the 'analysis' data folder instead of the 'listings' folder.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The raw data and derived data were submitted in the folder <\\Cdsub1\evsprod\NDA202192\0000\m5\datasets>. The analysis datasets were documented well. The raw data can be verified through Case Report Forms. The value of the derived variables can be verified by the raw data.

3.2 Evaluation of Efficacy

3.2.1 Study 351

3.2.1.1 Study Design and Endpoints

Study 351 is a randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ruxolitinib to placebo in subjects with Primary Myelofibrosis (PMF), Post Polycythemia-myelofibrosis (PPV-MF) or Post Essential Thrombocythemia myelofibrosis (PET-MF). Subjects were randomized with a 1:1 ratio to receive ruxolitinib or matching placebo tablets. The starting dose was determined based on baseline platelet count. Subjects with baseline platelet count > 200,000/ μL began a dose regimen of 20 mg twice daily. Subjects with baseline platelet count of 100,000/ μL to 200,000/ μL (inclusive) began a dose regimen of 15 mg twice daily. The dose could be adjusted by the investigator based on a standardized dosing paradigm, which was used to determine dose adjustments for safety and efficacy so that each subject was titrated to their most appropriate dose. Doses were not to exceed 25 mg twice daily. Subjects

randomized to placebo made the same adjustments in the number of matching placebo tablets to maintain the blind.

When half of the subjects remaining in the study (including subjects continuing on randomized treatment and those who had crossed over to ruxolitinib from placebo) completed the Week 36 visit and all subjects enrolled completed Week 24 or discontinued, the database was frozen and the primary analysis was conducted. Once this was complete, all subjects were unblinded. After the study was unblinded, subjects who had been randomized to placebo were given the opportunity to crossover to ruxolitinib treatment, provided hematology laboratory parameters were adequate; and subjects who had been randomized to ruxolitinib remained in the study if they were obtaining benefit from treatment.

The primary efficacy endpoint is the proportion of subjects achieving >35% reduction in spleen volume from baseline to Week 24 as measured by MRI (or by CT for applicable). The treatment difference in the proportion was tested by Fisher's exact test. A subject must have a baseline spleen volume in order to be included in the primary efficacy analysis. A subject with a missing Week 24 spleen volume was considered as having not achieved the >35% reduction. Subjects who dropped out of the study due to lack of efficacy or treatment-related adverse events, or made an early crossover to active treatment (placebo subjects only) prior to Week 24 visit were considered as having not achieved the >35% reduction.

Secondary endpoints include the proportion of subjects who have a 50% reduction from baseline to Week 24 in the total symptom score, change from baseline to Week 24 in the total symptom score and overall survival. The secondary efficacy endpoints was analyzed only when the study had reached the efficacy objective in the primary endpoint and was tested in a fixed sequence-testing procedure with each at the 0.05 alpha level in the order below:

1. The proportion of subjects who have a 50% reduction from baseline to Week 24 in the total symptom score
2. Change from baseline to Week 24 in the total symptom score; and
3. Overall Survival

Proportion of subjects achieving $\geq 50\%$ reduction from baseline in the Week 24 total symptom score were then calculated by treatment group. The 2 proportions were compared using the Chi-squared test. Only subjects who had a baseline total symptom score were included in the sponsor's analysis. A subject with a missing Week 24 total symptom score was considered as having not achieved the > 50% reduction. Subjects who dropped out of the study due to lack of efficacy or treatment related adverse events, or were unblinded prior to Week 24 for the early crossover to active treatment were considered as having not achieved the > 50% reduction.

The change from baseline to Week 24 in the total symptom score was analyzed using both parametric and non-parametric methods. The Wilcoxon Rank-Sum Test was used for a between-group comparison in the median change from baseline. Patients with missing baseline or Week 24 total symptom scores were not included in the analysis. The overall survival variable was analyzed using the Kaplan-Meier method.

Assuming that at least 30% of the active subjects would achieve a >35% reduction from baseline to Week 24, and that rate for the placebo subjects would be no more than 10%, a sample size of

240 subjects (120 per group) would provide a 97% power to detect a treatment difference in the primary endpoint at two-sided alpha level of 0.05 using the chi-square test.

3.2.1.2 Patient disposition

A total of 309 patients were randomized into the study (155 in the roxolitinib arm and 154 in the placebo arm). The number of patient withdrew from study early and the reasons of withdrawal are presented in Table 1 below.

Table 1. Patient Disposition (Study 351)

Treatment Arm	Ruxolitinib (N=155) n (%)	Placebo (N=154) n (%)
Number subjects withdrawn from study	21 (13.5)	37 (24.5)
Reasons for withdrawal from study		
Death	9 (5.8)	9 (6.0)
Adverse event	8 (5.2)	8 (5.3)
Disease progression	3 (1.9)	12 (7.9)
Consent withdrawn	1 (0.6)	5 (2.0)
Other	0 (0)	3 (2.0)

3.2.1.3 Demographics and baseline characteristic

Patient demographics and baseline characteristics are presented in Table 2 and Table 3 below.

Table 2. Patient Demographics (Study 351)

Variable	Ruxolitinib (N = 155)	Placebo (N = 154)
Age (yrs)		
<=65 years, n (%)	70 (45.2)	52 (33.8)
> 65 years, n (%)	85 (54.8)	102 (66.2)
Sex, n (%)		
Male	79 (51.0)	88 (57.1)
Female	76 (49.0)	65 (42.2)
Unknown	0 (0)	1 (0.6)
Race, n (%)		
Black or African American	6 (3.9)	7 (4.5)
White	138 (89.0)	139 (90.3)
Asian	5 (3.2)	4 (2.6)
Native Hawaiian or Other Pacific Islander	1 (0.6)	0 (0)
Other	5 (3.2)	4 (2.6)

Table 3. Baseline Characteristics (Study 351)

Variable	Ruxolitinib (N = 155)	Placebo (N = 154)
Disease subtype, n (%)		
PMF	70 (45.2)	84 (54.5)
PPV-MF	50 (32.3)	47 (30.5)
PET-MF	35 (22.6)	22 (14.3)
Unknown	0 (0)	1 (0.6)
Years since initial diagnosis		
Mean (STD)	4.9 (6.1)	4.6 (6.2)
Fibrosis grade at baseline, n (%)		
0	2 (1.3)	1 (0.6)
1	14 (9.0)	18 (11.7)
2	63 (40.6)	51 (33.1)
3	65 (41.9)	71 (46.1)
Unknown	11 (7.2)	13 (8.4)
Spleen volume, cm ³		
Mean (STD)	2745.7 (1247.0)	2797.6 (1388.5)
Palpable spleen length below the left costal margin, (cm)		
N	155	153
Mean (STD)	16.1 (5.7)	16.4 (6.3)
ECOG Performance Status		
0	47 (31.1)	38 (25.5)
1	87 (57.6)	82 (55.0)
2	14 (9.3)	25 (16.8)
3	3 (2.0)	4 (2.7)
Unknown	4 (2.6)	5 (3.3)
IWG risk category		
High	90 (58.1)	99 (64.3)
Intermediate 2	64 (41.3)	54 (35.1)
Unknown	1 (0.6)	1 (0.6)
Percent V617F at baseline		
Yes	113 (72.9)	123 (79.9)
No	40 (25.8)	27 (17.7)
Unknown	1 (0.6)	4 (0.3)

3.2.1.2 Efficacy Results

Primary endpoint

A significantly larger proportion of subjects in the ruxolitinib group achieved a $\geq 35\%$ reduction from baseline at Week 24 compared with the placebo group (41.9% vs. 0.7%, $p <$

0.0001 by Fisher's Exact test). Table 4 below presents a summary of the results of the primary endpoint.

Table 4. Proportion of subjects achieved a $\geq 35\%$ reduction from baseline at Week 24 (Study 351)

	Ruxolitinib (N = 155)	Placebo (N = 154)
Subjects achieving a $\geq 35\%$ reduction from baseline in spleen volume, n (%)	65 (41.9)	1 (0.7)
% Difference between treatments (95% CI ^a)	41.2 (32.8, 48.7)	
p-value (by Fisher's Exact test)	<0.0001	

a: By Agresti-Caffo method (Agresti and Caffo; The American Statistician, Vol. 54, No. 4, (Nov., 2000), pp.280-288)

Secondary endpoints

Results for the secondary endpoints are presented in Table 5 below. Survival data were not mature. Ten (6.5%) subjects in the ruxolitinib group and 14 (9.1%) subjects in the placebo group died. This includes 20 subjects who died during randomized treatment, after crossover, and up to 28 days after study withdrawal, and 4 subjects who died more than 28 days after withdrawal from the study and represents a hazard ratio of 0.668 ($p = 0.3268$).

Table 5. Results of secondary endpoints (Study 351)

	Ruxolitinib (N = 155)	Placebo (N = 154)
Number of evaluable subjects	148 (95.5)	152 (98.7)
Subjects achieving a $\geq 50\%$ improvement from baseline in total symptom score, n (%)		
Yes	68 (45.9)	8 (5.3)
No	80 (54.1)	144 (94.7)
p-value (by Fisher's Exact test)	< 0.0001	
Change from baseline to Week 24 in total symptom score		
N	131	105
Mean (SD)	-8.6 (10.0)	3.2 (9.4)
p-value (by Wilcoxon rank-sum test)	<0.0001	
Overall Survival		
Number of events	10 (6.5%)	14 (9.1%)
HR	0.668	
P-value (by log-rank test)	0.33	

Reviewers comment: Note that 24% (73/309) of the patients have missing value in change from baseline to Week 24 in total symptom score. To assess the impact of the missing data, this reviewer did a worst-case carried forward by imputing the missing scores in the following way:

1. *imputing the worst score in Week 4, Week 8, Week 12, Week 16 and Week 20 to the missing score on Week 24 in the ruxolitinib arm; and*
2. *imputing the best score in Week 4, Week 8, Week 12, Week 16 and Week 20 to the missing score on Week 24 in the placebo arm.*

After missing value imputation, there are still 6 patients missing in the ruxolitinib arm and 4 missing in the placebo arm. The means become -7.9 in ruxolitinib arm and 2.0 in the BAT arm, which is still statistically significantly different ($p < 0.0001$). Therefore, the result of this sensitivity analysis supports that of the primary analysis.

3.2.2 Study 352

3.2.2.1 Study Design and Endpoints

Study 352 is an open-label, 2:1 randomized study comparing the efficacy and safety of ruxolitinib tablets versus investigator-selected BAT in subjects with MF with splenomegaly of at least 5 cm below the costal margin by manual palpation, and either 2 (Intermediate-2 risk category) or 3 or more (High risk category) prognostic factors according to the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT). The starting dose of ruxolitinib was determined based on baseline platelet count; the maximum dose on study did not exceed 25 mg twice daily.

Patients were randomized 2:1 to the ruxolitinib and BAT arms. Randomization was stratified by baseline prognostic risk level in the following manner:

- Stratum 1: Intermediate risk level 2 (2 risk factors)
- Stratum 2: High risk (3 or more risk factors)

The duration of this study consisted of an enrollment period of 27 weeks, a period of 48 weeks before the primary analysis, and a period of 96 weeks after the last visit of the last ongoing subject for the primary endpoint. Patients in the BAT arm could cross over to ruxolitinib after progression.

The primary efficacy endpoint of this study was the proportion of subjects achieving $\geq 35\%$ reduction in spleen volume from baseline at Week 48 as measured by MRI or CT (for subjects unable to undergo MRI). The key secondary endpoint for this study was the proportion of subjects achieving a $\geq 35\%$ reduction of spleen volume as measured by MRI or CT from baseline at Week 24. Other secondary endpoints included the duration of maintenance of spleen volume reduction (DoMSR) $\geq 35\%$ reduction from baseline, the time to achieve a first $\geq 35\%$ reduction in spleen volume from baseline, progression-free survival (PFS), leukemia-free survival (LFS), overall survival (OS), transfusion dependency/independency, and a change in bone marrow histomorphology.

The percent change from baseline at Week 48 in spleen volume was calculated only for subjects who had an evaluable spleen volume at baseline. The proportion of subjects achieving a $\geq 35\%$ reduction in spleen volume from baseline at Week 48 was then calculated by treatment group. A subject was required to have a baseline spleen volume measurement to be included in the primary efficacy analysis. A subject with a missing Week 48 spleen volume measurement was

considered as not having achieved the $\geq 35\%$ reduction. Subjects who dropped out of the study due to any reason or who had a protocol-defined qualifying event of disease progression prior to Week 48 visit were considered as not having achieved the $\geq 35\%$ reduction. The two proportions were compared using the Cochran-Mantel-Haenszel (CMH) test stratified by prognostic category (Intermediate-2 or High risk).

The definition and analysis of the key secondary endpoint was identical to the definition and main analysis of the primary endpoint, the only difference being the timing of evaluation, at 24 weeks. This key secondary endpoint will be tested at 2-sided alpha level of 0.05 if the primary endpoint is statistically significant at two-sided alpha level of 0.05. The DoMSR was evaluated using Kaplan-Meier estimates for each treatment arm. The time to achieve $\geq 35\%$ reduction in spleen volume from baseline was performed on subjects who achieved a 35% reduction in spleen volume. A separate analysis of DoMSR was performed employing a different definition for duration of response, where the start date was defined as the first spleen volume measurement with $\geq 35\%$ reduction from baseline, and the end date was defined as the first scan that was no longer equal to a 35% reduction and that was a $>25\%$ increase over nadir. PFS, LFS, and OS were summarized using Kaplan-Meier estimates for each treatment arm. Bone marrow histomorphology was noted as fibrosis density and was tabulated by fibrosis grade at baseline and post-baseline. Descriptive statistics (number of subjects and subject percentages) were used.

The sample size of this study was originally calculated based on the primary efficacy variable, the proportion of subjects achieving 35% reduction in spleen volume from baseline at Week 48 as measured by MRI. This endpoint was analyzed using the Chi-square test for a treatment comparison. Assuming at least 35% of the active subjects would achieve a 35% reduction from baseline to Week 48, and that rate for the control subjects would be no more than 10%, a sample size of 150 subjects (100 in active and 50 in control) would provide at least 90% power to detect a treatment difference in the primary endpoint at a 2-sided alpha level of 0.05 using the Chi-square test.

3.2.1.2 Patient disposition

A total of 219 patients were randomized into the study (146 in the roxolitinib arm and 73 in the placebo arm). The number of patients who withdrew from the study early and the reasons of withdrawal are presented in Table 6 below.

Table 6. Patient disposition (Study 352)

	Ruxolitinib N=146	BAT N=73
Discontinued Randomized Treatment Phase	55 (37.7)	42 (57.5)
Reasons for discontinuation from Randomized Treatment Phase		
Entered extension phase ruxolitinib	29 (19.9)	18 (24.7)
Adverse event(s)	12 (8.2)	4 (5.5)
Consent withdrawn	2 (1.4)	9 (12.3)
Disease Progression	1 (0.7)	3 (4.1)

Protocol deviation	2 (1.4)	0
Non-compliance with study medication	2 (1.4)	0
Non-compliance with study procedures	0	1 (1.4)
Other	7 (4.8)	7 (9.6)

3.2.1.2 Demographics and baseline characteristics

Patient demographics and baseline characteristics are presented in Table 7 and Table 8 below.

Table 7. Patient Demographics (Study 352)

Variable	Ruxolitinib (N = 146)	BAT (N = 73)
Age (yrs)		
<=65 years, n (%)	69 (47.2)	36 (49.3)
> 65 years, n (%)	77 (52.8)	37 (50.7)
Sex, n (%)		
Male	83 (56.8)	42 (57.5)
Female	63 (43.2)	31 (42.5)
Race, n (%)		
White	118 (80.8)	67 (91.8)
Other	0	1 (1.4)
	28 (19.2)	5 (6.8)
Unknown	28 (19.2)	5 (6.8)

Table 8. Baseline characteristics (Study 352)

	Ruxolitinib (N = 146)	BAT (N = 73)
Type of MF – n (%)		
PMF	77 (52.7)	39 (53.4)
PPV-MF	48 (32.9)	20 (27.4)
PET-MF	21 (14.4)	14 (19.2)
Palpable spleen size (cm) below costal margin		
Mean (SD)	14.9 (6.45)	15.8 (6.71)
Spleen volume (cm ³)		
Mean (SD)	2662.1 (1351.26)	2631.1 (1405.27)
Prior hydroxyurea use – n (%)		
Yes	110 (75.3)	50 (68.5)
No	36 (24.7)	23 (31.5)
Prior splenic radiotherapy – n (%)		

Yes	0	4 (5.5)
No	146 (100)	69 (94.5)
V617F at baseline		
Yes	108 (74.0)	48 (65.8)
No	36 (24.7)	24 (32.9)
Unknown	2 (1.4)	1 (1.4)

3.2.1.2 Efficacy Results

A significantly larger proportion of subjects in the ruxolitinib group achieved a $\geq 35\%$ reduction from baseline at Week 48 and Week 24 compared with the placebo group ($p < 0.0001$ by Fisher's Exact test). Table 9 below presents a summary of results of the primary and key secondary endpoint.

Table 9. Results of primary and key secondary endpoint (Study 352)

	Ruxolitinib N=146	BAT N=73	% difference (95% CI ^a)	P value ^b
Primary Endpoint: % SVR $\geq 35\%$ at 48 weeks, n (%)	41 (28.1%)	0 (0)	28.1 (19.3, 34.8)	<0.0001
Key Secondary Endpoint: % SVR $\geq 35\%$ at 24 weeks, n (%)	46 (31.9%)	0 (0)	31.9 (22.5, 38.4)	<0.0001

a: By Agresti-Caffo method (Agresti and Caffo; The American Statistician, Vol. 54, No. 4, (Nov., 2000), pp.280-288)

b: Fisher's Exact test

Reviewers comment:

As specified in the protocol, patients with missing value for Week 48 and Week 24 spleen volumes were treated as non-responders for the primary and key secondary endpoints.

This study was originally planned with a sample size of 150. The actual number of patients enrolled is 219, which is 43% more than planned. However, even if the trial only accrued the first 150 patients, the result for the primary endpoint is still highly statistically significant (response rates are 26% and 0% in the ruxolitinib arm and BAT arm, respectively with p -value < 0.0001).

Survival data are not mature. A total of 6 (4.1%) patients in the ruxolitinib arm and 4 (5.5%) patients in the BAT arm died.

3.3 Evaluation of Safety

Please refer Dr. Deisseroth's clinical review for efficacy evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Results of subgroup analysis in age, gender and race for Study 351 and Study 352 are presented in Table 10 and 11 below. The proportions of subjects with $\geq 35\%$ reduction from baseline at Week 24 (Study 351) and Week 48 (Study 352) in the ruxolitinib group are consistently higher than those in the placebo group in all subgroups. However, with the response rate equal or close to 0 arm in both male and female groups within the placebo arm, the response rate in female group is much higher than that in the male group within the ruxolitinib arm (25% vs. 59% respectively in Study 351, $p < 0.0001$; 25% vs. 33% respectively in Study 351, $p = 0.26$).

Table 10. Subgroup analyses by gender, age and race (Study 351)

Subgroups	Ruxolitinib (n/N (%))	Placebo (n/N (%))	% difference	95% CI ^a for % difference
Gender				
Male	20/79 (25)	1/87 (1)	24	(14, 34)
Female	45/76 (59)	0/65 (0)	59	(46, 69)
Age				
≤ 65	32/70 (46)	0/52 (0)	46	(23, 56)
> 65	33/85 (39)	0/101 (0)	39	(28, 49)
Race				
White	56/138 (41)	1/138 (1)	40	(31, 48)
Non-White	9/17 (53)	0/14 (0)	53	(21, 72)

a: By Agresti-Caffo method (Agresti and Caffo; The American Statistician, Vol. 54, No. 4, (Nov., 2000), pp.280-288)

Table 11. Subgroup analyses by gender, age and race (Study 352)

Subgroups	Ruxolitinib (n/N (%))	BAT (n/N (%))	% difference	95% CI ^a for % difference
Gender				
Male	20/81 (25)	0/42 (0)	25	(13, 33)
Female	21/63 (33)	0/30 (0)	33	(21, 45)
Age				
≤ 65	20/68 (29)	0/36 (0)	29	(15, 39)
> 65	21/76 (28)	0/36 (0)	28	(14, 37)
Race				
White	33/116 (28)	0/67 (0)	28	(19, 36)
Non-White	0/0	0/1 (0)	NA	NA

a: By Agresti-Caffo method (Agresti and Caffo; The American Statistician, Vol. 54, No. 4, (Nov., 2000), pp.280-288)

4.2 Other Special/Subgroup Populations

Results of subgroup analysis based on important baseline characteristics are presented in Table 12 and 13 below. The proportions of subjects with $\geq 35\%$ reduction from baseline at Week 24

(Study 351) and Week 48 (Study 352) in the ruxolitinib group are consistently higher than those in the placebo group in all subgroups. However, with the response rate equal or close to 0 arm in both V617F positive and negative groups within the placebo arm, the response rate in V617F positive group is much higher than that in the V617F negative group within the ruxolitinib arm (48% vs. 28% respectively in Study 351, $p=0.03$; 33% vs. 14% respectively in Study 352, $p=0.03$).

Table 12. Subgroup analyses by baseline characteristics (Study 351)

Subgroups	Ruxolitinib (n/N (%))	Placebo (n/N (%))	% difference	95% CI ^a for % difference
HU-use				
User	29/52 (56)	1/51 (2)	54	(38, 66)
Non-user	36/103 (35)	0/102 (0)	35	(25, 44)
Tumor type				
PMF	27/70 (39)	1/82 (1)	37	(25, 48)
Post-PV	25/50 (50)	0/47 (0)	50	(34, 62)
Country				
USA	49/115 (43)	1/121 (1)	42	(38, 66)
Non-USA	16/40 (40)	0/32 (0)	40	(25, 44)
Baseline risk group				
High	32/90 (36)	1/98 (1)	35	(32, 50)
Intermediate	33/64 (52)	0/54 (0)	52	(22, 53)
V617F at baseline				
Positive	54/113 (48)	1/122 (1)	47	(37, 56)
Negative	11/40 (28)	0/27 (0)	28	(10, 40)

a: By Agresti-Caffo method (Agresti and Caffo; The American Statistician, Vol. 54, No. 4, (Nov., 2000), pp.280-288)

Table 13. Subgroup analyses by baseline characteristics (Study 352)

Subgroups	Ruxolitinib (n/N (%))	BAT (n/N (%))	% difference	95% CI ^a for % difference
HU-use				
User	28/108 (26)	0/49 (0)	26	(15, 33)
Non-user	13/36 (36)	0/23 (0)	36	(16, 50)
Tumor type				
PMF	14/76 (18)	0/38 (0)	18	(7, 27)
Post-PV	20/48 (42)	0/20 (0)	42	(21, 54)
PETM	7/20 (35)	0/14 (0)	35	(7, 53)
Baseline risk group				
High	17/70 (24)	0/35 (0)	24	(11, 34)
Intermediate	24/74 (32)	0/37 (0)	32	(19, 42)
V617F at baseline				
Positive	36/108 (33)	0/48 (0)	33	(27, 41)

Negative	5/35 (14)	0/20 (0)	14	(-3, 26)

a: By Agresti-Caffo method (Agresti and Caffo; The American Statistician, Vol. 54, No. 4, (Nov., 2000), pp.280-288)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Ruxolitinib arm had higher proportions of subjects with $\geq 35\%$ reduction from baseline at Week 24 (Study 351) and Week 48 (Study 352) than the control arm. The results for the primary endpoint of Study 351 and 352 are presented in Table 14 below. The results of secondary endpoints, except for overall survival, in both studies are supportive for that of the primary endpoint. Survival results are not mature in both studies.

Table 14. Results of primary endpoints in Study 351 and Study 352

	Ruxolitinib	Placebo
Study 351		
Subjects achieving a $\geq 35\%$ reduction from baseline in spleen volume at Week 24, n (%)	65 (41.9)	1 (0.7)
% Difference between treatments (95% CI ^a)	41.2 (32.8, 48.7)	
p-value (by Fisher's Exact test)	<0.0001	
Study 352		
Subjects achieving a $\geq 35\%$ reduction from baseline in spleen volume at Week 48, n (%)	65 (41.9)	1 (0.7)
% Difference between treatments (95% CI ^a)	41.2 (32.8, 48.7)	
p-value (by Fisher's Exact test)	<0.0001	

a: By Agresti-Caffo method (Agresti and Caffo; The American Statistician, Vol. 54, No. 4, (Nov., 2000), pp.280-288)

The results of secondary endpoints, except for overall survival, in both studies are supportive for that of the primary endpoint (See Table 5 and Table 9). Survival results are not mature in both studies. Results of subgroup analyses are also consistent with that of the primary endpoint (see Tables 10-13).

Across subgroups, response rate of the primary endpoint is consistently higher in the ruxolitinib group than those in the placebo group. However, with the response rate equal or close to 0 arm in both male and female groups within the placebo arm, the response rate in female group is much higher than that in the male group within the ruxolitinib arm in Study 351 and Study 352 (25% vs. 59% respectively in Study 351, $p < 0.0001$; 25% vs. 33% respectively in Study 351, $p = 0.26$). Similarly, the response rate in V617F positive group is much higher than that in the V617F negative group within the ruxolitinib arm in both Study 351 and Study 352 (48% vs. 28% respectively in Study 351, $p = 0.03$; 33% vs. 14% respectively in Study 351, $p = 0.03$).

5.2 Conclusions and Recommendations

Study 351 and Study 352 demonstrated that, compared with those in the control arm, patients in the ruxolitinib arm were more likely to achieved at least a 35% reduction in spleen volume from baseline at Week 24 in Study 351 (42% vs. 1%) and Week 48 in Study 352 (28% vs. 0%).

Across subgroups, response rate of the primary endpoint is consistently higher in the ruxolitinib group than those in the placebo group. However, the response rate in female group is much higher than that in the male group within the ruxolitinib arm in both studies (25% vs. 59% respectively in Study 351; 25% vs. 33% respectively in Study 351). And the response rate in V617F positive group is much higher than that in the V617F negative group within the ruxolitinib arm in both studies (48% vs. 28% respectively in Study 351; 33% vs. 14% respectively in Study 351).

CHECK LIST

Number of Pivotal Studies: 2

Study 351

Trial Specification

Specify for each trial:

Protocol Number (s): 351

Phase: 3

Control: Placebo Control

Blinding: double blind

Number of Centers: 89

Region(s) (Country): US, Canada, Australia

Duration: Five cycles. Five weeks in each cycle.

Treatment Arms: ruxolitinib

Treatment Schedule: Twice daily with varying dose

Randomization: Yes

Ratio: 1:1

Method of Randomization: central randomization without stratification

Primary Endpoint: Proportion of subjects achieved a >35% reduction from baseline at Week 24.

Primary Analysis Population: ITT

Statistical Design: Superiority

Primary Statistical Methodology: Fisher's exact test

Interim Analysis: No

Sample Size: 309 (planned at 240 subjects)

Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? Yes

Statistic = Fisher's exact

Power= 0.97

Response rate: 30% vs. 10%

α = 0.05

- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No.
- Did the Applicant perform **Sensitivity Analyses**? No.

How were the **Missing Data** handled? A subject with a missing Week 24 spleen volume will be considered as having not achieved the >35% reduction. Subjects who drop out of the study due to lack of efficacy or treatment-related adverse events, or make an early crossover to active treatment (placebo subjects only), prior to Week 24 visit will all be considered as having not

achieved the >35% reduction. Missing value for total symptoms scores are excluded from the analysis.

- Was there a **Multiplicity** involved? Yes.
- **Multiple Secondary Endpoints**: Are they being included in the label? Yes. Gate keeper method is used to adjust for multiplicity.

Were Subgroup Analyses Performed? Yes

- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? No.
- Overall, was the study positive? Yes.

Study 352

Trial Specification

Specify for each trial:

Protocol Number (s): 352

Phase: 3

Control: Placebo Control

Blinding: Open-label

Number of Centers: 57

Region(s) (Country): Europe

Duration: Five cycles. Five weeks in each cycle.

Treatment Arms: ruxolitinib

Treatment Schedule: Twice daily with varying dose

Randomization: Yes

Ratio: 2:1

Method of Randomization: central randomization stratified by

- Stratum 1: Intermediate risk level 2 (2 risk factors)
- Stratum 2: High risk (3 or more risk factors)

Primary Endpoint: Proportion of subjects achieved a >35% reduction from baseline at Week 48.

Primary Analysis Population: ITT

Statistical Design: Superiority

Primary Statistical Methodology: Fisher's exact test

Interim Analysis: No

Sample Size: 219 (planned at 150 subjects)

Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable? Yes

Statistic = Fisher's exact

Power= 0.9

Response rate: 35% vs. 10%

$\alpha = 0.05$

- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No.

- Did the Applicant perform **Sensitivity Analyses**? No.

How were the **Missing Data** handled? A subject with a missing Week 48 spleen volume will be considered as having not achieved the >35% reduction. Subjects who drop out of the study due to lack of efficacy or treatment-related adverse events, or make an early crossover to active treatment (placebo subjects only), prior to Week 24 visit will all be considered as having not achieved the >35% reduction.

- Was there a **Multiplicity** involved? No

- **Multiple Secondary Endpoints**: Are they being included in the label? No.

- **Were Subgroup Analyses Performed**? Yes

- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? No.

- Overall, was the study positive? Yes.

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/s/

HONG LU
09/19/2011

MARK D ROTHMANN
09/19/2011

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09/19/2011

Statistical Review and Evaluation CARCINOGENICITY STUDIES



IND/NDA Number: NDA 202-192
Drug name: INCB018424 (Phosphate salt)
Indication(s): Myelofibrosis
Applicant: Incyte
Documents Reviewed: Electronic submission
Electronically submitted dataset
Dated: 2011-06-03
Review Priority: Normal
Biometrics Division: Division of Biometrics 6
Statistical Reviewer: Matthew Jackson, PhD
Concurring Reviewer: Karl Lin, PhD
Medical Division: DHP
Reviewing Pharmacologists: Miyun M. Tsai-Turton, PhD
Wei Chen, PhD
Project Manager:
Keywords: Animal Mouse Carcinogenicity

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0.1 Background

In this submission the sponsor included reports of one animal carcinogenicity study, in Tg.rasH2 Mice. This study were intended to assess the carcinogenic potential of INCB018424 when administered by dermally, once daily at appropriate drug levels for about 26 weeks. Results of this review have been discussed with the reviewing pharmacologist, Dr. Tsai-Turton.

In this review, the phrase “dose response relationship” refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

0.2 Overview

Two separate studies were conducted; one each in male and female mice. Each study involved five groups of twenty five animals. One group was the control group, receiving by gavage a daily dose (10mL per kilogram of bodyweight) of the the vehicle, 0.5% methylcellulose. Three groups received doses of the test article, INCB018424, at daily doses of 15, 45, and 125 mg per kilogram of body weight, in the same vehicle (10 mL/kg). The fifth group was a positive control group, which recieved intraperitoneal injections of urethane (1g/kg) on days 1, 3, and 5. Animals in this group were sacrificed after 119 days (females) or 121 days (males), rather than at the end of the 26 week study.

Chapter 1

Carcinogenicity study

This chapter concerns the comparison of outcomes between the groups of animals treated with INCB018424 and the vehicle control.

1.1 Sponsor's analyses

1.1.1 Survival analysis

Kaplan-Meier survival estimates were constructed for each group within each sex, and the generalized Wilcoxon test was used to test for heterogeneity of survival between the INCB018424 treated groups and the control. Among males, no statistically significant findings were reported. Among females, the mid dose group were found to have significantly reduce survival compared with the control group, although no p -values are presented.

1.1.2 Tumor data analysis

The sponsor tested each reported tumor type, in each sex, separately, using Peto's [5] mortality prevalence method. For each tumor type, each treated group was compared with control, and a 1-tailed trend test was conducted across all four groups. Exact versions of the tests were used for tumor types with lower prevalence (how low is not specified), and tests were conducted at both the 1% and 5% significance levels.

No significant results were reported.

1.2 Reviewer's analysis

To verify the sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, independent survival and tumor data analyses were performed. Data used in these analyses were provided by the sponsor electronically.

1.2.1 Survival analysis

Intercurrent mortality data are presented in table 1.1. The results of the log-rank tests of survival (both tests of trend and of heterogeneity) are presented in table 1.2, and the results of log-rank tests of survival between individual treated groups and the control group are presented in table 1.3. Kaplan-Meier survival plots are displayed as figures 1.1 and 1.2. In both plots, the curve representing the control group cannot be seen because it coincides exactly with the curve for the high dose group; in both the studies of male and female mice, no early deaths were reported in either the control or high dose group.

Among females, there is evidence ($p = 0.0253$) of heterogeneity of survival across the dose groups, and for both sexes there is a statistically significant indication of increased mortality ($p = 0.0090$

for females and $p = 0.0311$ for males) in the mid dose group compared with the control group. However, there is no evidence of a dose related increase in mortality in males or females in either study, and it should be noted that the mortality rates were extremely low in both sexes — only nine mice in total (five female and four male) died before the end of the 26 week study. The significant results noted above are therefore based on the analyses of very small numbers of deaths.

It should also be noted that because deaths are so rare in this study, the various statistical tests used have very low power to detect even substantial increases in relative risk.

Table 1.1: Survival rates at key times

Species and Sex	Dose Group	Dose (mg per kg)	Number and percentage alive							
			Start	12 weeks (%)	19 weeks (%)	22 weeks (%)	Termination (%)	Termination (%)		
Mice — Female	Control	0	25	25	25	25	25	100%	25	100%
	Low dose	15	25	25	25	25	25	100%	24	96%
	Mid dose	45	25	25	24	24	24	96%	21	84%
	High dose	125	25	25	25	25	25	100%	25	100%
Mice — Male	Control	0	25	25	25	25	25	100%	25	100%
	Low dose	15	25	25	25	25	24	96%	24	96%
	Mid dose	45	25	25	24	24	24	96%	22	88%
	High dose	125	25	25	25	25	25	100%	25	100%

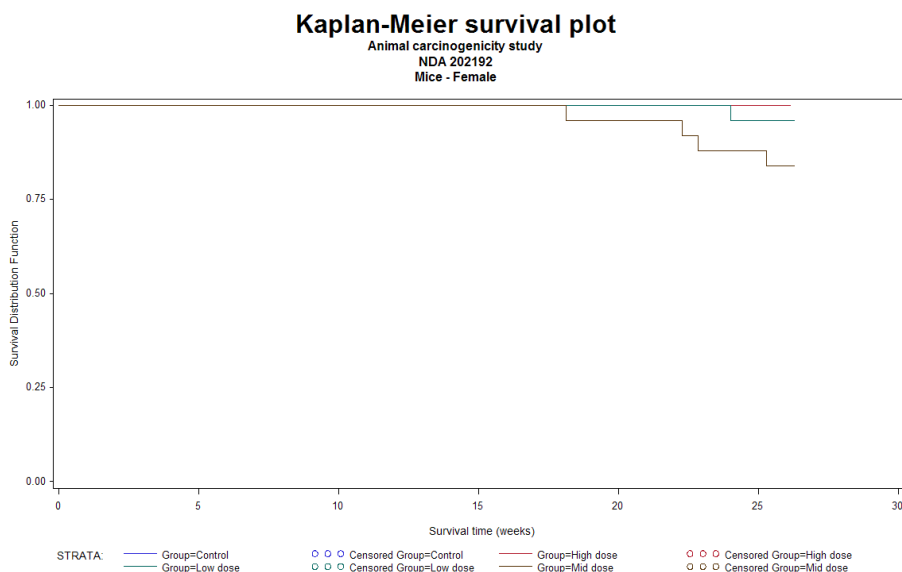
Table 1.2: Results of log-rank tests of survival

Species and Sex	Number of Groups	Test of homogeneity			Test of trend	
		χ^2 statistic	df	p -value	Two tailed p -value	One tailed p -value
Mice — Female	4	9.3181	3	0.0253	0.7364	0.6318
Mice — Male	4	6.2422	3	0.1004	0.7134	0.6433

Table 1.3: Log-rank tests of survival between treated groups and control

Species and Sex		Low dose	Mid dose	High dose
Mice — Female	χ^2 test statistic	0.4018	6.8189	0.0000
	p -value of comparison with control	0.5262	0.0090	1.0000
Mice — Male	χ^2 test statistic	0.5181	4.6488	0.0000
	p -value of comparison with control	0.4716	0.0311	1.0000

Figure 1.1: Survival curves for female mice



1.2.2 Tumor analysis

Theoretical underpinnings

The tumor data were analyzed for dose response relationships and pairwise comparisons of tumor incidence in each of the treated groups versus the vehicle control group. Both the dose response relationship tests and pairwise comparisons were performed using the poly- k method described in the paper of Bailer and Portier[1] and developed in the paper of Bieler and Williams[2]. In this method, given a tumor type T , an animal h that lives the full study period (w_m) or dies before the terminal sacrifice with at least one tumor of type T gets a score of $s_h = 1$. An animal that dies at week w_h before the end of the study without such a tumor gets a score of

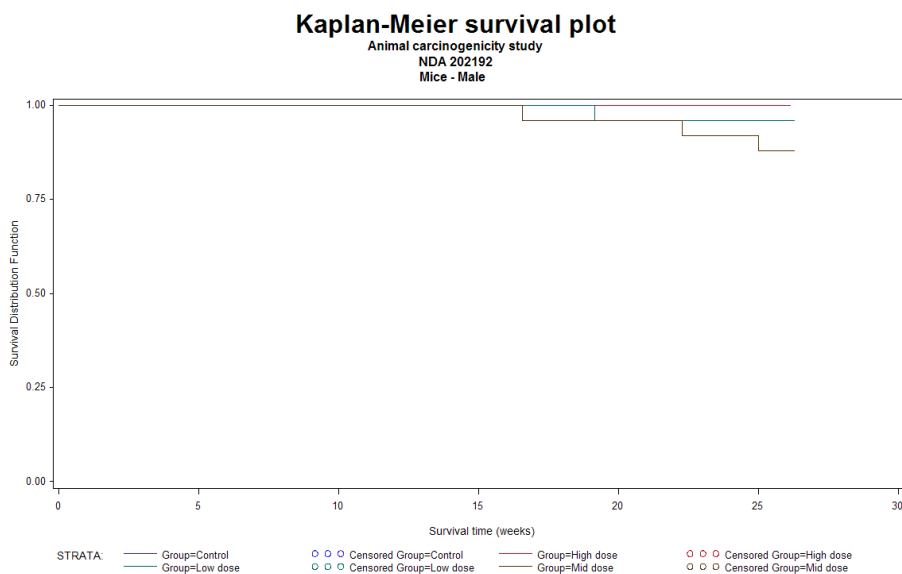
$$s_h = \left(\frac{w_h}{w_m} \right)^k < 1.$$

The adjusted group size is defined as $\sum_h s_h$. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops at least one tumor of type T , otherwise the adjusted group size is less than N . These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. The test is repeated for each tumor type T .

One critical point to consider in the application of the poly- k test is the choice of the appropriate value of k , which depends on the relationship between tumor onset time and increased dose. There is no consensus for the correct value to use for studies of transgenic mice. In the absence of such a consensus, this review uses the value $k = 1$, a value which is consistent with the assumption of constant hazard over the twenty six week period of the study. In any event, when there is little premature mortality (as is the case with this study — see section 1.2.1), the analyses are not very sensitive to variations in the value of k .

For the calculation of p -values, the exact permutation method was used. The tumor rates and the p -values of the tested tumor types are listed in tables 1.6 and 1.7. Corresponding tables for combination endpoints are presented in tables 1.8 and 1.9.

Figure 1.2: Survival curves for male mice



Under normal circumstances, since so many end points are being tested, it is appropriate to make some sort of multiplicity adjustment in order to control type I error. However, in the case of transgenic mice there is no guidance specifying how this should be done. Furthermore, in light of the fact that exact tests tend to be very conservative when considering rare events, the fact that there are only twenty five animals in each group, and the fact that tumorigenesis is very rare over the twenty six weeks that transgenic mouse studies typically run, it seems reasonable to consider test as having yielded positive findings whenever the p -value is below 0.05.

Analysis of tumor data

The electronic dataset used for this review does not list negative findings; organ-level records are present when neoplasms are found and when examinations conducted in some animals are not conducted in others. It follows that organs in which no tumors are found in any animals are not included in the submitted dataset. With this in mind, table 1.4 lists the organs which can definitely be inferred from the submitted dataset to have been examined in all or most animals. In the case, since no organs have been reported as being unexamined, we can actually infer that these organs underwent microscopic examination in all animals.

In addition, a number of combination endpoints were also tested at the pharmacology reviewer's request. These are listed in table 1.5.

The results of the statistical analyses of individual tumor types are reported in tables 1.6 and 1.7. Results of analyses of combination tumor types are presented in tables 1.8 and 1.9.

In addition to these standard analyses, and at the request of the reviewing pharmacologist, these analyses have been repeated with all three treated groups combined. The main advantage of combining the treated groups in this way is that when the a tumorigenic effect is believed to be sensitive to relatively low levels of the suspect tumorigenic agent. The results of these analyses are in the Appendix A. Note that in these tables, the p -values of the tests of trend are the same as the comparisons between the control and amalgamated treated group. This is an automatic consequence of the fact that the trend test is being taken across just two groups (control and treated).

No statistical tests, of either a single tumor type or combination yielded a p -value below 0.05. The study is therefore a negative study.

Table 1.4: Organs reported as being analyzed in most animals

Female mouse study		
adrenal glands	aorta	bone marrow, femur
bone marrow, sternum	bone, femur	bone, sternum
brain	cavity, nasal	esophagus
eyes	gall bladder	harderian glands
heart	intestine, cecum	intestine, colon
intestine, duodenum	intestine, ileum	intestine, jejunum
intestine, rectum	kidneys	liver
lungs with bronchi	lymph node, mandibular	lymph node, mediastinal
lymph node, mesenteric	mammary gland	multicentric
nerve, sciatic	ovaries	pancreas
parathyroid glands	pituitary gland	salivary glands
skeletal muscle (thigh)	skin	spinal cord, cervical
spinal cord, lumbar	spinal cord, thoracic	spleen
stomach	thymus	thyroid glands
trachea	urinary bladder	uterus
vagina		
Male mouse study		
adrenal glands	aorta	bone marrow, femur
bone marrow, sternum	bone, femur	bone, sternum
brain	cavity, nasal	epididymides
esophagus	eyes	gall bladder
harderian glands	heart	intestine, cecum
intestine, colon	intestine, duodenum	intestine, ileum
intestine, jejunum	intestine, rectum	kidneys
liver	lungs with bronchi	lymph node, mandibular
lymph node, mediastinal	lymph node, mesenteric	mammary gland
nerve, sciatic	pancreas	parathyroid glands
pituitary gland	prostate gland	salivary glands
seminal vesicles	skeletal muscle (thigh)	skin
spinal cord, cervical	spinal cord, lumbar	spinal cord, thoracic
spleen	stomach	testes
thymus	thyroid glands	trachea
urinary bladder		

Table 1.5: Combination endpoints tested

All hemangiosarcomas, regardless of site
All skin tumors

Table 1.6: Reported neoplastic tumors in study of female mice

Organ	Tumor type	Quantity	Control	Low dose	Mid dose	High dose
cavity, nasal	adenocarcinoma	<i>p</i> -value of test of trend or comparison	.9375	.4844	1	1
		Number of animals reported with tumor	1	2	0	0
		Poly-1 adjusted incidence rate	4.0%	8.0%	0.0%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0.1,20.4)	(0.98,27.0)	(0,14.2)	(0,13.7)
		Poly-1 adjusted number of animals at risk	25.0	24.9	24.4	25.0
		<i>p</i> -value of test of trend or comparison	.2822	1	1	.6954
		Number of animals reported with tumor	2	0	0	2
		Poly-1 adjusted incidence rate	8.0%	0.0%	0.0%	8.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0.98,26.0)	(0,14.2)	(0,14.2)	(0.98,26.0)
		Poly-1 adjusted number of animals at risk	25.0	24.9	24.4	25.0
lungs with bronchi	alveolar–bronchiolar adenoma	<i>p</i> -value of test of trend or comparison	.8929	.6465	.9403	.9451
		Number of animals reported with tumor	3	3	1	1
		Poly-1 adjusted incidence rate	12%	12%	4.1%	4.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(2.55,31.2)	(2.55,32.4)	(0.1,21.1)	(0.1,20.4)
		Poly-1 adjusted number of animals at risk	25.0	24.9	24.4	25.0
		<i>p</i> -value of test of trend or comparison	.7449	.4898		
		Number of animals reported with tumor	0	1	0	0
		Poly-1 adjusted incidence rate	0.0%	4.0%	0.0%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.1,21.1)	(0,14.2)	(0,13.7)
		Poly-1 adjusted number of animals at risk	25.0	24.9	24.4	25.0
multicentric	sarcoma	<i>p</i> -value of test of trend or comparison	.5000		.4898	
		Number of animals reported with tumor	0	0	1	0
		Poly-1 adjusted incidence rate	0.0%	0.0%	4.1%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0,14.2)	(0.1,21.1)	(0,13.7)
		Poly-1 adjusted number of animals at risk	25.0	24.9	24.5	25.0
		<i>p</i> -value of test of trend or comparison	.7475	.5000		
		Number of animals reported with tumor	0	1	0	0
		Poly-1 adjusted incidence rate	0.0%	0.0%	4.1%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0,14.2)	(0.1,21.1)	(0,13.7)
		Poly-1 adjusted number of animals at risk	25.0	24.9	24.5	25.0
skin	hemangiosarcoma	<i>p</i> -value of test of trend or comparison	.7475	.5000		
		Number of animals reported with tumor	0	1	0	0
		Poly-1 adjusted incidence rate	0.0%	4.0%	0.0%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.1,20.4)	(0,14.2)	(0,13.7)
		Poly-1 adjusted number of animals at risk	25.0	25.0	24.4	25.0
		<i>p</i> -value of test of trend or comparison	.7502	.2347	.2347	
		Number of animals reported with tumor	0	2	2	0
		Poly-1 adjusted incidence rate	0.0%	8.0%	8.1%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.98,27.0)	(0.98,27.0)	(0,13.7)
		Poly-1 adjusted number of animals at risk	25.0	24.9	24.4	25.0
spleen	hemangiosarcoma	<i>p</i> -value of test of trend or comparison	.7502	.2347	.2347	
		Number of animals reported with tumor	0	2	2	0
		Poly-1 adjusted incidence rate	0.0%	8.0%	8.1%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.98,27.0)	(0.98,27.0)	(0,13.7)
		Poly-1 adjusted number of animals at risk	25.0	24.9	24.4	25.0
		<i>p</i> -value of test of trend or comparison	.7502	.2347	.2347	
		Number of animals reported with tumor	0	2	2	0
		Poly-1 adjusted incidence rate	0.0%	8.0%	8.1%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.98,27.0)	(0.98,27.0)	(0,13.7)
		Poly-1 adjusted number of animals at risk	25.0	24.9	24.4	25.0

Table 1.6: Reported neoplastic tumors in study of female mice (continued)

Organ	Tumor type	Quantity	Control	Low dose	Mid dose	High dose
stomach	Poly-1 adjusted number of animals at risk		25.0	24.9	24.5	25.0
	<i>p</i> -value of test of trend or comparison		1	1	1	1
	Number of animals reported with tumor		1	0	0	0
	Poly-1 adjusted incidence rate		4.0%	0.0%	0.0%	0.0%
	95% CI for Poly-1 adjusted incidence rate (%)		(0.1,20.4)	(0,14.2)	(0,14.2)	(0,13.7)
	Poly-1 adjusted number of animals at risk		25.0	24.9	24.4	25.0
thymus	<i>p</i> -value of test of trend or comparison		.5551		.1099	
	Number of animals reported with tumor		0	0	3	0
	Poly-1 adjusted incidence rate		0.0%	0.0%	12%	0.0%
	95% CI for Poly-1 adjusted incidence rate (%)		(0,13.7)	(0,14.2)	(2.55,32.4)	(0,13.7)
	Poly-1 adjusted number of animals at risk		25.0	24.9	24.4	25.0

Table 1.7: Reported neoplastic tumors in study of male mice

Organ	Tumor type	Quantity	Control	Low dose	Mid dose	High dose
cavity, nasal	adenocarcinoma		.7449	.4898		
	Number of animals reported with tumor		0	1	0	0
	Poly-1 adjusted incidence rate		0.0%	4.0%	0.0%	0.0%
	95% CI for Poly-1 adjusted incidence rate (%)		(0,13.7)	(0.1,21.1)	(0,14.2)	(0,13.7)
	Poly-1 adjusted number of animals at risk		25.0	24.7	24.5	25.0
	<i>p</i> -value of test of trend or comparison		.6044	1	1	.8827
harderian glands	adenoma		2	0	0	1
	Number of animals reported with tumor		8.0%	0.0%	0.0%	4.0%
	Poly-1 adjusted incidence rate		(0.98,26.0)	(0,14.2)	(0,14.2)	(0.1,20.4)
	95% CI for Poly-1 adjusted incidence rate (%)		25.0	24.7	24.5	25.0
	Poly-1 adjusted number of animals at risk		25.0	24.7	24.5	25.0
	<i>p</i> -value of test of trend or comparison		.5000		.4898	
liver	hepatocellular adenoma		0	0	1	0
	Number of animals reported with tumor		0.0%	0.0%	4.1%	0.0%
	Poly-1 adjusted incidence rate		(0,13.7)	(0,14.2)	(0.1,21.1)	(0,13.7)
	95% CI for Poly-1 adjusted incidence rate (%)		25.0	24.7	24.5	25.0
	Poly-1 adjusted number of animals at risk		.5138	.6798	.4800	.6954
	<i>p</i> -value of test of trend or comparison		2	2	3	2
lungs with bronchi	alveolar–bronchiolar adenoma		8.0%	8.1%	12%	8.0%
	Number of animals reported with tumor		(0.98,26.0)	(0.98,27.0)	(2.55,32.4)	(0.98,26.0)
	Poly-1 adjusted incidence rate		25.0	24.7	24.5	25.0
	95% CI for Poly-1 adjusted incidence rate (%)		25.0	24.7	24.5	25.0
	Poly-1 adjusted number of animals at risk					

Table 1.7: Reported neoplastic tumors in study of male mice (continued)

Organ	Tumor type	Quantity	Control	Low dose	Mid dose	High dose
skeletal muscle (thigh)	hemangioma	<i>p</i> -value of test of trend or comparison	.2551			.5000
		Number of animals reported with tumor	0	0	0	1
		Poly-1 adjusted incidence rate	0.0%	0.0%	0.0%	4.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0,14.2)	(0,14.2)	(0.1,20.4)
		Poly-1 adjusted number of animals at risk	25.0	24.7	24.5	25.0
		<i>p</i> -value of test of trend or comparison	.7475	.5000		
skin	sarcoma	Number of animals reported with tumor	0	1	0	0
		Poly-1 adjusted incidence rate	0.0%	4.0%	0.0%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.1,20.4)	(0,14.2)	(0,13.7)
		Poly-1 adjusted number of animals at risk	25.0	25.0	24.5	25.0
		<i>p</i> -value of test of trend or comparison	.5000		.4898	
		Number of animals reported with tumor	0	0	1	0
sp/leen	sarcoma	Poly-1 adjusted incidence rate	0.0%	0.0%	4.1%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0,14.2)	(0.1,21.1)	(0,13.7)
		Poly-1 adjusted number of animals at risk	25.0	24.7	24.5	25.0
		<i>p</i> -value of test of trend or comparison	.5000		.4898	
		Number of animals reported with tumor	0	0	1	0
		Poly-1 adjusted incidence rate	0.0%	0.0%	4.0%	0.0%
thyroid glands	adenoma	95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0,14.2)	(0.1,21.1)	(0,13.7)
		Poly-1 adjusted number of animals at risk	25.0	24.7	24.8	25.0
		<i>p</i> -value of test of trend or comparison	.1894		.4898	.5000
		Number of animals reported with tumor	0	0	1	1
		Poly-1 adjusted incidence rate	0.0%	0.0%	4.1%	4.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0,14.2)	(0.1,21.1)	(0.1,20.4)
testes	hemangiosarcoma	Poly-1 adjusted number of animals at risk	25.0	24.7	24.5	25.0
		<i>p</i> -value of test of trend or comparison	1	1	1	1
		Number of animals reported with tumor	1	0	0	0
		Poly-1 adjusted incidence rate	4.0%	0.0%	0.0%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0.1,20.4)	(0,14.2)	(0,14.2)	(0,13.7)
		Poly-1 adjusted number of animals at risk	25.0	24.7	24.5	25.0
	adenoma	<i>p</i> -value of test of trend or comparison	.7449	.4898		
		Number of animals reported with tumor	0	1	0	0
		Poly-1 adjusted incidence rate	0.0%	4.0%	0.0%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.1,21.1)	(0,14.2)	(0,13.7)
		Poly-1 adjusted number of animals at risk	25.0	24.7	24.5	25.0
		<i>p</i> -value of test of trend or comparison				

Table 1.8: Reported combinations in study of female mice

Endpoint	Quantity	Control	Low dose	Mid dose	High dose
All hemangiosarcomas	<i>p</i> -value of test of trend or comparison	.8219	.1173	.2347	
	Number of animals reported with tumor	0	3	2	0
	Poly-1 adjusted incidence rate	0.0%	12%	8.1%	0.0%
	95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(2.55,31.2)	(0.98,27.0)	(0,13.7)
	Poly-1 adjusted number of animals at risk	25.0	25.0	24.5	25.0
All skin tumors	<i>p</i> -value of test of trend or comparison	.7475	.5000		
	Number of animals reported with tumor	0	1	0	0
	Poly-1 adjusted incidence rate	0.0%	4.0%	0.0%	0.0%
	95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.1,20.4)	(0,14.2)	(0,13.7)
	Poly-1 adjusted number of animals at risk	25.0	25.0	24.4	25.0

Table 1.9: Reported combinations in study of male mice

Endpoint	Quantity	Control	Low dose	Mid dose	High dose
All hemangiosarcomas	<i>p</i> -value of test of trend or comparison	.3758	1	.4844	.7551
	Number of animals reported with tumor	1	0	2	1
	Poly-1 adjusted incidence rate	4.0%	0.0%	8.2%	4.0%
	95% CI for Poly-1 adjusted incidence rate (%)	(0.1,20.4)	(0,14.2)	(0.98,27.0)	(0.1,20.4)
	Poly-1 adjusted number of animals at risk	25.0	24.7	24.5	25.0
All skin tumors	<i>p</i> -value of test of trend or comparison	.5052		.2347	
	Number of animals reported with tumor	0	0	2	0
	Poly-1 adjusted incidence rate	0.0%	0.0%	8.0%	0.0%
	95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0,14.2)	(0.98,27.0)	(0,13.7)
	Poly-1 adjusted number of animals at risk	25.0	24.7	24.9	25.0

1.3 Unexamined and Autolytic organs

1.3.1 Missing animals

There are no animals reported as being completely unexamined.

1.3.2 Unexamined organs

With the exception of the mediastinum, which as reported as being unexamined in every animal, no organs are reported as being unexamined.

1.3.3 Autolytic organs

No organs are reported as being autolyzed to the extent that a usable sample could not be obtained.

Chapter 2

Urethane study

2.1 Sponsor's analyses

2.1.1 Survival analysis

Kaplan-Meier survival estimates were constructed for each group within each sex, and the generalized Wilcoxon test was used to test for a difference in survival between the urethane groups and the controls. In both sexes, the animals treated with urethane experienced a significant reduction in survival compared with the control group. No statistics or p -values were reported.

2.1.2 Tumor data analysis

The sponsor tested each reported tumor type, in each sex, separately, using Peto's [5] mortality prevalence method. For each tumor type, the urethane group was compared with the control group. Exact versions of the tests were used for tumor types with lower prevalence (how low is not specified), and tests were conducted at both the 1% and 5% significance levels.

Significant results are reported for alveolar-bronchiolar adenomas, carcinomas, and for adenomas and carcinomas combined, for splenic hemangiosarcomas, and for the combination endpoints of hemangioma and hemangiosarcomas at all sites, and mesenchymal tumors at all sites. This level of specificity is slightly misleading however, as the only tumors reported in the urethane group were bronciolo-alveolar adenomas and carcinomas, and hemangiosarcomas.

2.2 Reviewer's analysis

To verify the sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, independent survival and tumor data analyses were performed. Data used in these analyses were provided by the sponsor electronically.

2.2.1 Survival analysis

Intercurrent mortality data are presented in table 2.1 (although note that the termination date for the urethane animals was 119 days (female animals) or 121 days (male animals), whereas the termination date for the control group was 182 days). The results of the log-rank test of survival between the urethane group and the control group are presented in table 2.2. Kaplan-Meier survival plots are displayed as figures 2.1 and 2.2.

It is abundantly clear that the urethane treatment is associated with sharply increased mortality.

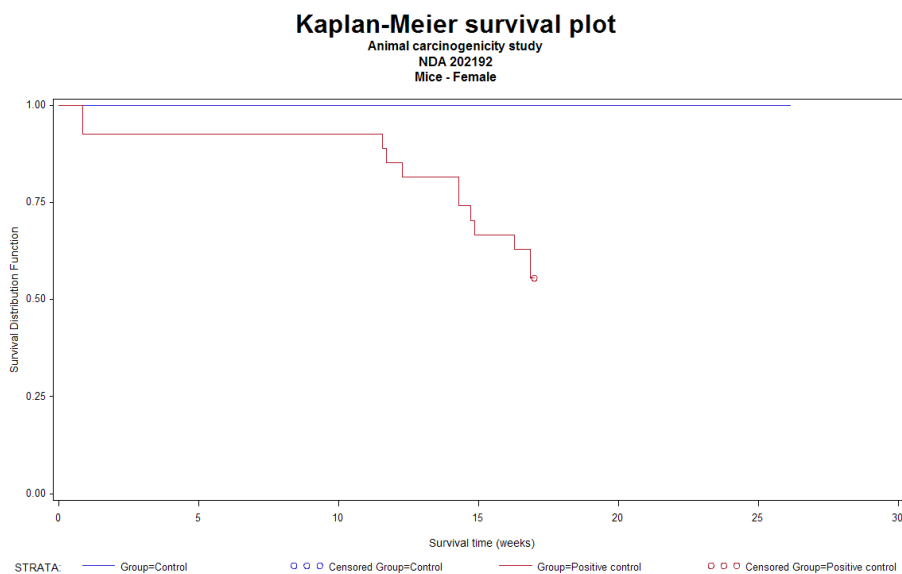
Table 2.1: Survival rates at key times (urethane study)

Species and Sex	Dose Group	Dose (mg per kg)	Number and percentage alive			
			Start	12 weeks (%)	Termination	(%)
Mice — Female	Control	0	25	25 100%	25	100%
	Positive control	1000	27	23 85%	15	60.0%
Mice — Male	Control	0	25	25 100%	25	100%
	Positive control	1000	25	24 96%	13	52.0%

Table 2.2: Log-rank tests of survival between urethane group and control (urethane study)

Species and Sex		Low dose	Mid dose	High dose
Mice — Female	χ^2 test statistic	0.4018	6.8189	0.0000
	p -value of comparison with control	0.5262	0.0090	1.0000
Mice — Male	χ^2 test statistic	0.5181	4.6488	0.0000
	p -value of comparison with control	0.4716	0.0311	1.0000

Figure 2.1: Survival curves for female mice (urethane study)



2.2.2 Tumor analysis

Analysis of tumor data The animals in the urethane group only had their lungs, with bronchi, and spleens examined microscopically. There were no exceptions to this; every urethane treated animal had these two organs examined, and none had any additional organs examined. Accordingly, comparison with the control group is only possible for tumors in these sites.

As can be seen, administration of urethane is strongly associated with an increased incidence of alveolar-bronchiolar adenomas and carcinomas and splenic hemangiosarcomas in both male and female mice, and of hemangiosarcomas in the lungs and bronchi in male mice.

Figure 2.2: Survival curves for male mice (urethane study)

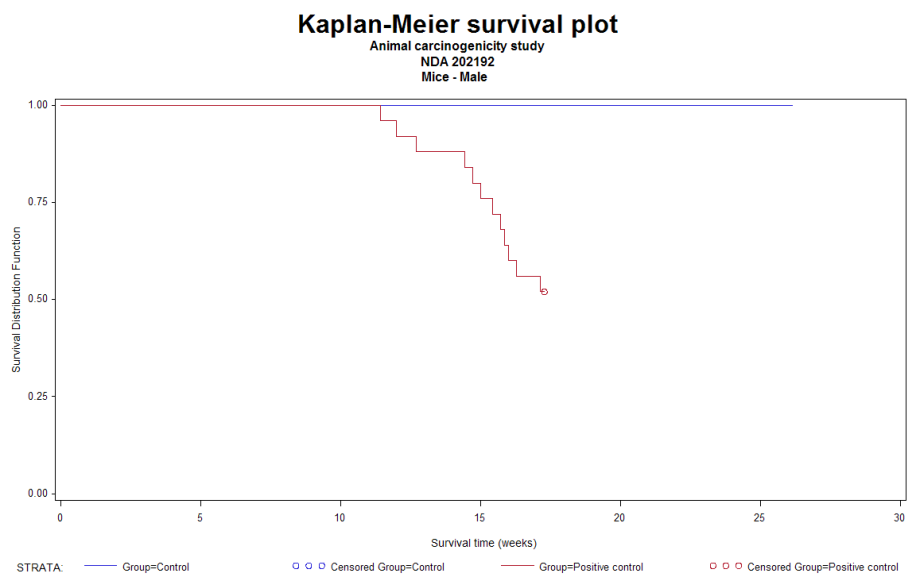


Table 2.3: Reported neoplastic tumors in study of female mice (urethane study)

Organ	Tumor type	Quantity	Control	Treated
lungs with bronchi	alveolar–bronchiolar adenoma	P–value of test of trend or comparison	< 0.0001	< 0.0001
		Number of animals reported with tumor	3	25
		Poly–1 adjusted incidence rate	12%	100%
		95% CI for poly–1 adjusted incidence rate (%)	(2.55,31.2)	(86.3,100)
		Poly–1 adjusted number of animals at risk	25.0	25.0
		P–value of test of trend or comparison	< 0.0001	< 0.0001
		Number of animals reported with tumor	0	18
		Poly–1 adjusted incidence rate	0.0%	82%
		95% CI for poly–1 adjusted incidence rate (%)	(0,13.7)	(59.7,97.0)
		Poly–1 adjusted number of animals at risk	25.0	21.9
spleen	hemangiosarcoma	P–value of test of trend or comparison	.3750	.3750
		Number of animals reported with tumor	0	1
		Poly–1 adjusted incidence rate	0.0%	6.4%
		95% CI for poly–1 adjusted incidence rate (%)	(0,13.7)	(0.16,31.9)
		Poly–1 adjusted number of animals at risk	25.0	15.7
		P–value of test of trend or comparison	< 0.0001	< 0.0001
		Number of animals reported with tumor	0	24
		Poly–1 adjusted incidence rate	0.0%	98%
		95% CI for poly–1 adjusted incidence rate (%)	(0,13.7)	(79.6,100)
		Poly–1 adjusted number of animals at risk	25.0	24.5

Table 2.4: Reported neoplastic tumors in study of male mice (urethane study)

Organ	Tumor type	Quantity	Control	Treated
lungs with bronchi	alveolar–bronchiolar adenoma	P–value of test of trend or comparison	< 0.0001	< 0.0001
		Number of animals reported with tumor	2	25
		Poly–1 adjusted incidence rate	8.0%	100%
		95% CI for poly–1 adjusted incidence rate (%)	(0.98,26.0)	(86.3,100)
		Poly–1 adjusted number of animals at risk	25.0	25.0
		P–value of test of trend or comparison	0.0003	0.0003
		Number of animals reported with tumor	0	8
		Poly–1 adjusted incidence rate	0.0%	44%
		95% CI for poly–1 adjusted incidence rate (%)	(0,13.7)	(20.3,69.2)
		Poly–1 adjusted number of animals at risk	25.0	18.2

Table 2.4: Reported neoplastic tumors in study of male mice (urethane study) (continued)

Organ	Tumor type	Quantity	Control	Treated
	hemangiosarcoma	P-value of test of trend or comparison	0.0180	0.0180
		Number of animals reported with tumor	0	4
		Poly-1 adjusted incidence rate	0.0%	24%
		95% CI for poly-1 adjusted incidence rate (%)	(0,13.7)	(6.81,52.4)
		Poly-1 adjusted number of animals at risk	25.0	17.0
spleen	hemangiosarcoma	P-value of test of trend or comparison	< 0.0001	< 0.0001
		Number of animals reported with tumor	0	24
		Poly-1 adjusted incidence rate	0.0%	98%
		95% CI for poly-1 adjusted incidence rate (%)	(0,13.7)	(79.6,100)
		Poly-1 adjusted number of animals at risk	25.0	24.4

Chapter 3

Evaluation of the validity of negative studies

3.1 Issues of concern when selecting the dose levels

The selection of an appropriate dose level for the high dose group is made difficult by the need to satisfy two competing imperatives: on the one hand, if the dose level is insufficiently high, then genuine carcinogenicity effects may not be apparent, but on the other hand, if the dose level is too high, then there is a risk of non-carcinogenic toxic effects killing the animals before they have a chance to demonstrate a carcinogenicity effect.

Criteria for the retrospective assessment of dose levels are better established for two year studies, but have not been studied systematically for 26 week studies. Nonetheless, the basic principles should still apply. It is therefore reasonable to assess the dose levels in a 26 week study by reasoning from the following concepts.

Haseman [4] suggested that a satisfactory balance between these two imperatives has been found when the following two conditions are both satisfied:

1. Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
2. Were dose levels high enough to pose a reasonable tumor challenge to the animals?

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward [3], the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met:

1. A dose is considered adequate if there is a detectable loss in weight gain in a dosed group relative to the controls.
2. The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical.
3. In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls.

3.2 Assessment of the validity of the carcinogenicity study

There is clearly no reason to suppose that the dose levels were excessive. Table 3.1 shows the mean weight changes by group over the course of the study. It appears from these results that INCB018424 is associated with diminished weight gain in both male and female mice. The dose levels should therefore be considered appropriate.

Table 3.1: Weight changes by group

Species and Sex	Betamethasone dipropionate						
	Δ_C	Δ_L	$\frac{\Delta_L}{\Delta_C} - 1$	Δ_M	$\frac{\Delta_M}{\Delta_C} - 1$	Δ_H	$\frac{\Delta_H}{\Delta_C} - 1$
Mice — Female	4.66	4.34	+1.7%	4.01	-0.6%	3.98	-10.5%
Mice — Male	6.43	5.79	+1.0%	4.30	-2.0%	5.74	-9.5%

3.3 Assessment of the validity of the urethane study

The urethane study is clearly a positive study, with very strong indications that urethane is strongly associated with increased incidences of lung tumors and hemangiosarcomas. However, since the experimental procedure was different for the urethane studies and the control animals, with different histopathological analyses carried out and different dosing regimes, it is hard to see how the success of this trial adds weight to the study of INCB018424.

Chapter 4

Conclusion

4.1 Carcinogenicity study

4.1.1 Tumor findings

The study is a negative study. Few tumors of any kind were reported in the study, and there were no statistically significant results. While survival levels were very high across all groups, there is evidence of a dose related diminution of weight gain, and so the dose levels can be concluded to have been adequate.

There were no organs reported as unexamined or autolytic.

4.2 Urethane study

The group treated with urethane showed clear indications of increases incidence of lung tumors (bronchio-alveolar adenomas and carcinomas, splenic hemangiosarcomas, and, in the males, hemangiosarcomas of the lungs. In that sense, the study was a success, with clear (intended) positive findings. However, given that these animals did not undergo comparable analyses, the success of this trial is of little relevance when assessing the reliability of the INCB018424 study.

Appendix A

Tumor incidence calculations with all treated groups combined

Table A.1: Reported neoplastic tumors in study of female mice (treated groups combined)

Organ	Tumor type	Quantity	Control	Treated
cavity, nasal	adenocarcinoma	<i>p</i> -value of test of trend or comparison	.8438	.8438
		Number of animals reported with tumor	1	2
		Poly-1 adjusted incidence rate	4.0%	2.7%
		95% CI for Poly-1 adjusted incidence rate (%)	(0.1,20.4)	(0.32,9.4)
		Poly-1 adjusted number of animals at risk	25.0	74.3
harderian glands	adenoma	<i>p</i> -value of test of trend or comparison	.9514	.9514
		Number of animals reported with tumor	2	2
		Poly-1 adjusted incidence rate	8.0%	2.7%
		95% CI for Poly-1 adjusted incidence rate (%)	(0.98,26.0)	(0.32,9.4)
		Poly-1 adjusted number of animals at risk	25.0	74.3
lungs with bronchi	alveolar–bronchiolar adenoma	<i>p</i> -value of test of trend or comparison	.8919	.8919
		Number of animals reported with tumor	3	5
		Poly-1 adjusted incidence rate	12%	6.7%
		95% CI for Poly-1 adjusted incidence rate (%)	(2.55,31.2)	(2.2,15.1)
		Poly-1 adjusted number of animals at risk	25.0	74.3
multicentric	alveolar–bronchiolar carcinoma	<i>p</i> -value of test of trend or comparison	.7475	.7475
		Number of animals reported with tumor	0	1
		Poly-1 adjusted incidence rate	0.0%	1.3%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.03,7.3)
		Poly-1 adjusted number of animals at risk	25.0	74.3
skin	sarcoma	<i>p</i> -value of test of trend or comparison	.7475	.7475
		Number of animals reported with tumor	0	1
		Poly-1 adjusted incidence rate	0.0%	1.3%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.03,7.3)
		Poly-1 adjusted number of animals at risk	25.0	74.5
spleen	hemangiosarcoma	<i>p</i> -value of test of trend or comparison	.7475	.7475
		Number of animals reported with tumor	0	1
		Poly-1 adjusted incidence rate	0.0%	1.3%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.03,7.3)
		Poly-1 adjusted number of animals at risk	25.0	74.4
	hemangiosarcoma	<i>p</i> -value of test of trend or comparison	.3057	.3057
		Number of animals reported with tumor	0	4
		Poly-1 adjusted incidence rate	0.0%	5.4%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(1.47,13.3)
		Poly-1 adjusted number of animals at risk	25.0	74.3

Table A.1: Reported neoplastic tumors in study of female mice (treated groups combined) (continued)

Organ	Tumor type	Quantity	Control	Treated
stomach		Poly-1 adjusted number of animals at risk	25.0	74.5
		<i>p</i> -value of test of trend or comparison	1	1
		Number of animals reported with tumor	1	0
		Poly-1 adjusted incidence rate	4.0%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0.1,20.4)	(0,4.9)
thymus		Poly-1 adjusted number of animals at risk	25.0	74.3
		<i>p</i> -value of test of trend or comparison	.4133	.4133
		Number of animals reported with tumor	0	3
		Poly-1 adjusted incidence rate	0.0%	4.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.83,11.4)
		Poly-1 adjusted number of animals at risk	25.0	74.3

Table A.2: Reported neoplastic tumors in study of male mice (treated groups combined)

Organ	Tumor type	Quantity	Control	Treated
cavity, nasal	adenocarcinoma	<i>p</i> -value of test of trend or comparison	.7475	.7475
		Number of animals reported with tumor	0	1
		Poly-1 adjusted incidence rate	0.0%	1.3%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.03,7.3)
		Poly-1 adjusted number of animals at risk	25.0	74.2
harderian glands	adenoma	<i>p</i> -value of test of trend or comparison	.9853	.9853
		Number of animals reported with tumor	2	1
		Poly-1 adjusted incidence rate	8.0%	1.3%
		95% CI for Poly-1 adjusted incidence rate (%)	(0.98,26.0)	(0.03,7.3)
		Poly-1 adjusted number of animals at risk	25.0	74.2
liver	hepatocellular adenoma	<i>p</i> -value of test of trend or comparison	.7475	.7475
		Number of animals reported with tumor	0	1
		Poly-1 adjusted incidence rate	0.0%	1.3%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.03,7.3)
		Poly-1 adjusted number of animals at risk	25.0	74.2
lungs with bronchi	alveolar–bronchiolar adenoma	<i>p</i> -value of test of trend or comparison	.5934	.5934
		Number of animals reported with tumor	2	7
		Poly-1 adjusted incidence rate	8.0%	9.4%
		95% CI for Poly-1 adjusted incidence rate (%)	(0.98,26.0)	(3.84,18.5)
		Poly-1 adjusted number of animals at risk	25.0	74.2

Table A.2: Reported neoplastic tumors in study of male mice (treated groups combined) (continued)

Organ	Tumor type	Quantity	Control	Treated
skeletal muscle (thigh)	hemangioma	<i>p</i> -value of test of trend or comparison	.7475	.7475
		Number of animals reported with tumor	0	1
		Poly-1 adjusted incidence rate	0.0%	1.3%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.03,7.3)
		Poly-1 adjusted number of animals at risk	25.0	74.2
		<i>p</i> -value of test of trend or comparison	.7475	.7475
		Number of animals reported with tumor	0	1
		Poly-1 adjusted incidence rate	0.0%	1.3%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.03,7.3)
		Poly-1 adjusted number of animals at risk	25.0	74.5
skin	hemangiosarcoma	<i>p</i> -value of test of trend or comparison	.7475	.7475
		Number of animals reported with tumor	0	1
		Poly-1 adjusted incidence rate	0.0%	1.3%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.03,7.3)
		Poly-1 adjusted number of animals at risk	25.0	74.2
		<i>p</i> -value of test of trend or comparison	.7475	.7475
		Number of animals reported with tumor	0	1
		Poly-1 adjusted incidence rate	0.0%	1.3%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.03,7.3)
		Poly-1 adjusted number of animals at risk	25.0	74.2
spleen	hemangiosarcoma	<i>p</i> -value of test of trend or comparison	.5568	.5568
		Number of animals reported with tumor	0	2
		Poly-1 adjusted incidence rate	0.0%	2.7%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.32,9.4)
		Poly-1 adjusted number of animals at risk	25.0	74.2
		<i>p</i> -value of test of trend or comparison	.7475	.7475
		Number of animals reported with tumor	0	1
		Poly-1 adjusted incidence rate	0.0%	1.3%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.03,7.3)
		Poly-1 adjusted number of animals at risk	25.0	74.6
testes	hemangiosarcoma	<i>p</i> -value of test of trend or comparison	.5568	.5568
		Number of animals reported with tumor	0	2
		Poly-1 adjusted incidence rate	0.0%	2.7%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.32,9.4)
		Poly-1 adjusted number of animals at risk	25.0	74.2
		<i>p</i> -value of test of trend or comparison	1	1
		Number of animals reported with tumor	1	0
		Poly-1 adjusted incidence rate	4.0%	0.0%
		95% CI for Poly-1 adjusted incidence rate (%)	(0.1,20.4)	(0,4.9)
		Poly-1 adjusted number of animals at risk	25.0	74.2
thyroid glands	adenoma	<i>p</i> -value of test of trend or comparison	.7475	.7475
		Number of animals reported with tumor	0	1
		Poly-1 adjusted incidence rate	0.0%	1.3%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.03,7.3)
		Poly-1 adjusted number of animals at risk	25.0	74.2
		<i>p</i> -value of test of trend or comparison	.7475	.7475
		Number of animals reported with tumor	0	1
		Poly-1 adjusted incidence rate	0.0%	1.3%
		95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.03,7.3)
		Poly-1 adjusted number of animals at risk	25.0	74.2

Table A.3: Reported combinations in study of female mice (treated groups combined)

Endpoint	Quantity	Control	Treated
All hemangiosarcomas	<i>p</i> -value of test of trend or comparison	.2252	.2252
	Number of animals reported with tumor	0	5
	Poly-1 adjusted incidence rate	0.0%	6.7%
	95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(2.2,15.1)
All skin tumors	Poly-1 adjusted number of animals at risk	25.0	74.5
	<i>p</i> -value of test of trend or comparison	.7475	.7475
	Number of animals reported with tumor	0	1
	Poly-1 adjusted incidence rate	0.0%	1.3%
	95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.03,7.3)
	Poly-1 adjusted number of animals at risk	25.0	74.4

Table A.4: Reported combinations in study of male mice (treated groups combined)

Endpoint	Quantity	Control	Treated
All hemangiosarcomas	<i>p</i> -value of test of trend or comparison	.7362	.7362
	Number of animals reported with tumor	1	3
	Poly-1 adjusted incidence rate	4.0%	4.0%
	95% CI for Poly-1 adjusted incidence rate (%)	(0.1,20.4)	(0.83,11.4)
All skin tumors	Poly-1 adjusted number of animals at risk	25.0	74.2
	<i>p</i> -value of test of trend or comparison	.5568	.5568
	Number of animals reported with tumor	0	2
	Poly-1 adjusted incidence rate	0.0%	2.7%
	95% CI for Poly-1 adjusted incidence rate (%)	(0,13.7)	(0.32,9.4)
	Poly-1 adjusted number of animals at risk	25.0	74.6

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Applicant: Novartis

Stamp Date: 6/3/11

Drug Name: Ruxolitinib

NDA/BLA Type: NDA

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Information requests:

- For Study 352, provide a one record per subject dataset including primary, secondary endpoints, patient demographics and disposition.

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.				To be checked
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	x			
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				To be checked
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician

Date

Supervisor/Team Leader

Date

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/s/

HONG LU
07/22/2011

MARK D ROTHMANN
07/22/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202192Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

23 August 2011

NDA: 202192/N-000

Drug Product Name

Proprietary:

N/A.

Non-proprietary:

ruxolitinib phosphate.

Review Number:

1.

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
03 JUN 2011	03 JUN 2011	29 JUN 2011	30 JUN 2011

Applicant/Sponsor

Name:

Incyte Corporation.

Address:

Route 141 & Henry Clay Road.

Building 336

Wilmington, DE 19880

Representative:

Ronald C. Falcone, Ph.D.

Telephone:

302-498-6846

Name of Reviewer:

John W. Metcalfe, Ph.D.

Conclusion:

Recommended for approval.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** A 505(b)(1) NDA.
2. **SUBMISSION PROVIDES FOR:** Marketing authorization.
3. **MANUFACTURING SITE:**
DSM Pharmaceuticals, Inc.
5900 Martin Luther King Jr. Highway
Greenville, NC 27834
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Tablet.
 - Oral.
 - 5, 10, 15, 20 and 25 mg.
5. **METHOD(S) OF STERILIZATION:** Not applicable, the product is not sterile.
6. **PHARMACOLOGICAL CATEGORY:** The subject drug product is indicated for the treatment of myelofibrosis.
- B. **SUPPORTING/RELATED DOCUMENTS:** None.
- C. **REMARKS:**
The subject NDA is submitted electronically in the CTD format.

File Name: N202192R1.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – NDA 202192/N-000 is recommended for approval on the basis of product quality microbiology.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable.

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** -  (b) (4)
- B. **Brief Description of Microbiology Deficiencies** - There are no microbiology deficiencies identified.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

III. Administrative

- A. **Reviewer's Signature** _____
John W. Metcalfe, Ph.D.
- B. **Endorsement Block** _____
Bryan S. Riley, Ph.D.
- C. **CC Block**
N/A

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/s/

JOHN W METCALFE
08/23/2011

BRYAN S RILEY
08/23/2011
I concur.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202192Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW**

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

1 Background

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

2 Submission Contents Related to Genomics

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

3 Key Issues and Summary of Findings

3.1 Effect of JAK mutation status on response

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

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

3.2 Safety

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

4 Summary and Conclusions

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

5 Recommendations

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

5.1 Post-marketing studies

No recommendations from the Genomics Group for PMR/PMC.

5.2 Label Recommendations

None.

Christian Grimstein, Ph.D.
Reviewer, Genomics Group, OCP

Issam Zineh, PharmD., M.P.H.
Associate Director, Genomics Group, OCP

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/s/

CHRISTIAN GRIMSTEIN
11/07/2011

ISSAM ZINEH
11/07/2011
Concur

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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

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1 EXECUTIVE SUMMARY

JAKAFI (Ruxolitinib Phosphate) is an orally administered inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs) that is proposed for the treatment of patients with myelofibrosis (MF) including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPVMF) and post-essential thrombocythemia myelofibrosis (PETMF). The proposed starting dose of JAKAFI is

(b) (4) 15 mg given orally twice daily for patients with a platelet count between $100 \times 10^9/L$ and $200 \times 10^9/L$, and 20 mg twice daily for patients with a platelet count of $> 200 \times 10^9/L$.

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

Based on a population pharmacokinetic/pharmacodynamic model, exposure-response relationships were simulated for efficacy and safety endpoints. The simulations support the proposed initial dosing based on baseline platelet count and the titration to a maximum of 25 mg BID. These doses will likely achieve effective reductions in mean spleen volume and symptom scores with a low probability causing severe thrombocytopenia (i.e., platelet count $< 50 \times 10^9/L$). However, patients on average daily doses ≤ 10 mg (5 mg BID) did not yield a 35% reduction in spleen volume or symptom score (based on limited data).

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

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

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

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

1.1 Recommendation

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

1.2 Post Marketing Requirements

- None

1.3 Post Marketing Commitments

- None

1.4 Comments to the Applicant

- None

1.5 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

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

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

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

Importantly, if a patient were to be maintained at a dose of 5mg BID, a high risk of thrombocytopenia (platelet < 50 g/L) would be present with minimal, if any, benefit in spleen volume reduction and total symptom score.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Signatures

Joseph A. Grillo, Pharm.D
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 5

Satjit Brar, Pharm.D., Ph.D.
Pharmacometrics Reviewer
Division of Pharmacometrics

Christine Garnett, Pharm.D.
Pharmacometrics Team Leader
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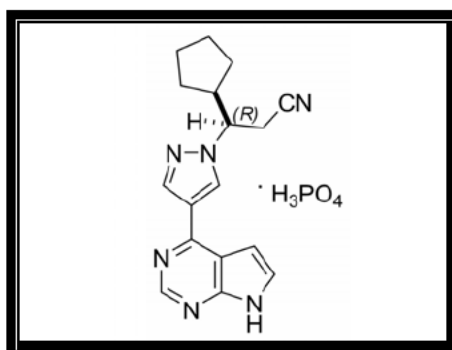
Julie M. Bullock, Pharm.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology 5

Jian Wang, Ph.D
Pharmacometrics Reviewer
Division of Clinical Pharmacology 5

2 QUESTION BASED REVIEW

2.1 General Attributes

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



Established name:	ruxolitinib phosphate
Molecular Weight:	404.36 g/mole, (306.37 g/mole for free base)
Molecular Formula:	C ₁₇ H ₂₁ N ₆ O ₄ P; (C ₁₇ H ₁₈ N ₆ for free base)
Chemical Name:	(R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate
Description:	Ruxolitinib phosphate is a non-hygroscopic, white to off-white to light pink powder.
Polymorphism:	(b) (4)
Solubility:	The drug substance in aqueous medium is pH dependent. It is most soluble in pH 1.0 buffer (0.54 mg/mL), and least soluble in pH 7.4 medium (0.15 mg/mL). It is also very soluble in MeOH, EtOH, 2-propanol and DMSO (at 25°C and 50°C) and freely soluble in acetonitrile (at 25°C and 50°C) and dichloromethane (at 25°C).
pKa-Values:	4.3 and 11.8.
Partition Coefficient:	Octanol/pH 1.0 Buffer - 0.057 ± 0.004; Octanol/pH 4.3 Buffer - 2.562 ± 0.065; and Octanol/pH 7.4 Buffer - 2.814 ± 0.028

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

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

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

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

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

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

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

Table 1: Proposed starting doses

Platelet Count	Starting dose
> 200 × 10 ⁹ /L	20 mg orally twice daily
100 × 10 ⁹ /L to 200 × 10 ⁹ /L	15 mg orally twice daily

(b) (4)

Source: Applicant's proposed labeling

The applicant proposes that complete blood counts be monitored every 2-4 weeks until doses are stabilized, and then as clinically indicated. Treatment should be interrupted for platelet counts less than 50 X 10⁹/L or absolute neutrophil counts less than 0.5 X 10⁹/L. After recovery of platelet and neutrophil counts above these levels, dosing may be restarted at 5 mg twice daily and gradually increased based on careful monitoring of counts. Dose reductions should be considered if the platelet counts decrease below 100 X 10⁹/L with the goal of avoiding dose interruptions for thrombocytopenia.

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

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

2.2 General Clinical Pharmacology

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

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

Table 2: Clinical Studies with Ruxolitinib

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

Source: Applicant's proposed labeling

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

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

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

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

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

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

Yes (see Section 2.6).

2.2.4 Exposure-response

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

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

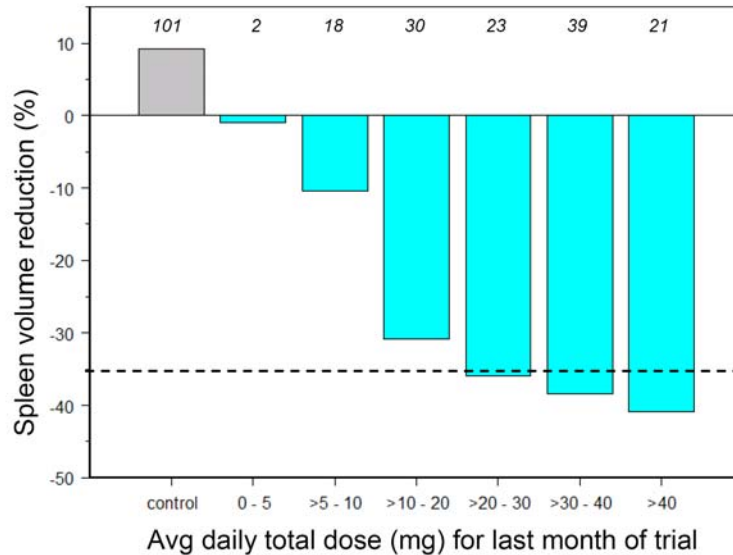


Figure 1: FDA analysis of spleen volume reduction as a function of average daily total dose for trial 351. Grey bar represents the placebo arm and the lighter grey bars represent the ruxolitinib average daily doses ranging from 0-5 mg to >40 mg. The dashed line represents the clinically relevant effect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

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

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

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

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

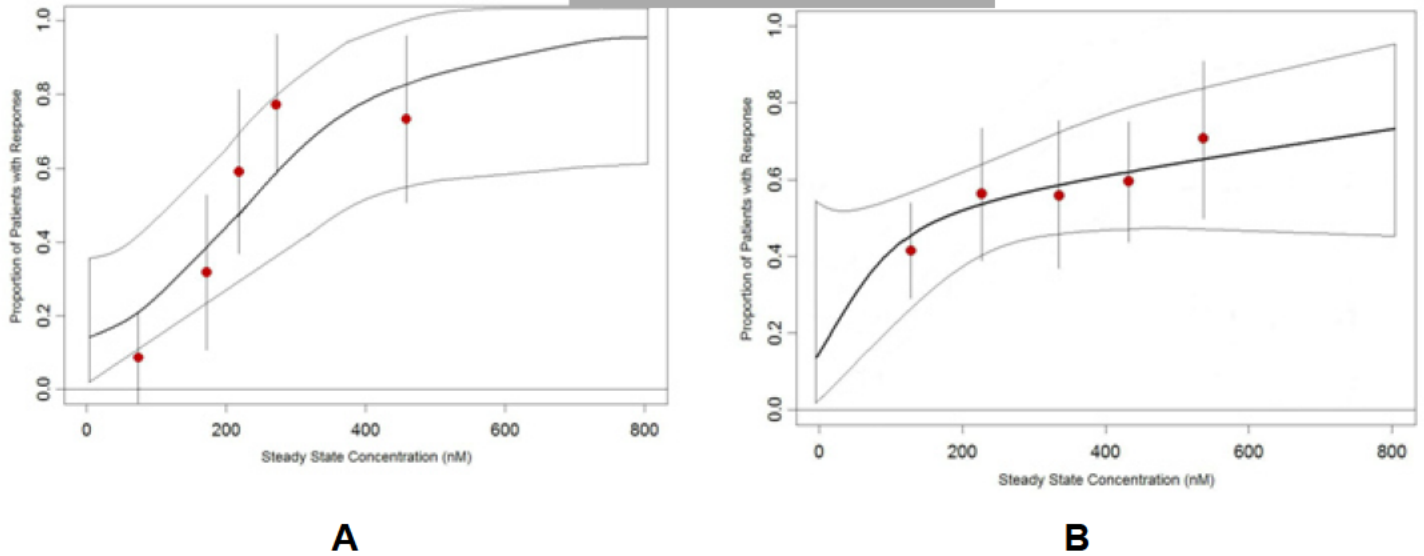


Figure 2: Proportion of patients achieving $\geq 35\%$ spleen volume reduction (A) and $\geq 50\%$ reduction in total symptom score (B) versus average steady state concentrations of ruxolitinib in trial 351. Solid round symbols represent the observed efficacy measure in each $C_{ss \text{ average}}$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

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

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

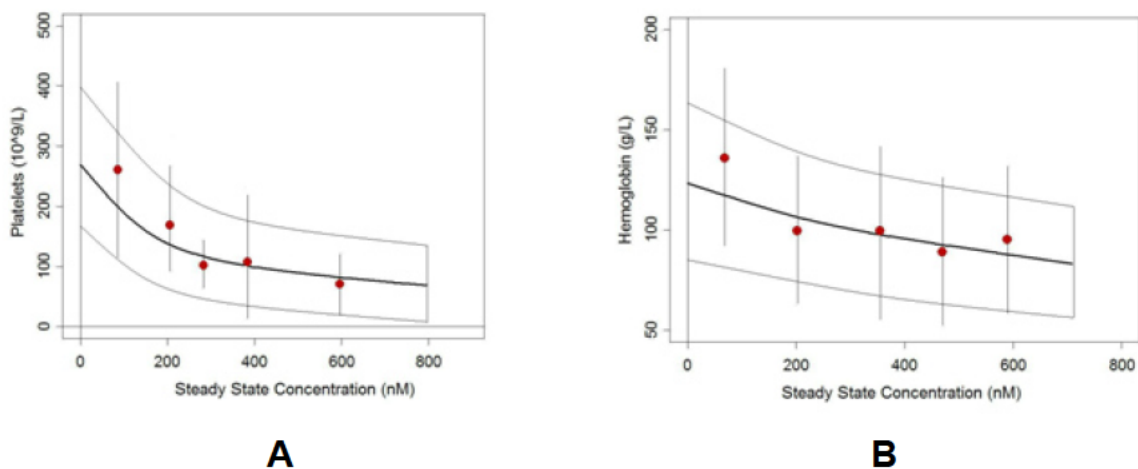


Figure 3: FDA Analysis of platelet count (A) and hemoglobin (B) versus average steady state concentrations of ruxolitinib in trial 351. Solid round symbols represent the observed efficacy measure in each $C_{ss \text{ average}}$ quantile. The vertical black bars represent the CI_{95} . The model predicted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

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

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

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

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

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

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

Source: 09/06/2011 IRT consult

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

The exposure-response relationship for efficacy and safety does support the recommended initial dose based on platelet count, as proposed in the label. The PK/PD model for platelet count over time was utilized to perform simulations for the continual dosing of 15 mg BID for those patients with an initial platelet count at $100 \times 10^9/L$ and 20 mg BID with an initial platelet count of $200 \times 10^9/L$. On average, platelet counts were above the threshold of $50 \times 10^9/L$ for both dosing groups, further supporting the applicant’s dosing justification for initial platelet count.

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

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

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

On the other hand, patients on average daily doses ≤ 10 mg (≤ 5 mg BID) did not yield a clinically meaningful benefit of 35% reduction in spleen volume. (b) (4)

Importantly, if a patient were to be maintained at a dose of 5mg BID, a high risk of thrombocytopenia (platelet < 50 g/L) would be present with minimal, if any, benefit in spleen volume reduction and total symptom score. Using the exposure-response relationship for platelet count, simulations for a typical patient with a baseline platelet count of 50 g/L, maintained at a 5 mg BID dose, was performed (Figure 4). Results show that an individual, with low platelet count, maintained on a dose of 5 mg BID would be at risk of thrombocytopenia.

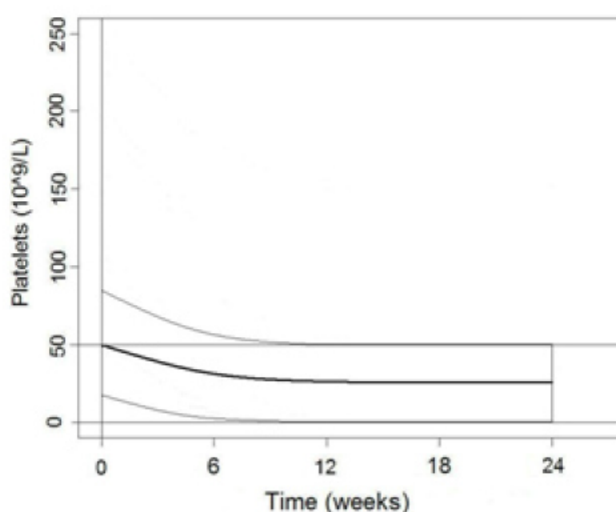


Figure 4: Simulated average platelet count over time for maintaining a starting dose of 5 mg BID for a baseline platelet count of $50 \times 10^9/L$. Dark line represents model prediction along with 95% prediction interval. The minimum threshold for platelet count is denoted by the solid black line at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

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

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

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

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

Dose	n	C _{max} (nM)	T _{max} (h)	t _{1/2} (h)	AUC _{0-∞} (nM·h)	CL/F (L/h)	Vz/F (L)
5 mg	12	205 ± 72.8 195	1.7 ± 0.69 1.5	2.8 ± 1.1 2.6	862 ± 273 823	20.7 ± 6.45 19.8	83 ± 40.1 74.9
10 mg	6	382 ± 114 368	2.1 ± 1.2 1.7	3.6 ± 1.5 3.4	1790 ± 395 1750	19.0 ± 3.87 18.6	95 ± 34.5 90.7
25 mg	6	1090 ± 607 934	2.4 ± 2.0 1.8	3.1 ± 0.67 3.0	4330 ± 1470 4110	21.0 ± 7.92 19.9	87.7 ± 20.7 85.7
50 mg	6	1760 ± 515 1700	1.2 ± 0.68 1.0	2.7 ± 0.56 2.7	7160 ± 1950 6930	24.4 ± 7.09 23.5	96.9 ± 41.8 90.5
100 mg	6	4570 ± 1360 4390	1.6 ± 0.80 1.4	2.7 ± 0.51 2.7	16900 ± 4710 16400	20.6 ± 5.69 19.9	78.7 ± 13.8 77.7
200 mg	6	7100 ± 1350 7010	1.9 ± 1.3 1.6	5.0 ± 2.0 4.7	30700 ± 2640 30600	21.4 ± 1.77 21.3	155 ± 64.6 146

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

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

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

Dose (mg)	n	C _{max} (nM)	T _{max} (h)	t _{1/2} (h)	AUC _{0-t} (nM·h)	AUC _{0-∞} (nM·h)	CL/F (L/h)	Vz/F (L)
25	47	1510 ± 400 1460	0.96 ± 0.5 0.86	2.6 ± 0.9 2.5	5290 ± 1640 5060	5320 ± 1680 5080	16.8 ± 5.01 16.1	59.1 ± 11.4 58.0
200	48	11500 ± 3120 11100	1.1 ± 0.4 1.1	2.7 ± 0.55 2.6	42800 ± 14300 40600	43000 ± 14500 40700	16.9 ± 5.45 16.0	62.6 ± 15.0 60.9

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

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

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

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

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

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

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

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

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

Regimen	n	C _{max} (nM)	T _{max} (h)	t _{1/2} (h)	C _{min} (nM)	AUC _{0-τ} (nM*h)	Cl/F (L/h)	Vz/F (L)
15 mg q12h	8	681 ± 223 649	1.7 ± 0.6 1.7	2.9 ± 0.8 2.8	37.2 ± 19.6 31.5	2716 ± 770 2610	19.6 ± 6.47 18.7	82.2 ± 34.8 76.7
25 mg q12h	18	1200 ± 306 1160	1.6 ± 1.1 1.4	3.1 ± 1.0 2.9	54.6 ± 37.1 45.1	4535 ± 1412 4330	19.7 ± 5.91 18.8	82.3 ± 19.7 79.7
50 mg q12h	6	2710 ± 972 2570	1.2 ± 0.4 1.2	3.2 ± 0.8 3.1	111 ± 85.9 80.1	8513 ± 2660 8170	20.8 ± 6.44 20.0	89.7 ± 13.4 88.9
50 mg q24h	9	2360 ± 649 2290	1.2 ± 0.5 1.1	2.9 ± 0.8 2.8	6.6 ± 9.5 n/a	7764 ± 2138 7470	22.9 ± 7.68 21.9	90.2 ± 21.4 87.9
100 mg q24h	9	4890 ± 1060 4780	1.3 ± 0.2 1.3	3.9 ± 0.7 3.8	25.9 ± 23.5 16.8	17135 ± 4628 16600	20.4 ± 5.97 19.7	111 ± 31.2 108

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

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

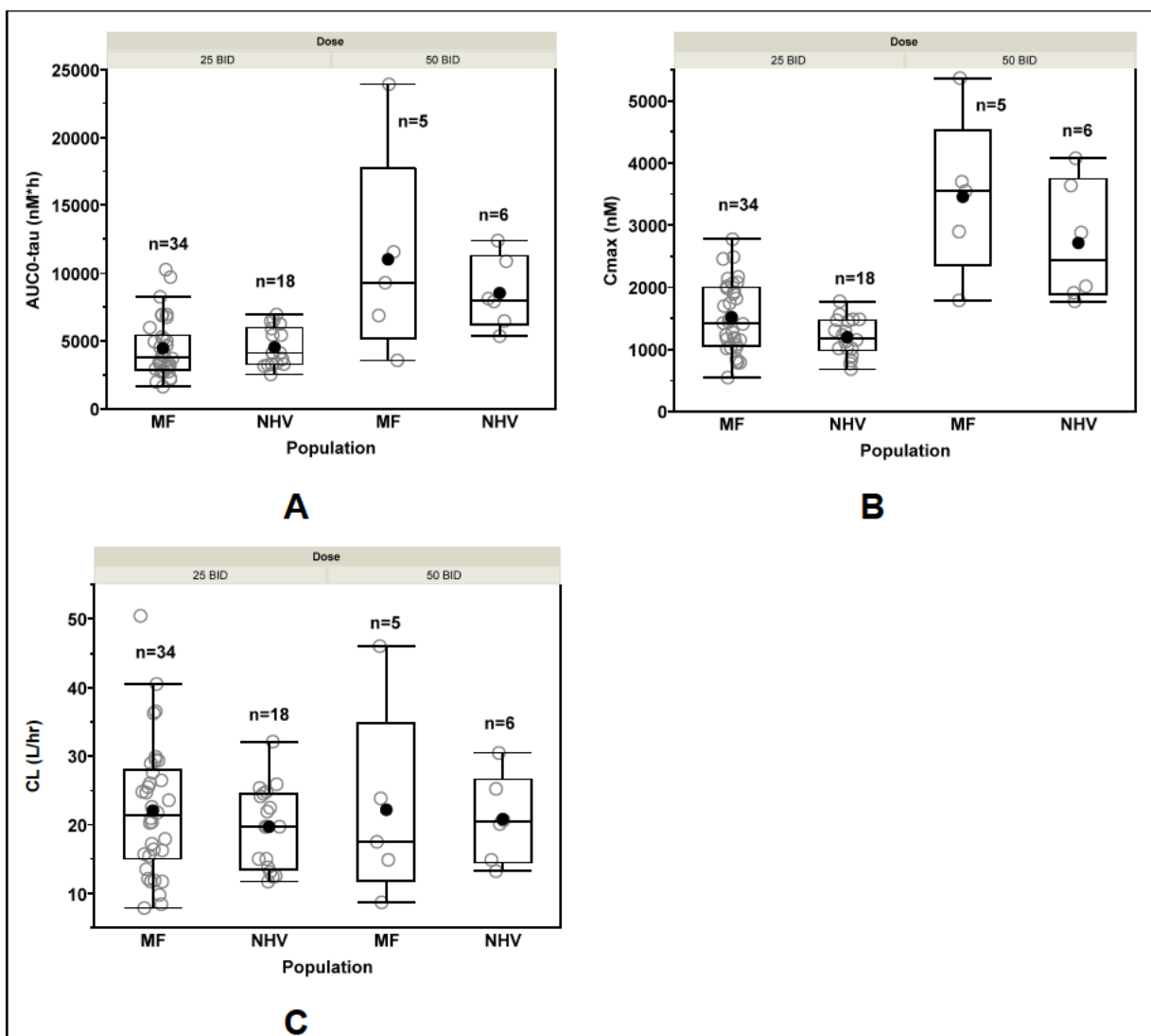
The safety, efficacy, pharmacokinetics and pharmacodynamics of ruxolitinib was evaluated a multicenter, open-label, non-randomized, dose escalation study to subjects with Primary Myelofibrosis (PMF), Post Polycythemia Vera Myelofibrosis (PPV-MF), or Essential Thrombocythemia Myelofibrosis (PET-MF). Part 1 evaluated two dose levels of 25 mg bid and 50 mg bid, Part 2 studied five dose regimens of 10 mg bid, 25 mg bid, 25 mg qd, 50 mg qd and 100 mg qd and Part 3 assessed six dose regimens of 10 mg bid, 15 mg bid, 25 mg bid, 50 mg qd, 100 mg qd and 200 mg qd. Plasma concentration data from rich sample collection during Cycle 1 for subjects in Part 1 and 2 were used for non-compartmental analysis while all plasma concentration data were used for population PK analysis. The pharmacokinetic parameters at steady state are summarized in Table 9, respectively and are deemed acceptable by the reviewer.

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

Regimen	n	C _{max} (nM)	t _{max} (h)	C _{min} (nM)	t _{1/2} (h)	AUC _{0-τ} (nM*h)	Cl/F (L/h)	Vz/F (L)
Part 1								
25 mg bid	27	1481 ± 575 1374	0.83 ± 0.45 0.74	47 ± 54 –	1.94 ± 0.50 1.88	4363 ± 2066 3949	22.7 ± 10.1 20.7	60 ± 23 56
50 mg bid	5	3460 ± 1305 3255	0.87 ± 0.58 0.71	173 ± 273 47	1.99 ± 0.82 1.86	9832 ± 5631 8547	22.2 ± 14.3 19.1	56 ± 30 51
Part 2								
25 mg qd	6	1417 ± 150 1410	0.84 ± 0.38 0.78	0 ± 0 –	1.60 ± 0.36 1.57	3567 ± 777 3494	23.9 ± 5.5 23.4	53 ± 6.7 53
50 mg qd	1	3380	1.00	16	3.14	15211	10.7	49
100 mg qd	3	4607 ± 101 4606	1.00 ± 0.50 0.91	37 ± 55 13	1.95 ± 0.64 1.88	17020 ± 3351 16808	19.7 ± 3.65 19.4	53 ± 7.4 53
10 mg bid	12	518 ± 229 486	1.04 ± 0.54 0.92	18 ± 19 11	1.80 ± 0.41 1.77	1514 ± 756 1380	25.6 ± 10.1 23.7	65 ± 27 60
25 mg bid	7	1650 ± 506 1578	0.79 ± 0.49 0.68	85 ± 102 43	1.96 ± 0.59 1.90	4939 ± 2566 4463	19.9 ± 8.1 18.3	53 ± 16 50

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

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



Values are data points (grey circles), arithmetic mean (solid circle) and quartile box-plot.

Source: Raw data sets for trials INCB 18424-132 and 18424-251

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

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

2.2.5.3 What are the characteristics of drug absorption?

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

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

In Caco-2 cell monolayers, ruxolitinib exhibited a high apparent permeability. Transport experiments from study INCYTE-DMB-08.147.1 using different concentrations of ruxolitinib (1, 10, 50, and 100 μM) resulted in similar Papp values (28.6, 20.0, 21.5, and $17.9 \times 10^{-6} \text{ cm/sec}$, respectively) and suggest that concentration-independent permeability is likely and saturable transport is unlikely in the absorption process. Further, in the presence of P-glycoprotein (P-gp) inhibitors (i.e., cyclosporine A and quinidine), the bi-directional transport ratio was not significantly altered (Table 10), indicating that it is unlikely that ruxolitinib is a substrate of P-gp.

Table 10: Permeability of INCB018424 in Caco-2 Monolayers

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

* N=3 - 6

** In the presence of 4% bovine serum albumin (BSA)

NA = not applicable

Source: Study report for study INCYTE-DMB-08.147.1

These findings are deemed acceptable by the reviewer.

2.2.5.4 What are the characteristics of drug distribution?

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

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

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

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

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

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

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

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

Source: Study report for study INCB 18424-134

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

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

Source: Study report for study INCB 18424-134

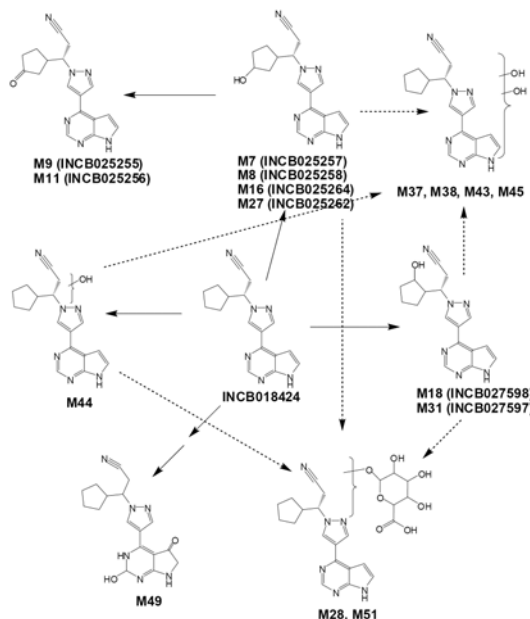
2.2.5.6 What are the characteristics of drug metabolism? (This may include data on extraction ratio; metabolic scheme; enzymes responsible for metabolism; fractional clearance of drug.)

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

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

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

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



Source: Study report for study INCB 18424-134

Figure 6: Proposed Metabolic Pathways for Ruxolitinib in Human Plasma

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

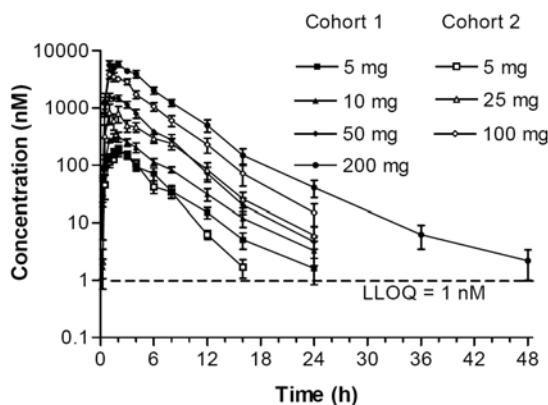
2.2.5.7 What are the characteristics of drug excretion?

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

In similar cross-study comparison, terminal phase elimination half-life values for ruxolitinib ranged from 2.3 to 4.0 hours with grand mean from all studies of 3.1 hours. Following a single oral dose of ¹⁴C-INCB018424 solution in healthy male volunteers, the terminal t_{1/2} of total drug-related material (ruxolitinib + metabolites) in plasma was estimated to be 5.8 h (CV = 13%). The typical apparent terminal elimination (β) half-life for ruxolitinib in MF patients (INCB 18424-251, INCB 18424-351 and INCB 18424-352) estimated from the final population PK model was approximately 3.76 hours for males and 4.07 hours for females.

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

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



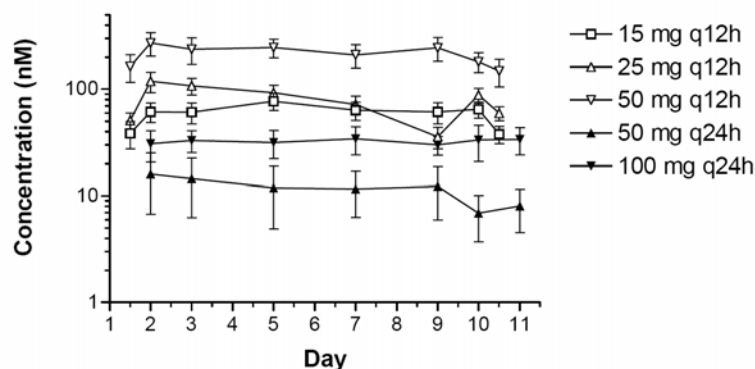
Source: Study report for trial INCB 18424-131

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

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

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

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



Source: Study report for trial INCB 18424-132

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

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

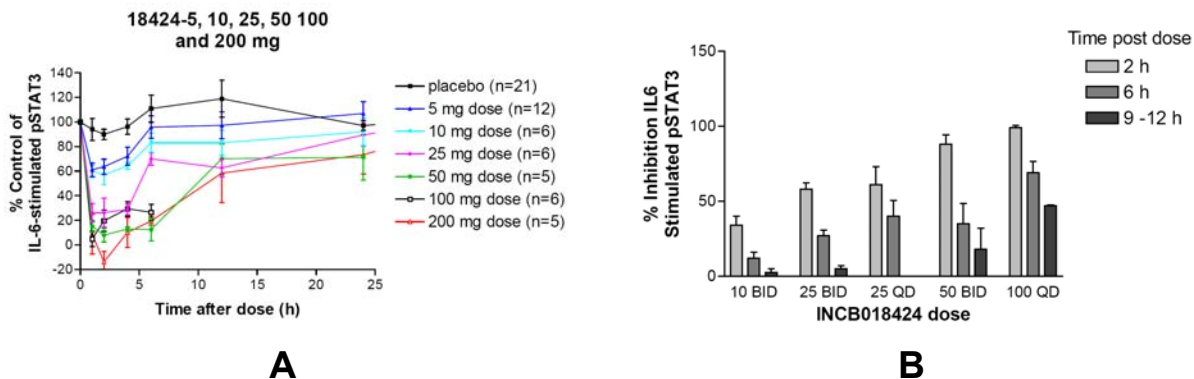
The ruxolitinib pharmacokinetic parameters reported in the single dose trial INCB 18424-131 in healthy volunteers exhibited intersubject variability (CV%), ranging from 19.0% (200 mg) to 55.9% (25 mg) for C_{max} and from 8.59% (200 mg) to 34.0% (25 mg) for AUC_{0-∞}. In multiple dose trial INCB 18424-132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

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

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

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

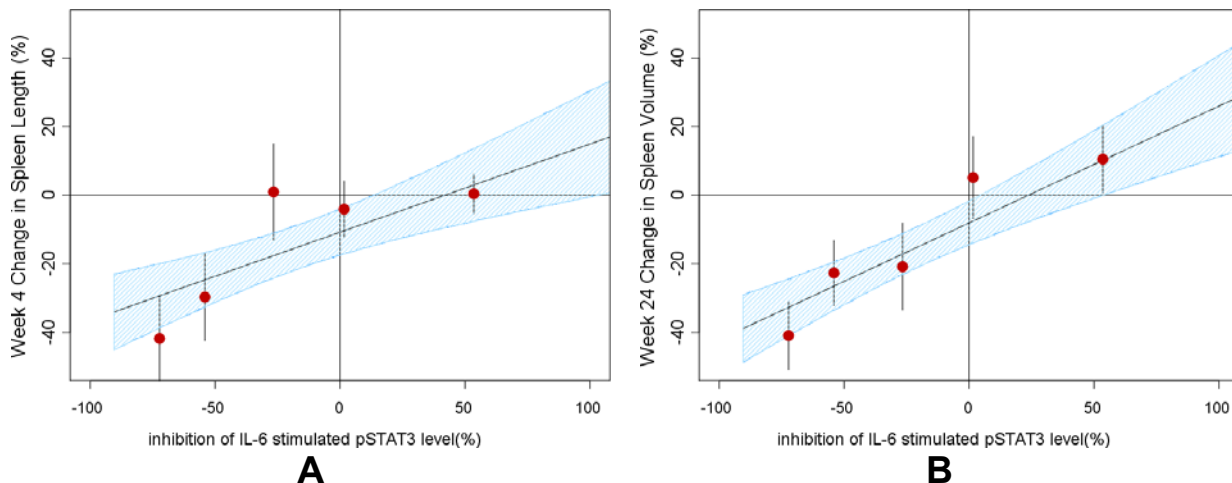
administration for all doses, coincident with maximal ruxolitinib plasma concentrations and returned to near baseline by 8-10 hours in both healthy subjects and myelofibrosis patients (Figure 9). Across multiple studies in healthy subjects, the calculated IC_{50} value for IL-6 induced pSTAT3 inhibition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



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

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

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



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

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

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

STAT3 phosphorylation (Table 13). Based on these IC₅₀ values, the contribution of these metabolites to pharmacodynamic activity relative to parent is estimated to be 15-18% in healthy subject studies. This contribution changes in when various intrinsic or extrinsic factors are present (see Sections 2.3 and 2.4).

Table 13: Activity of INCB018424 Metabolites *In Vitro*

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

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

2.3 Intrinsic Factors

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

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

Body Weight

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

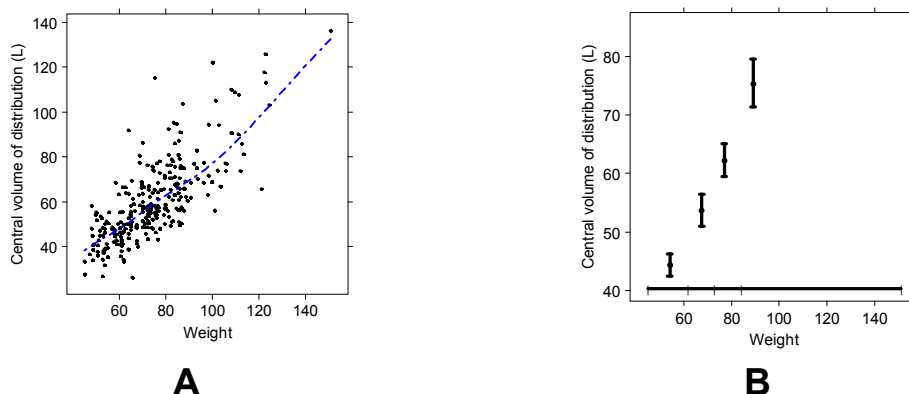


Figure 11: Inter-individual variability of CL vs weight by Scatter plot (A) and Quantile Plot (B)

Gender

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

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

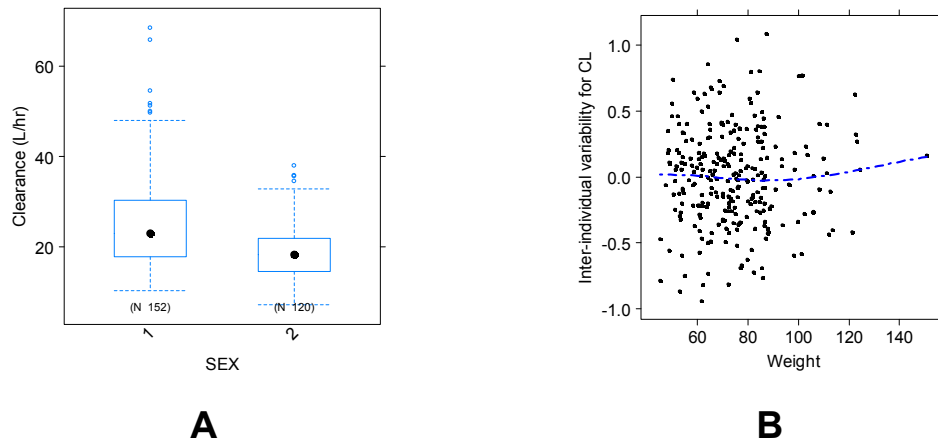


Figure 12: Plots of CL vs sex (A) and Inter-individual variability of CL vs. body weight (B) under the final model with sex as a covariate for clearance.

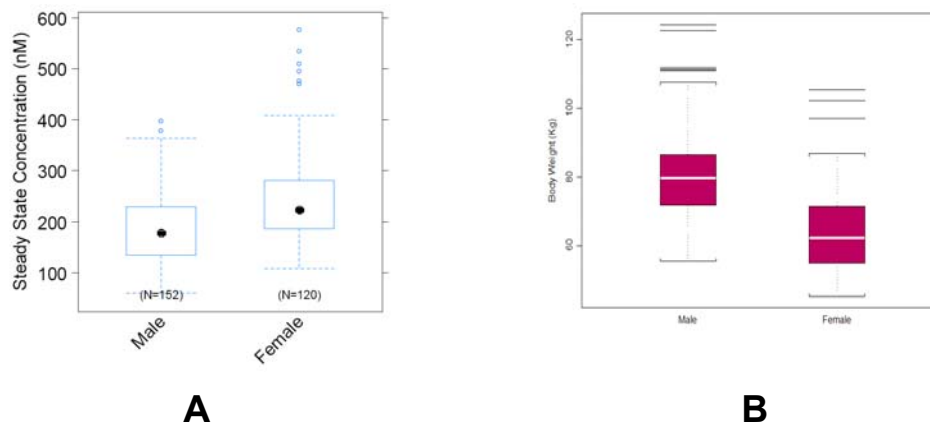


Figure 13: Comparisons of steady state concentration at 15 mg daily dose (A) and the body weight (B) between male and female patients.

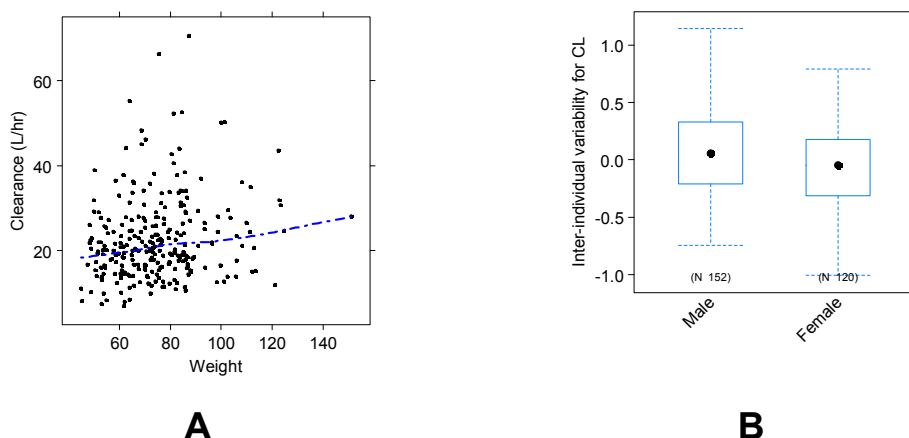


Figure 14: Plots of CL vs weight (A) and Inter-individual variability of CL vs sex (B) under the final model with body weight as a covariate for clearance.

Renal impairment

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

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

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

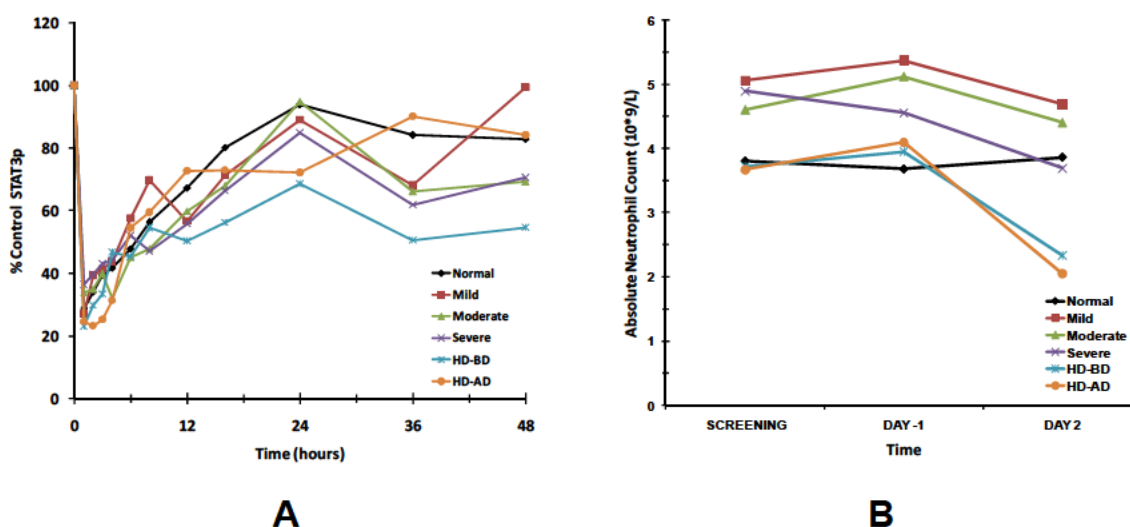
Table 14: Geometric Mean Relative Change in AUC_{combined} compared to the Normal Renal Impairment Group

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

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

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

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



BD=before dose; AD=after dose

Source: Applicants reports INCB 18424-142

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

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

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

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

Hepatic impairment

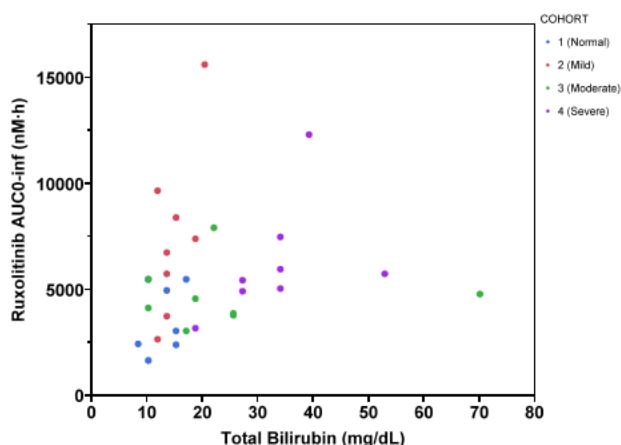
The applicant conducted an open-label trial (INCB 18424-137) of the effect of various degrees of hepatic impairment on the pharmacokinetics of a single 25 mg dose of ruxolitinib. The trial included healthy subjects and patients with varying degrees of hepatic impairment (mild, moderate and severe hepatic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

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

	Ruxolitinib		Ruxolitinib + Metabolites
	C _{max}	AUC _{0-∞}	AUC _{combined}
Normal	1	1	1
Mild	0.92	1.87	1.77
Moderate	0.78	1.28	1.21
Severe	0.85	1.65	1.59

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

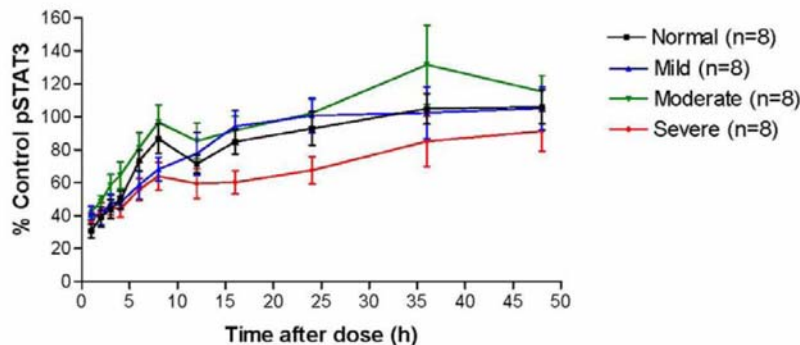
While the mean ruxolitinib AUC in each of the three hepatic impairment cohorts was higher than that of the healthy subjects, it did not necessarily coincide with the severity of hepatic impairment. It is not clear why this discrepancy exists; however, the higher AUC in the mild group can be assigned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



Source: Applicants raw dataset for report INCB 18424-137

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

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



Source: Applicants raw dataset for report INCB 18424-137

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

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

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

2.3.2.1 Elderly

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

2.3.2.2 Pediatric patients

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

2.3.2.3 Gender

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

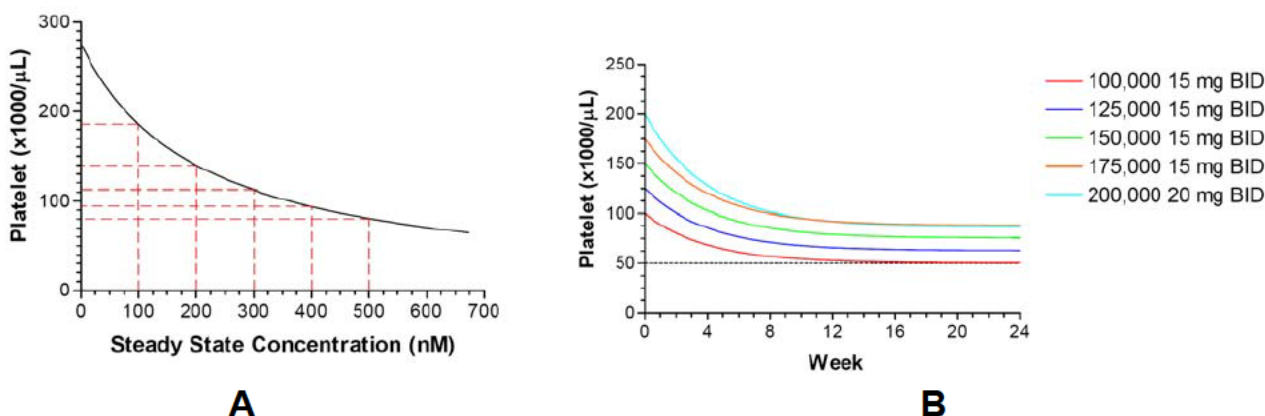
2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

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

2.3.2.5 Renal impairment

Based on the reports from trial INCB 18424-142 and the metabolite analysis INCYTE DMB-10.55.1 the applicant proposes (b) (4)

As demonstrated in Figure 18a, as steady state concentrations of ruxolitinib increase above 300 nM the relative effect on platelet count at week 24 is much less pronounced. Further, Figure 18b suggests, from a safety perspective, it is of greater importance to exposure match patients with baseline platelet counts between 100-150 × 10⁹/L to assure exposure does not go beyond that expected for 15 mg bid.



Source: Applicant's report INCYTE-DMB-11.05.1

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

Therefore, the reviewer recommends that the applicant's proposal be modified such that only patients with a baseline platelet count between 100 × 10⁹/L and 150 × 10⁹/L and moderate (Cl_{cr} 30-50 mL/min) or severe renal impairment (Cl_{cr} less than 30 mL/min) should have the starting dose of JAKAFI reduced to 10 mg twice daily. JAKAFI should be avoided in patients with any

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

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

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

Yellow = baseline platelet count $> 200 \times 10^9/L$; Grey = baseline platelet count $100-200 \times 10^9/L$; Blue = baseline platelet count $151-200 \times 10^9/L$; Green = baseline platelet count $100-150 \times 10^9/L$

a = normal values for C_{ss} represent mean values from trials 251 and 351

b= based on relative change in AUC_{combined} from Table 14

Source: Applicants reports INCB 18424-142 and INCYTE-DMB-11.05.1

2.3.2.6 Hepatic impairment

Based on the reports from trial INCB 18424-137 and the metabolite analysis INCYTE DMB-10.55.1 the applicant proposes

(b) (4)

Therefore, the reviewer again attempted to further optimize the applicant's proposed JAKAFI dose modifications using the same approach and rationale discussed in section 2.3.2.5. Based on this approach the reviewer recommends that the applicant's proposal be modified such that only patients with a baseline platelet count between $100 \times 10^9/L$ and $150 \times 10^9/L$ and any degree of hepatic impairment should have the starting dose of JAKAFI reduced to 10 mg twice daily. JAKAFI should be avoided in patients with any degree of hepatic impairment and a baseline platelet count $< 100 \times 10^9/L$. As indicated in Table 17 below, this proposed regimen allows for exposure matching of the patient population most at risk for thrombocytopenia while allowing maximum potential benefit for other patients at lower risk for thrombocytopenia. Additional dose modifications should be made with careful monitoring of safety and efficacy.

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

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

Yellow = baseline platelet count $> 200 \times 10^9/L$; Grey = baseline platelet count $100-200 \times 10^9/L$; Blue = baseline platelet count $151-200 \times 10^9/L$; Green = baseline platelet count $100-150 \times 10^9/L$

a = normal values for C_{ss} represent mean values from trials 251 and 351

b= based on relative change in AUC_{0-∞} from Table 15

c= based on relative change in AUC_{combined} from Table 15

Source: Applicants reports INCB 18424-137 and INCYTE-DMB-11.05.1

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

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

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

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

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

None

2.4 Extrinsic Factors

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

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

Drugs that are inhibitors of CYP3A4

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

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

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

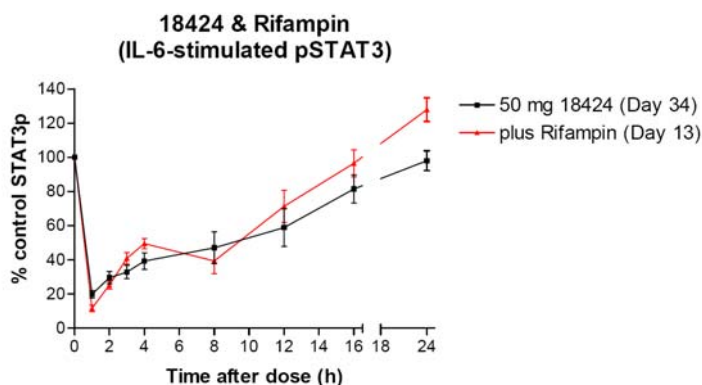
the applicant's position that dose modification is not required for co-administration with mild to moderate CYP3A4 inhibitors.

Drugs that are strong inducers of CYP3A4

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

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

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



18424 = ruxolitinib

Source: Applicants report INCB 18424-135

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

Two possible explanations were provided by the applicant regarding this discrepancy. First, at a dose of 50 mg of ruxolitinib, the average plasma concentration (calculated as average AUC_{0-t/24h}) over the 24 hour period post-dose (421 nM, on Day 34) was greater than the IC₅₀ value (234 nM) for STAT3 phosphorylation. The pSTAT3 inhibition vs. ruxolitinib plasma concentration relationship is described by a sigmoidal curve and data from a 50 mg dose is expected to fall on the non-linear portion of that sigmoidal curve such that changes in plasma concentration of ruxolitinib will not necessarily result in proportional changes in pSTAT3 inhibition. Second, an increased contribution to the PD activity from active metabolites may be expected following metabolic induction with rifampin and therefore plasma concentrations of the eight ruxolitinib metabolites were determined with and without rifampin treatment. The total AUC values of ruxolitinib metabolites, on average, were nearly unchanged, but the relative abundance of the metabolites (expressed as percent of ruxolitinib AUC) increased by more than 2-fold. The

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

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

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

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

Source: Applicants report INCYTE DMB-10.55.1

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

2.4.2.1 Drugs that are strong inhibitors of CYP3A4

Based on the reports from trial INCB 18424-133 the applicant propose (b) (4)

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

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

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

^a Pink = baseline platelet count $\geq 100 \times 10^9/L$

^a = normal values for C_{ss} represent mean values from trials 251 and 351

^b = based on relative change in AUC_{0-∞} from Section 2.4.1

Source: Applicants reports INCB 18424-133

2.4.2.2 Drugs that are strong inducers of CYP3A4

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

2.4.3 Drug-drug interactions

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

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

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

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

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

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

Ruxolitinib did not appear to be a potent inhibitor of recombinant or microsomal CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 with IC_{50} values $>25 \mu\text{M}$. Although ruxolitinib inhibited recombinant CYP3A4 activity using the fluorescent probe substrate screening assay (IC_{50} of 8.8 μM), ruxolitinib did not appear to show inhibition of human liver microsomal CYP3A4 using two preferred probe substrates, midazolam and testosterone, with some inhibition at the highest concentration tested (IC_{50} values $>25 \mu\text{M}$). In addition, microsomal CYP3A4 enzyme activity was not inhibited when ruxolitinib was pre-incubated with NADPH, indicating ruxolitinib is an unlikely mechanism-based inhibitor of CYP3A4. The reviewer agrees with the applicant's position that, since the mean C_{max} at the highest proposed therapeutic dose for ruxolitinib in humans (25 mg bid) is 1.2 μM (0.04 μM unbound), the ratio of $\text{C}_{\text{max}}/\text{IC}_{50}$ for the CYPs tested is <0.1 , suggesting the potential for ruxolitinib to cause clinical drug interactions via inhibition of these CYPs is low.

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

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

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

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

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

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

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

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

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

Table 20: IC₅₀ values for Inhibition of Human Transporters by Ruxolitinib and M18

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

NS: Not studied

NI: No inhibition at the highest concentration tested (50 μM for ruxolitinib; 3 μM for M18)

PHIP: 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine

MPP+: 1-methyl-4-phenylpyridinium

Source: Applicant's clinical pharmacology summary

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

No.

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

No expected co-medications.

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

No.

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

Not applicable.

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

No.

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

None.

2.5 General Biopharmaceutics

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

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

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

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

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

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

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

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

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

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

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

Exposure from the tablet formulation of ruxolitinib (25 mg strength) was evaluated following an overnight fast or immediately following a high-fat meal in a two period cross-over study in 12 healthy, primarily male subjects. The tablet formulation evaluated was not the to-be-marketed formulation. Administration of the 25 mg ruxolitinib tablet with a high-fat, high-calorie meal prolonging the median (range) T_{max} from 1 (0.25 - 3) to 2.5 (0.25 - 6) hours, and lowered the mean (C_{I₉₀}) C_{max} by 24% (76% (63% - 91%)) compared to fasting administration. The AUC appeared unaffected (104% (97 - 113%)). Pharmacodynamic parameters were not evaluated.

Given the C_{I₉₀} for the relative C_{max} was outside of the 80-125% equivalence criteria, a food effect can not be ruled out; however, the 24% reduction in C_{max} alone is unlikely to significantly impact efficacy (see Section 2.2.4.1). Not using the to-be-marketed formulation of Ruxolitinib is a limitation, but is acceptable given requested waivers are deemed acceptable by ONDQA in its 10/20/11 review of this NDA. Therefore, the reviewer agrees with the applicant's proposal that Ruxolitinib may be administered without regard to meals.

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

Not applicable

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

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

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

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

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

Not applicable

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

Not applicable.

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

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

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

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

2.6 Analytical Section

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

In submitted clinical studies the turbo ion spray LC/MS/MS method in the applicant's report DMB-07.111.1 was used to quantify ruxolitinib in human plasma with K₃EDTA as the anticoagulant. Ruxolitinib was extracted from 50 µL of human plasma by a liquid/liquid extraction procedure using methyl t-butyl ether (MTBE), with INCB028452 as the internal standard. The LC/MS/MS assay conditions are listed in Table 21.

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

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

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

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

Table 22: Summary of Validation Parameters for Assay DMB-07.111.1	
Parameter¹	Experimental Results
Calibration Curve ²	All of standards within ± 15% of nominal concentration
Intra-Day Accuracy	Overall Range 90.9% to 108%
Inter-Day Accuracy	Overall Range 96.3 – 100%
Intra-Day Precision	Overall Range 1.8 – 6.0%
Inter-Day Precision	Overall Range 4.7 – 7.1%
Sensitivity	Mean Conc. Range 98.1 – 106% % CV Range 2.9 – 4.6%
Selectivity	
Blank Matrix	No interference observed
Selectivity at LLOQ	%CV 2.9% with mean concentration 94.6% of nominal

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

1 The QC samples were prepared at concentrations of 1.00 (LLOQ), 3.0, 50.0, 800 and 1000. In addition, a dilution QC (QC6) was prepared at a concentration of 5000 nM

2 The calibration curve standard sample concentrations were 1.0, 2.5, 5.0, 10, 25, 50, 100, 250, 500, and 1000 nM

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

The applicant's cross validation DMB-08-151-1 using of this assay using K₂EDTA in place of K₃EDTA as the anticoagulant in human plasma ruxolitinib sample was also within these limits and deemed acceptable.

In submitted clinical studies where metabolites were evaluated the turbo ion spray LC/MS/MS method in the applicant's report DMB-10.14.1 was used to quantify ruxolitinib and selected active metabolites in human plasma with K₃EDTA as the anticoagulant. Ruxolitinib and the selected active metabolites were extracted from 100 µL of human plasma by a liquid/liquid extraction procedure using methyl t-butyl ether (MTBE), with INCB028452 as the internal standard. The LC/MS/MS assay conditions are listed in Table 23.

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

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

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

Experimental results from the validation of this bioanalytical method are listed in Appendix 4.1. This validation appears consistent with the guidance “Bioanalytical Method Validation” with the exception that 1) long-term frozen stability (653 days) of the minor metabolites INCB025257 and INCB041092 were outside $\pm 15\%$ range for % diff from day 0, 2) the extraction recovery was consistent but low for the metabolites, and 3) cross-validation was not conducted for K₂EDTA samples actually collected in the metabolite studies. Despite these limitations this validation is considered adequate for quantification of the active metabolites. The applicant’s states that concentrations of ruxolitinib in the metabolite studies that were above the limit of quantification (ULQL of 1000 nM) for DMB-10.14.1 were not reanalyzed because DMB-10.14.1 was not considered the primary assay quantification of ruxolitinib. Therefore, quantification of ruxolitinib by assay DMB-07.111.1 was used preferentially in the review of these metabolite studies.¹ The applicant did not cross validate assay DMB-10.14.1 to DMB-07.111.1.

2.6.2 Which metabolites have been selected for analysis and why?

Metabolites INCB025255 (IC₅₀= 0.43 μ M), INCB025256 (IC₅₀= 0.97 μ M), INCB025257 (IC₅₀= 1.5 μ M), INCB025258 (IC₅₀= 0.78 μ M), INCB025262 (IC₅₀= 0.66 μ M), INCB025264 (IC₅₀= 1.25 μ M), INCB027598 (IC₅₀= 1.5 μ M), and INCB041092 (IC₅₀= 1.5 μ M) are considered active based on their comparative pSTAT3 IC₅₀ to ruxolitinib (IC₅₀= 0.28 μ M). Combined these account for approximately 18% to the pharmacodynamic activity relative to ruxolitinib in healthy subjects. Active metabolites play a greater role in subjects with renal impairment (see Section 2.3.2). Therefore these eight metabolites were selected for analysis in Studies INCB 18424-138 (Healthy volunteers), INCB 18424-135 (rifampin DDI), INCB 18424-137 (hepatic impairment), INCB 18424-142 (renal impairment). Metabolites from these studies were not analyzed as part of each respective study, but rather *en masse* in a separate metabolite report. This split presentation is unorthodox and less than ideal for comprehensively reviewing the impact of metabolites on exposure and safety with the various intrinsic and extrinsic factors studied and recommending dosing adjustments. These data were ultimately deemed acceptable following extensive additional analysis by FDA.

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

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

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

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

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

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

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

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

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

2.6.4 What bioanalytical methods are used to assess concentrations?

See Section 2.6.1

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

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

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

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

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

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

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

See Section 2.6.1

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

See Section 2.6.1.³

2.6.9 What is the QC sample plan?

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

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

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

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

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

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

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

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

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

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

This ELISA method and validation are acceptable.

3 DETAILED LABELING RECOMMENDATIONS

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

4 APPENDICES

4.1 Summary of Validation Parameters for Assay DMB-10.14.1

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

1 The calibration curve standard sample concentrations were 1.0, 2.5, 5.0, 10, 25, 50, 100, 250, 500, and 1000 nM for INCB018424 and metabolites.

2 Criteria: No interference > 20% of LLOQ

3 QC concentration for Extraction Efficiency: 3.0, 50.0, 800 nM

4 Criteria: Peak area of blank ≤ 20% of mean LLOQ peak area

5 stored 391 days at 2 – 8 C.

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

4.2 Proposed labeling (Original and Annotated)

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

4.3 Consult Reviews

4.3.1 IRT

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

4.3.2 Pharmacometrics

**OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW**

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

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1 SUMMARY OF FINDINGS

1.1 Key Review Questions

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

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

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

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

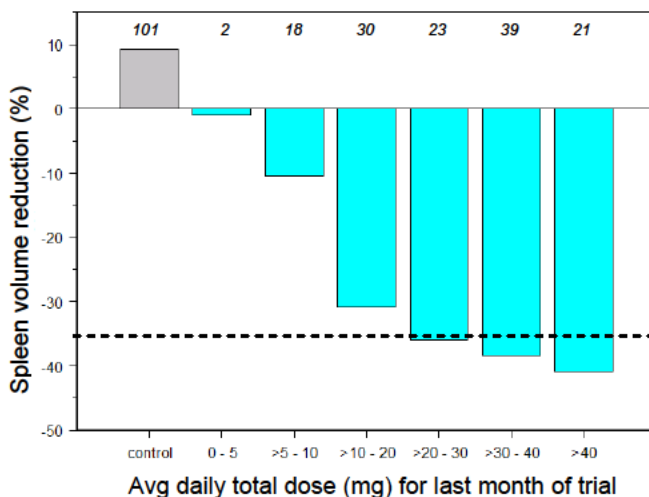


Figure 1. FDA analysis of spleen volume reduction as a function of average daily total dose for trial 351. Grey bar represents the placebo arm and the lighter grey bars represent the ruxolitinib average daily doses ranging from 0-5 mg to >40 mg. The dashed line represents the clinically relevant effect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

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

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

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

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

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

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

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

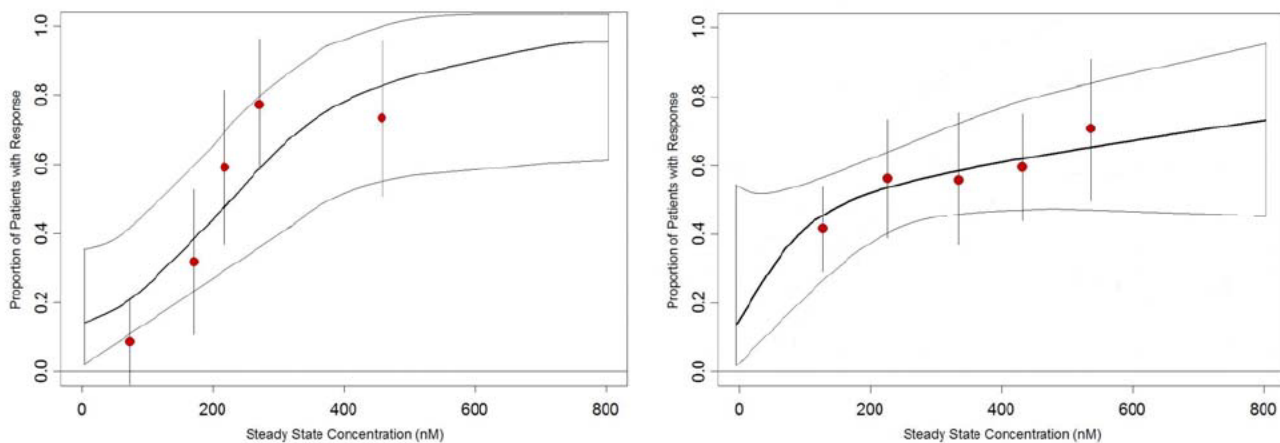


Figure 2. Proportion of patients achieving $\geq 35\%$ spleen volume reduction (left) and $\geq 50\%$ reduction in total symptom score (right) versus average steady state concentrations of ruxolitinib in trial 351. Solid round symbols represent the observed efficacy measure in each C_{ss} average quantile.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

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

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

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

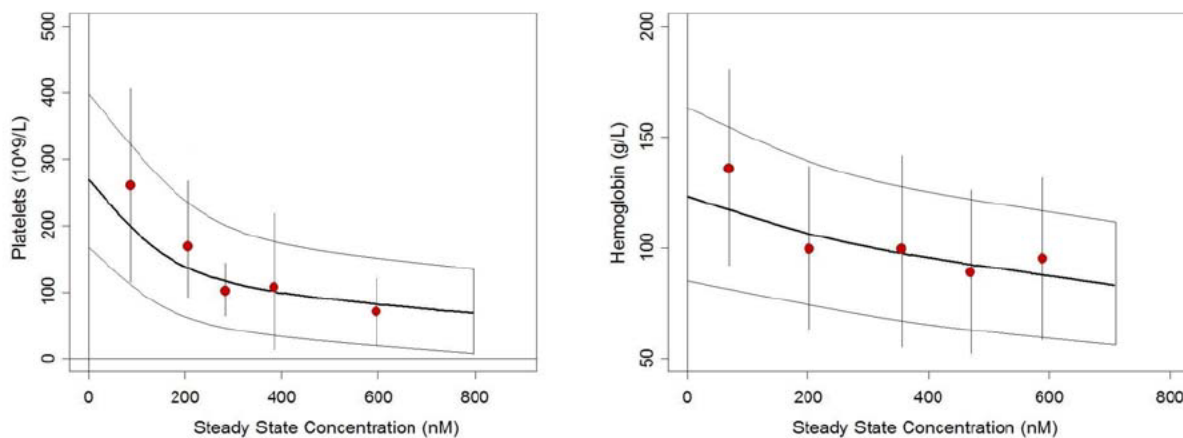


Figure 3. FDA Analysis of platelet count (left) and hemoglobin (right) versus average steady state concentrations of ruxolitinib in trial 351. Solid round symbols represent the observed efficacy measure in each C_{ss} average quantile. The vertical black bars represent the 95% confidence interval. The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

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

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

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

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

The exposure-response relationship for efficacy (i.e., SVR and TSS) and safety *does support* the recommended initial dose based on platelet count, as proposed in the label. The PK/PD model for platelet count over time was utilized to perform simulations for the continual dosing of 15 mg BID for those patients with an initial platelet count at $100 \times 10^9/L$ and 20 mg BID with an initial platelet count of $200 \times 10^9/L$ (Figure 5). On average, platelet counts were above the threshold of $50 \times 10^9/L$ for both dosing groups, further supporting the Sponsor's dosing justification for initial platelet count.

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

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

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

On the other hand, patients on average daily doses ≤ 10 mg (≤ 5 mg BID) did not yield a clinically meaningful benefit for spleen volume and total symptom score. (b) (4)

Importantly, if a patient were to be maintained at a dose of 5mg BID, a high risk of thrombocytopenia (platelet < 50 g/L) would be present with minimal, if any, benefit in spleen volume reduction and total symptom score. Using the exposure-response relationship for platelet count, simulations

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

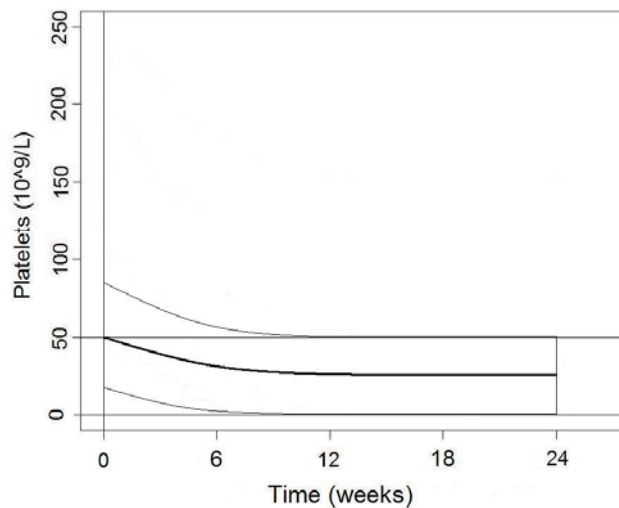


Figure 4. Simulated average platelet count over time for maintaining a starting dose of 5 mg BID for a baseline platelet count of 50 x 10⁹/L. Dark line represents model prediction along with 95% prediction interval. The minimum threshold for platelet count is denoted by the solid black line at 50 g/L.

1.2 Recommendations

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

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

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

1.3 Label Statements

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

2. DOSAGE AND ADMINISTRATION

2.2 Monitoring and Dose Modification Guidelines

(b) (4)

2 PERTINENT REGULATORY BACKGROUND

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

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Exposure-Response Analysis for Effectiveness

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

3.1.1 Data

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

3.1.2 Methods and Results

Exposure-Response Analysis for Spleen Volume:

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

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

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

Where the covariate effects on IC₅₀ were described using the following equation:

$$IC_{50j} = (414 \times (1 - JAK_j) + 206 \times JAK_j) \times (1 - 0.41 \times SEF_j)$$

Gender and JAK2V617F mutation status were both significant predictors of IC₅₀. Females exhibit a 41% reduction in IC₅₀ compared to males. No statistically significant influence was found on spleen volume for the other covariates tested.

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

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

^a %CV= percent coefficient of variation, ^b %SEM = percent standard error of the mean, ^c E_{plc} = placebo effect, ^d SD=standard deviation, ^e k_{out}=first-order spleen volume removal rate constant, ^f I_{max}= maximum fractional inhibition in spleen volume, ^g NE=not estimated, ^h IC₅₀ = C_{ss(ave)} producing 50% of maximal inhibition (nM), ⁱ JAK = Janus kinase, ^j RV=residual variability, ^k NA=not applicable.

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

Reviewer's comments:

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

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

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

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

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

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

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

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

Table 4. Parameters of the Final Indirect Response PK/PD Model for MFSAF Total Symptom Score

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

^a %CV= percent coefficient of variation, ^b %SEM = percent standard error of the mean, ^c E_{plc} = placebo effect, ^d SD=standard deviation, ^e k_{out}=first-order TSS equilibration rate constant, ^f I_{max}= maximum inhibition in TSS, ^g IC₅₀ = C_{ss(ave)} producing 50% of maximal inhibition (nM), ^h NE=not estimated, ⁱ NA=not applicable, ^j RV=residual variability.

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

Reviewer's comments:

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

3.2 Exposure-Response Analysis for Safety

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

3.2.1 Data

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

3.2.2 Methods and Results

Exposure-Response Analysis for platelet count:

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

The final population PK/PD model for the time course in platelet counts in the per protocol population was an indirect response model that characterized the effect of INCB018424 through an inhibitory $E_{\max}$ model applied to the production rate (k_{in}) of platelets. A placebo effect parameter was not incorporated into the structural PK/PD model. No covariates were found to be statistically significant predictors of platelet response. The base (and final) model for the time course of platelets is as follows:

$$\frac{dPLT}{dt} = k_{in} \times I(C_{ss}^{ave}) - k_{out} \times PLT$$
$$I(C_{ss}^{ave}) = 1 - \left(\frac{I_{max} \cdot C_{ss}^{ave}}{IC_{50} + C_{ss}^{ave}} \right)$$

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

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

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

^a %CV= percent coefficient of variation, ^b %SEM = percent standard error of the mean, ^c k_{out}=first-order platelet removal rate constant, ^d I_{max}= maximum inhibition of platelet count formation, ^e NE=not estimated, ^f IC₅₀ = C_{ss(ave)} producing 50% of maximal inhibition (nM), ^g RV=residual variability, ^h SD=standard deviation, ⁱ NA=not applicable.

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

Reviewer's comments:

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

3.3 Population PK Analysis

3.3.1 Methods

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

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

Table 6: Studies Used for the Population PK Model

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

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

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

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

3.3.2 Results

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

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

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

^a %CV = percent coefficient of variation

^b %SEM = percent standard error of the mean

^c k_a = first-order absorption rate constant

^d ALAG₁ = absorption lag time

^e NE = not estimated

^f CL/F = apparent oral clearance

^g V_c/F = apparent volume of distribution for the central compartment,

$$V_c / F_j = 58.6 \times \left(\frac{WT KG_j}{72.9} \right), \text{ where } j \text{ represents the } j\text{th subject}$$

^h V_p/F = apparent volume of distribution for the tissue (peripheral) compartment

ⁱ Q/F = apparent intercompartmental clearance

^j RV = residual variability

^k NA = not applicable

(Source: Table 16 from Sponsor's Population PK Modeling Analysis Report - dmb-11-04-1, page 65)

3.3.3 Sponsor's Conclusions

- The PK of INCB018424 are well described by a 2-compartment disposition model with first-order absorption (with an absorption lag time) and linear elimination.

- Apparent oral clearance is 22.1 L/hr and 17.7 L/hr for a typical male and female subject, respectively, with 39.1 % CV unexplained IIV.
- The apparent central volume of distribution increases linearly with respect to body weight and is 58.6 L for a typical subject weighing 72.9 kg. The remaining unexplained variability in V_c/F is 28.0 %CV. The apparent total volume of distribution at steady-state is 69.8 L for a typical subject, with 102.0 %CV unexplained IIV in the apparent peripheral volume of distribution.
- Absorption of INCB018424 is rapid, with a short absorption lag time (approximately 3 minutes) and an estimated absorption half-life of approximately 10 minutes.
- Although gender and body weight were statistically significant predictors of INCB018424 PK, the geometric mean ratios in both cases fell within 50% to 200% bounds.
- No covariates were found to be statistically significant predictors of k_a or V_p/F .
- Based upon formal covariate analysis, no notable differences were observed between subjects with varying degrees of hepatic or renal dysfunction.
- Based upon the current data and analysis methods, there is no statistically significant influence of the concomitant administration of CYP3A4 inducers, CYP3A4 inhibitors, warfarin, digoxin, or prednisone on INCB018424 PK.
- The predicted typical value of the apparent terminal elimination half-life using the parameter estimates from the final population model was 3.76 hours and 4.07 hours for male and female subjects, respectively, weighing 72.9 kg. The individual estimates of the apparent terminal elimination half-life were moderately variable with means (%CV) of 4.72 hours (64.5%) and 4.12 (41.4%) for the Phase 1/2 and Phase 3 subjects, respectively.
- The study data did not allow for a conclusive assessment of dose proportionality, although based upon the available data and the analyses performed, the PK of INCB018424 appear dose proportional for doses ranging from 10 mg to 200 mg.

Reviewer's comments on Sponsor's Population PK Analysis:

- *Reviewer's analysis showed that log-transformed data produces better goodness-of-fit. The parameter estimates (e.g. CL) are comparable between reviewer's and sponsor's analysis. Please see reviewer's analysis in Section 3 for details.*
- *The effects of both sex and body weight was further explored as covariates for PK. Inclusion of sex as a covariate for CL resulted in the reduction in the objective function value (OFV) by 42. Inclusion of body weight as covariate for CL covariates resulted in the reduction in the objective function value (OFV) by 36. By using sex or body weight as the covariate, the inter-patient variability for CL are 40% and 42%, respectively. See the section of Reviewer's analysis for details.*
- *Sponsor's population PK analysis is generally adequate and acceptable.*

4 REVIEWER'S ANALYSIS

4.1 Objectives

The reviewer's analysis objectives are:

1. to determine if the exposure-response relationship for the efficacy endpoints: spleen volume reduction and total symptom score;
2. to determine is there is exposure-response relationship for safety endpoints, platelet count and hemoglobin;
3. to determine is the exposure-response relationship for efficacy and safety supports the proposed dosing recommendations;
4. to quantify sources of inter-patient variability in INCB018424 exposure.

4.2 Methods

4.2.1 Data Sets

Data sets used are summarized in Table 8.

Table 8. Analysis Data Sets

Study Number	Name	Link to EDR
INCB 18424-351 (Study 351)	aseff3.xpt	\\Cdsub1\evsprod\NDA202192\0000\m5\datasets\incb-18424-351\listings
INCB 18424-352 (Study 352)	aseff3.xpt	\\Cdsub1\evsprod\NDA202192\0000\m5\datasets\incb-18424-352\listings
pooled PK w/ phase 2 study INCB 18424-251 (Study 251)	pk_all.xpt	\\cdsub1\EVSPROD\NDA202192\0000\m5\datasets \\cdsub1\EVSPROD\NDA202192\0000\m5\datasets\dmb-11-04-1\analysis\programs\pk
pooled PK/PD	pd2votc.xpt pd2votw.xpt pd2mfsa.xpt pd2plta.xpt	\\Cdsub1\evsprod\NDA202192\0000\m5\datasets\dmb-11-04-1\analysis\datasets

4.2.2 Software

S-PLUS, SAS and NONMEM were used for the reviewer's analyses. R 2.10.1 (www.r-project.org) was used in combination with the population PK tool library in order to generate diagnostic and pertinent covariate plots.

4.2.3 Models

For simulations, the models described in section 3.2.2 were used for both the efficacy measures (i.e., spleen volume and total symptom score) and safety measures (i.e., platelet count).

4.3 Results

4.3.1 Exposure-Response Analysis

Dose and exposure-response relationship was conducted for the reduction in spleen volume (SPV) and total symptom score (TSS) for the efficacy the pivotal trial. Safety measures, including platelet counts and hemoglobin, were also assessed for an exposure-response relationship.

For the dose-response relationship the exposure measure used was the average daily total dose for the last month of the trial. For the exposure-response relationships, the exposure measure used for the analysis was the average steady state ruxolitinib (C_{ss} average), calculated for each subject from the average daily dose and the individual estimate of apparent drug clearance derived from the population PK model.

The PK/PD model was further utilized to perform simulations for the proposed dosing of 15 mg BID for patients with platelet count between 100 and 200 $\times 10^9/L$ and 20 mg BID with an initial platelet count of $> 200 \times 10^9/L$ (Figure 5). In addition and simulation was performed evaluating 5 mg BID for those patients with low platelet counts (patients with platelet counts between 50 $\times 10^9/L$ and 100 $\times 10^9/L$) (Figure 4).

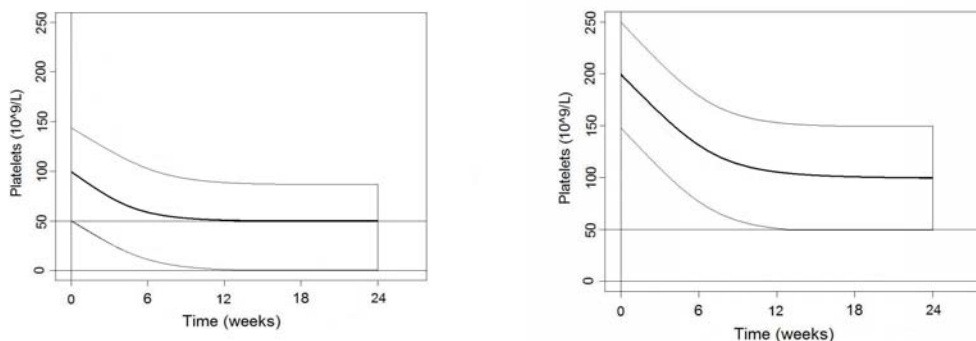


Figure 5. Simulated average platelet count over time for a maintenance dose of 15 mg (left) and 20 mg (right). Dosing varied according to baseline platelet count, and simulations

represent the worst-case scenario for the platelet range. The minimum threshold for platelet count is denoted by the solid black line at $50 \times 10^9/L$.

4.3.2 Subgroup Analysis

A differential response in spleen volume reduction was observed with sub group populations within the registration trials. Response rates in trial 351, for different population subgroups, are shown in the figure below.

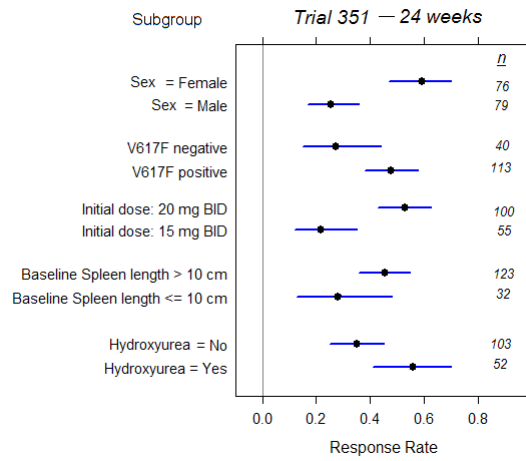


Figure 6. Forest plot evaluating the individual covariate effects on response rates in spleen size reduction for the pivotal trial.

Sex differences in response rates differed in trial 351 with females having a response rate of ~ 60% while males ~25%. Moreover, 47% of JAK2V617F mutation status positive patients were responders compared to the ~27% mutation negative patients. To further explore the response rates of sex and mutation status, simulations were performed to assess the time course of spleen volume reduction.

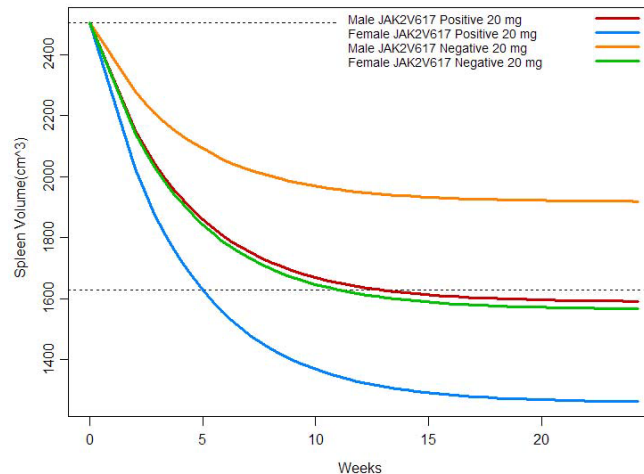


Figure 7. Simulated spleen volume vs. time for both mutation status and sex differences. Females respond more than males and mutation positive patients more than negative patients. PK differences in exposure between females and males, these differences only explain a minor portion of the overall difference in response rates between males and females, suggesting a PD difference between sexes. Based on the PK/PD model for spleen volume, IC50 for women is ~59% of that for men.

To account for these confounding factors, the proportion of subjects who achieved a $\geq 35\%$ reduction in spleen volume from baseline to last observation was analyzed using a logistic regression model, including factors such as ruxolitinib exposure (average steady state concentration), baseline spleen volume, age, prior hydroxyurea use, gender and JAK 2V617F mutation. The step-wise logistic regression analysis identified average ruxolitinib steady state concentration, as well as V617F mutation and gender, as significant predictors of response in trial 351. All factors deemed as significant were tested for interaction between the factors. No significant interactions were observed in the analysis.

Table 9. Parameter Estimates from Multivariate Logistic regression Analysis for Responders ($\geq 35\%$ spleen volume reduction)

Predictors (Reference / comparator)	Parameter Estimate	Std Error	p-value	Odds ratio	Lower 95%CI	Upper 95%CI
Sex (Female / Male)	-0.856	0.414	0.037	1.61	1.18	2.23
Age (≤ 65 / > 65)	0.42	0.391	0.643	0.791	0.215	2.74
Baseline Spleen-Volume ($\leq$ median / $>$ median)	0.000314	0.00022	0.066	1.46	1.02	2.12
Prior hydroxyurea use (No / Yes)	0.161	0.192	0.526	1.14	0.436	1.95
V617F Mutation (Positive / Negative)	-0.724	0.382	0.043	2.27	1.37	7.83
Average C _{ss} (log transformed)	3.42	0.510	0.027	4.21	1.48	9.13
<i>Sex : V617F Mutation interaction</i>	0.167	0.056	0.081			

4.3.3 Dose-response and Achieving Both Spleen Volume Reduction and Total Symptom Score

A discordance was observed with the proportion of patients who achieved both clinically relevant spleen volume reduction (SVR $\geq 35\%$) and a clinically relevant reduction in total symptom score (TSS $\geq 50\%$) (see Table 10 below). Graphical exploration of the dose-

response relation for both endpoints was performed to determine if average daily dose was a determining factor for clinically relevant achievement of both endpoints.

Table 10. Percent of Responders Who Reached Both Efficacy Endpoints

	Reduction in SVR $\geq$ 35%	Reduction in TSS $\geq$ 50%
Evaluable patients	155	148
Responders	65	68
Patients reaching both	35/65	35/68
% reaching both	54%	51%

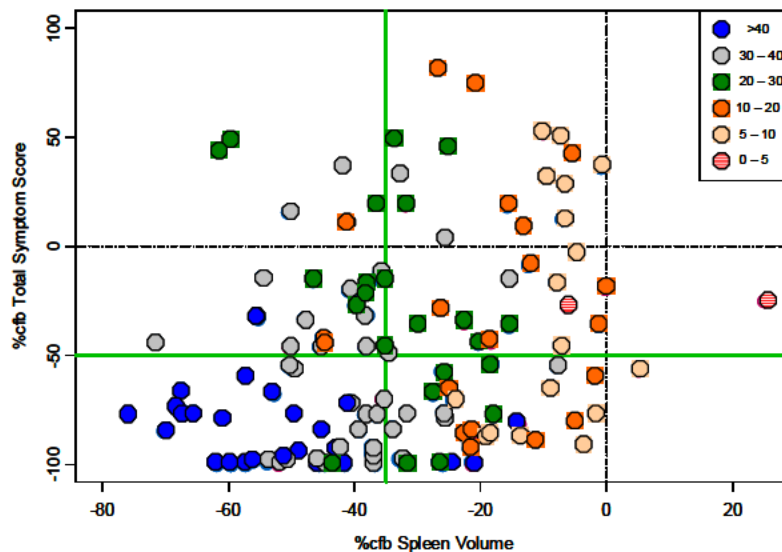


Figure 8. Individual level data for % change from baseline (cfb) in total symptom score and spleen volume reduction for all active arm patients in trial 351. The solid lines represent the clinically beneficial effect of 35% spleen volume reduction and 50% reduction in symptom score. Each individual is categorized by average total daily dose with the highest average daily total dose being 40 mg (>20 mg BID).

Table 11. Percent of Responders Who Reached Both Efficacy Endpoints in Each Average Daily Dose Group

Average daily dose (mg)	>40	>30-40	>20-30	>10-20	>5-10	0-5
% reaching both TSS and SPV	81%	39%	8%	0%	0%	0%

4.3.4 Population Pharmacokinetic Analysis

An independent analysis for population pharmacokinetics was conducted. Reviewer's analysis showed that log-transformation of the PK data improves the model fit. The difference of the parameter estimates (e.g. CL) are slightly different between reviewer's analysis and sponsor's analysis (see Table 12).

Table 12. Summary of Ruxolitinib population PK model parameter estimates.

	Fixed-Effects Parameters	Estimate	RSE(%)	CI95
1	CL/F (Clearance (L/hr))	23.1	3.506	(21.51-24.69)
2	V2/F (Central volume of distribution	59.1	2.792	(55.87-62.33)
3	Q (Q)	1.74	13.68	(1.274-2.206)
4	V3 (V3)	14.3	25.59	(7.127-21.47)
5	KA (KA)	3.56	5.421	(3.182-3.938)
6	ALAG1 (ALAG1)	0.057	4.632	(0.05183-0.06217)
7	CLFE	18.1	3.536	(16.85-19.35)
8	PROP	0.451	5.455	(0.4028-0.4992)
9				
10	Inter-Individual Variability	Estimate	RSE(%)	Shrinkage(%)
11	CL/F	40.74	5.151	9.604
12	Corr(CL-V2)	0.7297	9.051	-
13	V2/F	26.57	12.61	29.89
14	V3	125.7	31.65	-
15	KA	108.6	8.178	-
16				
17	Intra-Individual Variability	Estimate	RSE(%)	Shrinkage(%)
18	PRO	1	-	11.14

Goodness-of-fit

Goodness-of-fit plots for ruxolitinib population PK final model are shown in Figure 9 .

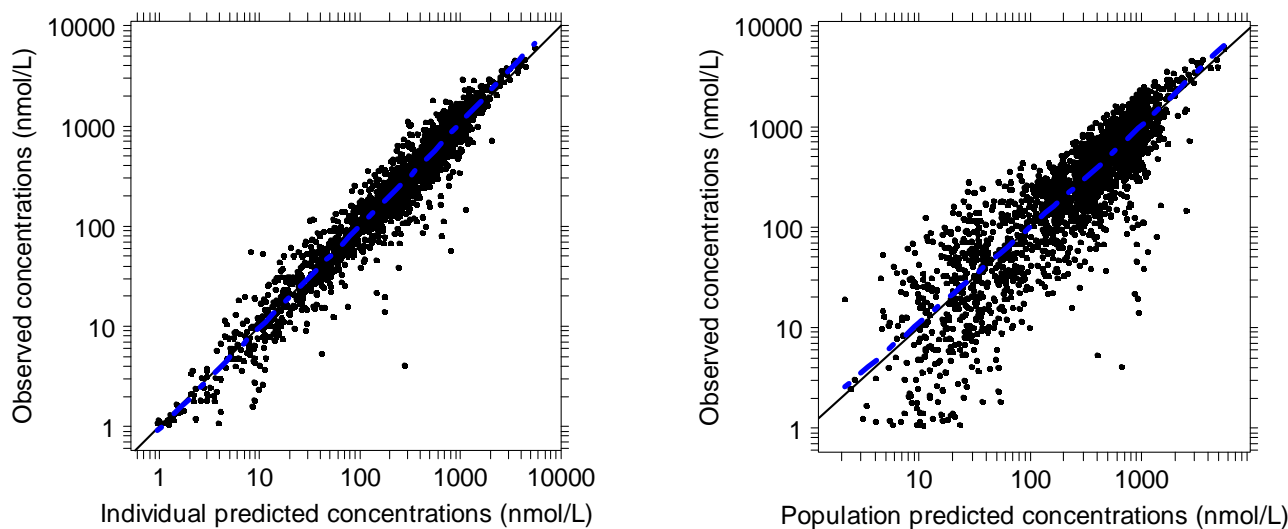


Figure 9. The goodness-of-fit graphs for Ruxolitinib population PK model

CL vs Body Weight or Sex

The effects of sex and body weight on clearance were examined by the reviewer. Inclusion of sex or body weight as covariate for clearance covariates resulted in the reduction in the objective function value (OFV) by 42 and 36, respectively (Figure 10). Sex explains ~8% of inter-subject variability on ruxolitinib clearance.

The sex difference in pharmacokinetics can be primarily explained by the difference of body weight between males and females. Males have higher body weight and lower exposure at steady state compared to female patients (Figure 11). After replacing sex with body weight in the final model, no trend was observed regarding inter-patient variability of clearance vs. sex (Figure 12). After including sex or body weight as the covariate, the inter-patient variability for clearance are 40% and 42%, respectively.

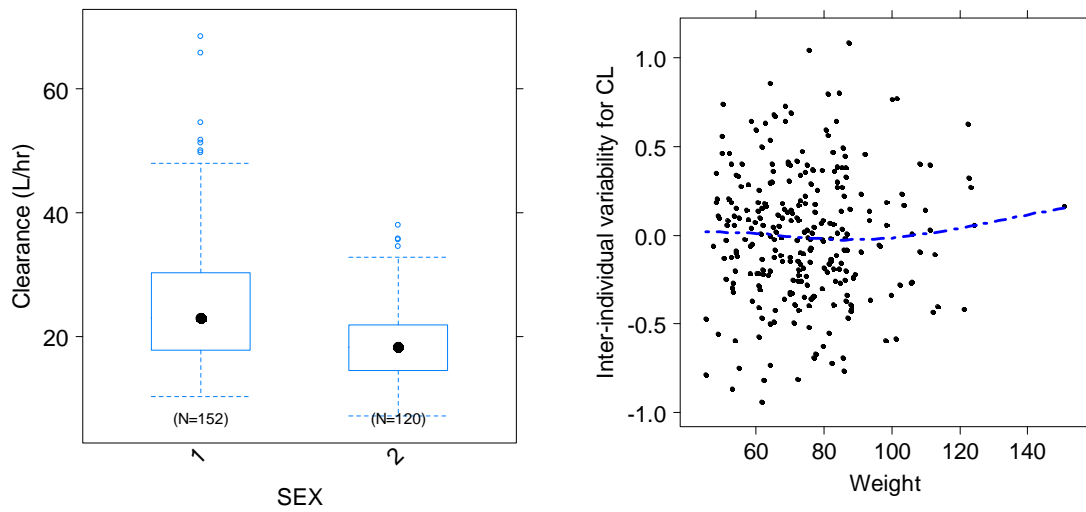


Figure 10. Plots of CL/F vs sex (left) and Inter-individual variability of CL/F vs. body weight (right) under the final model with sex as a covariate for clearance.

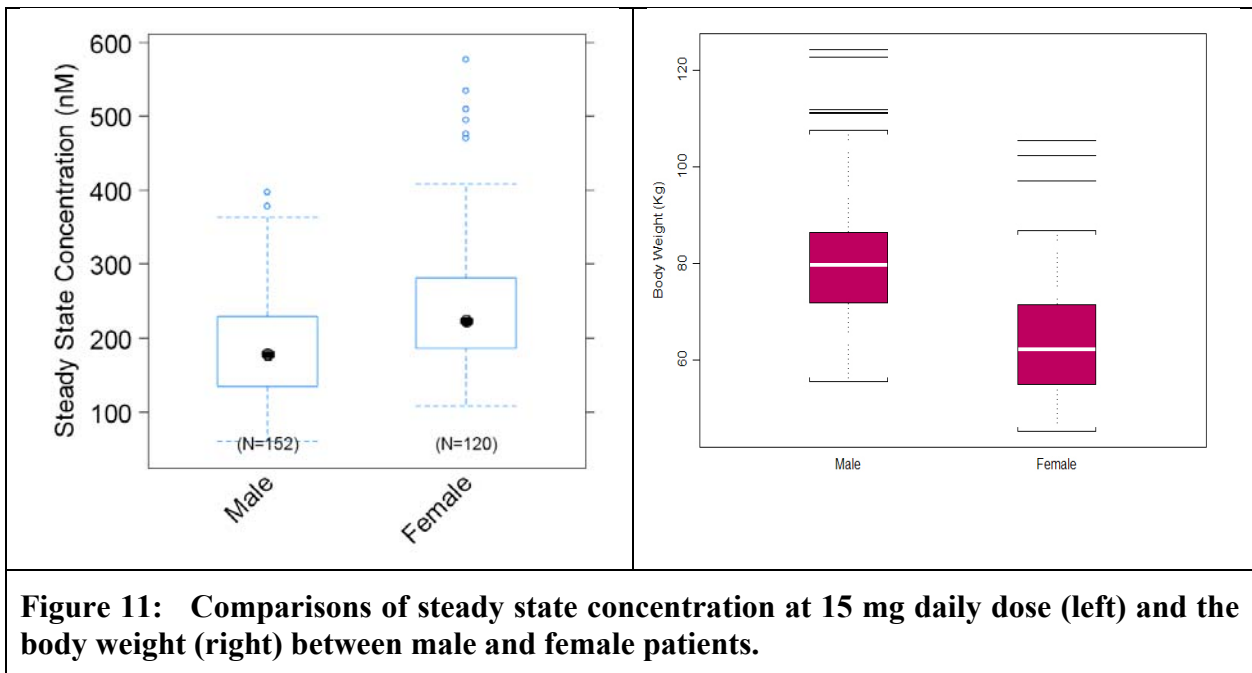


Figure 11: Comparisons of steady state concentration at 15 mg daily dose (left) and the body weight (right) between male and female patients.

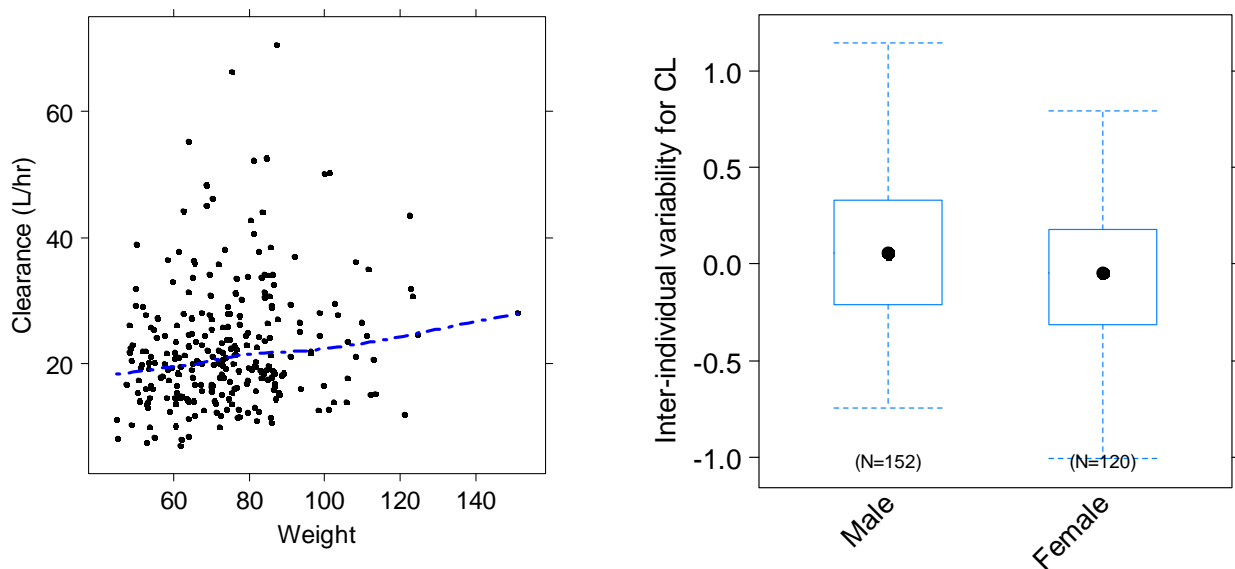


Figure 12: Plots of CL/F vs weight (left) and Inter-individual variability of CL/F vs sex (right) under the final model with body weight as a covariate for clearance.

CYP Inducers and Inhibitors

Ruxolitinib is a CYP3A4 substrate. In presence of moderate or strong CYP inhibitors, patients have a lower median CL of ruxolitinib as compared in absence of CYP inhibitors, indicating higher drug exposure are expected for patients co-administrated with moderate or strong CYP inhibitors.

A slight trend is observed between inter-individual variability on clearance and CYP inhibitors (CIH, Figure 13). Population PK results support the findings of a dedicated CYP inhibitor study where increased exposures were observed in subjects when ruxolitinib was administered in combination with ketoconazole as compared to ruxolitinib administered alone. However, caution should be taken as only one patient received a strong CYP inhibitor and the dose and the timings for the administration of inducers are unclear. A dedicated study for CYP3A4 inducers and inhibitors were conducted by the sponsor. Please see review by Dr. Joe Grillo for details.

Patients taking CYP3A4 weak and moderate inducers showed a slightly increased ruxolitinib clearance. A slight trend is observed between inter-individual variability on clearance and CYP inducers (CID, Figure 6). No strong CYP3A4 inducers are included in the PopPK analysis. A dedicated study was conducted for CYP3A4 inducers. Please see review by Dr. Joe Grillo for details.

The PopPK finding provides supportive evidence for the effects of CYP inducers on drug exposure.

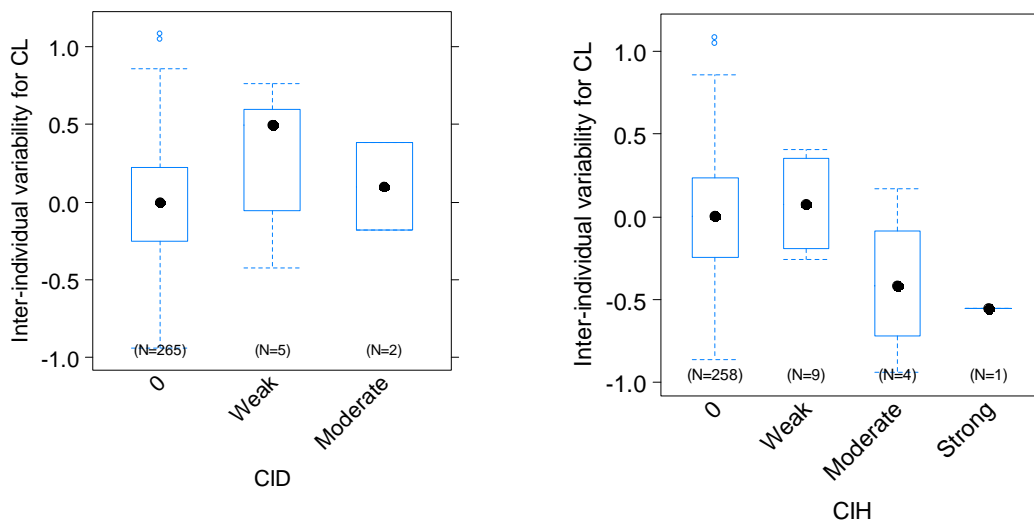


Figure 13: Inter-individual variability on clearance vs. concomitant use of CYP3A4 inducers(left) and inhibitors (right).

Renal and hepatic impairment

A slight trend is observed between inter-individual variability on clearance and renal function. Figure 14 shows that the median CL for subjects with severe renal impairment was lower (16.0 L/hr) compared to normal subjects (25.6 L/hr). Thus, a 0.6-fold increase in median dose-normalized AUC is expected for subjects with severe renal impairment. This analysis is limited because of the low patient number in the severe impairment group (N=2), but does imply that a stronger relation is likely to exist for patients with severe renal impairment and thus needs to be further explored by a dedicated study. This result provided supportive evidence for the necessity of dose adjustment for patients with renal impairments.

Boxplot of the inter-individual variability on clearance show that there is no systematic trend between inter-individual variability on clearance and hepatic function. Similarly, no trend is observed for aspartate aminotransferase (AST) or Modification of Diet in Renal Disease (MDRD) levels.

Note: *The NCI Organ Dysfunction Working Group (ODWG) criteria for hepatic impairment were used to identify subjects with varying degrees of hepatic impairment. Subjects were classified as normal (bilirubin $\leq$ 1.0 ULN and AST $\leq$ 1.0 ULN (ULN, upper limit of normal)), mild impairment B1 (bilirubin $\leq$ 1.0 ULN and AST $>$ 1.0 ULN), mild impairment B2 (bilirubin $>$ 1.0 to $\leq$ 1.5 ULN), moderate impairment (bilirubin $>$ 1.5 to $\leq$ 3 ULN) and severe impairment (bilirubin $>$ 3 ULN). The mild B1 and B1 are combined together in reviewer's covariate analysis.*

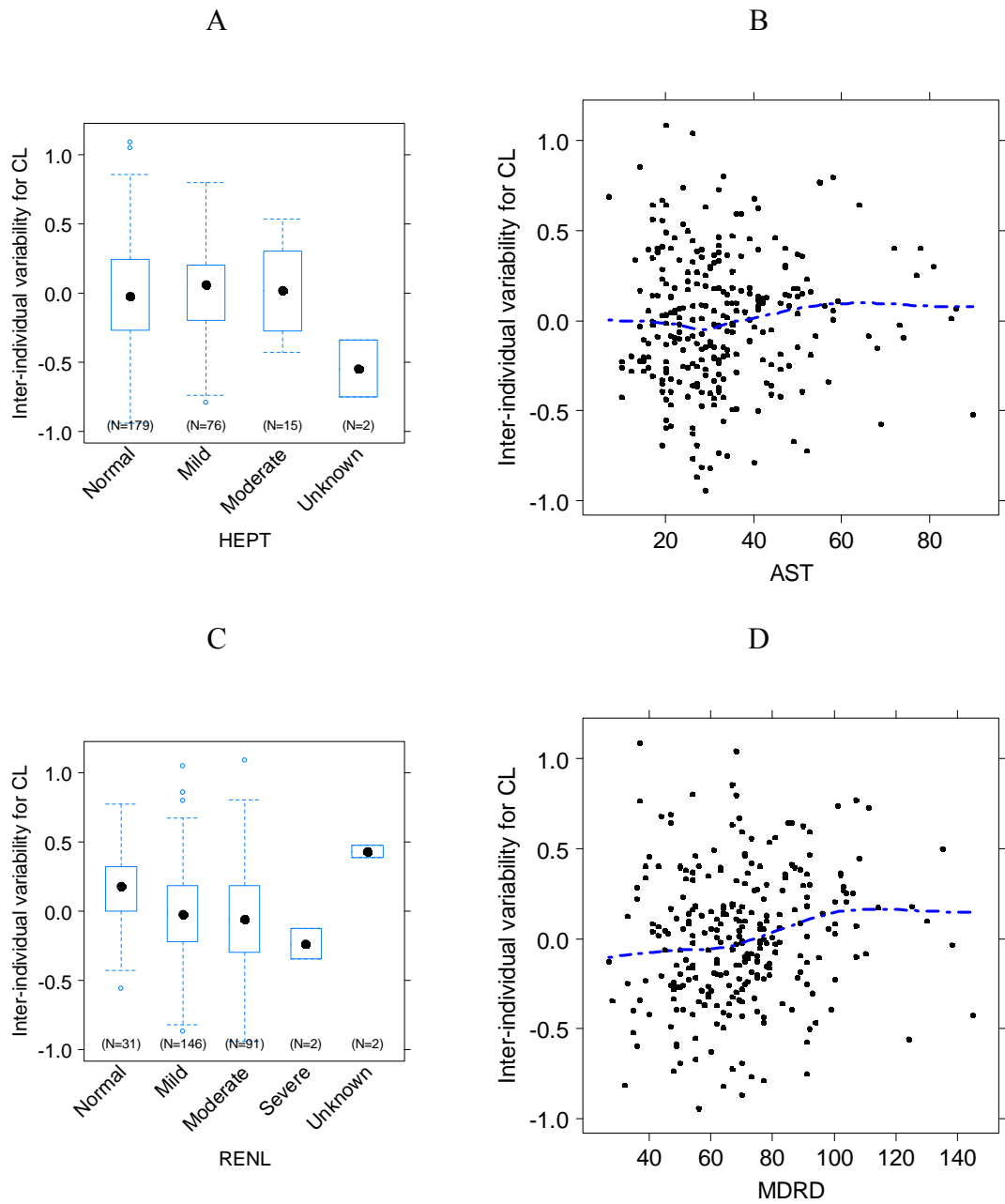


Figure 14: Plots of Inter-individual variability on clearance vs. hepatic impairment (A), AST levels (B), renal impairment (C) and MDRD levels (D)

4.4 Summary

Reviewer's summary is below:

1. *The relatively small effect of body weight on exposure does not support body-size based dosing. The exposure difference between males and females explains 26% of the difference of spleen volume reductions between male and female patients. With regard to PD, IC₅₀ for spleen volume reduction in women is ~59% of that in men. Although there are additive PK and PD differences between males and females, ruxolitinib will be titrated to a maximal dose tolerated, therefore gender-based dose adjustment is not necessary.*
2. *The exposure-response relationship for efficacy and safety does support the titration of ruxolitinib to 25 mg BID. Based on the dose-response analysis for the reduction in spleen volume the maximal effect was observed at daily doses >40 mg (>20 mg BID).*
3. *Average daily doses ≤10 mg (≤5 mg BID) did not yield a clinically meaningful benefit of 35% reduction in spleen volume. Patients maintained at a dose of 5mg BID would be at a high risk of thrombocytopenia (platelet < 50 g/L) with minimal, if any, benefit in spleen volume reduction.*
4. *Sex explains ~8% of inter-subject variability on ruxolitinib clearance. The sex difference in pharmacokinetics can be mainly explained by the difference of body weight in males and females. After including sex or body weight as the covariate, the inter-patient variability for clearance are 40% and 42%, respectively. Body weight was found to be a significant covariate for central volume of distribution (V_c).*
5. *Log-transformation of the PK data improves the model fit. The difference of the parameter estimates (e.g. clearance) are slightly different between reviewer's analysis and sponsor's analysis.*

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
platelet_ER_BINS.ssc	Exposure-response evaluation and simulations for platelet count	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews \Ruxolitinib_NDA202192_SB \ER Analyses\Platelets
SPV_ER_BINS.ssc	Exposure-response evaluation, simulations and logistic regression for Spleen volume reduction (SVR)	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews \Ruxolitinib_NDA202192_SB \ER Analyses\SpleenVol
TSS_ER_BINS.ssc	Exposure-response evaluation and simulations for Total Symptom Score (TSS)	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews \Ruxolitinib_NDA202192_SB \ER Analyses\TSS
TSS_SVR.ssc	Dose-response evaluation for SVR and TSS	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews \Ruxolitinib_NDA202192_SB \ER Analyses\TSS_SVR

4.4 Cover sheet and OCPB Filing/Review Form

**CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology			
<i>New Drug Application Filing and Review Form</i>			
<i>General Information About the Submission</i>			
NDA/BLA Number	Information	Brand Name	Information
20191	5	Jakafi	Ruxolitinib Phosphate Tablets
OCF Division (I, II, III, IV, V)	Drug Class	Generic Name	Indication(s)
Medical Division	DHP	Jakafi	Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.
OCF Reviewer	Joseph Grillo	Dose Form	Tablets
OCF Team Leader	Jake Hallock	Pharmacoformulation	Pharmacoformulation
Pharmacoformulation Reviewer	Jian Wang/ Saqib Brar	Dosing Regimen	(b) 20 mg PO bid start based on patient count then titrate to a maximum of 25 mg PO bid
Date of Submission	June 3, 2011	Route of Administration	Oral
Estimated Due Date of OCP Review	9/9/11	Sponsor	Incyte
Medical Division Due Date	9/25/11	Priority Classification	Priority (4 months)
FDUTA Due Date	10/3/11		
Clin. Pharm. and Biopharm. Information			
	"X" if included as filing	Number of studies submitted	Number of studies reviewed
STUDY TYPE			Critical Comments If any
Table of Contrast: present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
BEK Summary	X		
Labeling	X		
Reference Bioanalytical and Analytical Method	X	4	
I. Clinical Pharmacology			
Mass balance	X	1	
Enzyme characterization	X	3	
Blood/plasma ratio	X		
Plasma protein binding	X	2	
In vivo Metabolite Characterization & Quant	X	3	
Pharmacokinetics (e.g., Phase I)			
Healthy Volunteers			
single dose	X	1	
multiple dose	X	1	
Patient			
single dose			
multiple dose	X		
Dose proportionality			
fasting / non-fasting single dose	X		
fasting / non-fasting multiple dose	X		
Drug-drug interaction studies			
In vivo effects on primary drug	X	3	
In vivo effects of primary drug			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

**Best Available
Copy**

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M/CHECKLIST FOR NDA/BLA or Supplement**

In-vitro:	X	10	
Subpopulation studies -			
Weight:	X		Pop-PE
ethnicity:	X		Pop-PE
gender:	X		Pop-PE
pediatrics:			
geriatrics:	X		No PK, PD safety/efficacy
renal impairment:	X	1	
hepatic impairment:	X	1	
PD			
Phase 1:			
Phase 2/3:			
PK/PD			
Phase 1 and/or 2 proof of concept:	X	1	
Phase 3 clinical trial:	X	2	
Population Analyses			
Data rich:	X	1	
Data sparse:	X	2	
II. Biopharmaceutics			
Absolute bioavailability			
Relative bioavailability -			
solution as reference:	X		ADME not compared to tab
alternate formulation as reference:	X	1	SR for formulation
Bioequivalence studies			
traditional design: single / single dose:			
replicate design: single / single dose:			
Food-drug interaction studies	X		Part of NHV SD
Bio-waiver request based on BCS	X		2 submitted
BCS class:	X	3	
Dissolution study to evaluate alcohol induced dose dumping			
III. Other C/PB Studies			
Genotype/phenotype studies			
Chromopharmacokinetic	X		waiver
Pediatric development plan			4 submitted
Literature References	X		
ECG Monitoring	X	1	TOI
Biomarkers	X	1	pSTAT3 across studies
Immunogenicity Testing			
Metabolic activity	X	1	
Total Number of Studies		43	

On initial review of the NDA/BLA application for filing

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		Bioequivalency submitted for 1) BE for 10 mg, 15 mg, 20 mg and 25 mg tabs 2) BE of dispersed sol/susp and tabs
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			EOP2 agreement
4	Did the sponsor submit data to allow the evaluation of	X			

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	Content Parameter	Yes	No	N/A	Comment
5	the validity of the analytical assay?	X			
6	Has a rationale for dose selection been submitted?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
8	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			Some errors
9	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		Will IR
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

Reference ID: 3034751

**CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

	Content Parameter	Yes	No	N/A	Comment
	provided in this submission?				

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
— Yes —

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Please provide a complete study report and raw data set in electronic format (i.e., SAS transport files) for the Nasogastric tube study summarized in Section 1.4 of module 3 2 P 8
- Please provide a table listing the different tablet formulations used in the various human clinical studies or affirm that the to-be-marketed image was used in all studies
- (b) (4)
- Please confirm that the formulation used in the food effect sub-study in study INCB 18424-131 was the to-be-marketed formulation
- We note in both your hepatic impairment (INCB 18424-137) and renal impairment (INCB 18424-142) studies that the fraction unbound parameter was part of your PK analysis plan yet these data are not present in your report or your raw data sets. Please provide your analysis of this parameter and the respective raw data set in electronic format (i.e., SAS transport files) for each of these studies. If this information has already been submitted please provide the location in the eCTD
- Please provide the raw data set in electronic format (i.e., SAS transport files) for each of the following studies:
 - DMB-10 43 1
 - DMB-10 55 1
 - DMB-06 168 1
 - IN VITRO-11 01 1
- Please provide file definitions for the raw datasets associated with study INCB 18424-251
- Please provide the Provide Bioanalytical Report(s) for studies DMB-10 43 1 and DMB-10 55 1

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY
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- 9 We noticed that you submitted the dataset for PopPK analysis and PK/PD analyses. Please submit the each PK and PD datasets for each clinical study and the programs you used to support the individual PK analysis in each study.
- 10 In PopPK dataset, please clarify the difference regarding the coding for the following variables:
- a Variable "HEPCLS": both 2 and 3 are coded for "Mild impairment" in the Define PDF file
 - b Variable "CYPInd" both 3 and 4 are coded for "weak inducers" in the Define PDF file

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**CLINICAL PHARMACOLOGY
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Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSEPH A GRILLO
10/26/2011

JIAN WANG
10/26/2011

SATJIT S BRAR
10/26/2011

CHRISTINE E GARNETT
10/27/2011

JULIE M BULLOCK
10/27/2011
I concur

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	202-192/N-000
Submission Date:	06/03/11, 07/07/11, 09/27/11, and 10/19/11
Related IND:	77,456
Brand Name:	Jakafi
Generic Name:	Ruxolitinib Phosphate
Formulation:	Immediate release (IR) oral tablets
Strength:	5, 10, 15, 20, and 25 mg
Applicant:	Incyte
Type of submission:	Original (Priority review; 6 months)
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Background:

Ruxolitinib phosphate was developed by Incyte for the treatment of myelofibrosis. The Applicant developed 5 strengths; 5, 10, 15, 20, and 25 mg IR oral tablets. The Applicant conducted the phase 3 clinical trials using only the 5 mg tablet strength. The phase 3 formulation is the same as the to-be-marketed (TBM) formulation. The TBM tablets are uncoated (b) (4)

NDA Submission:

On 06/03/11, the Applicant submitted a new NDA 202-192 for ruxolitinib phosphate IR tablets, 5, 10, 15, 20, and 25 mg. It is a new molecular entity (NME) and the first in its class of action for the unmet medical needs. Therefore, the above NDA was designated for a priority review (6 months). On 06/29/11 and 09/16/11, requests for additional information regarding CMC and Biopharmaceutics issues were sent to the Applicant. The Applicant responded on 07/07/11 and 09/27/11, respectively.

Relevant Communications Submitted Under the IND

- **BCS Designation:** The Applicant submitted *in vitro* and *in vivo* data on 02/27/09 to IND 77,456 (SN-082) and requested the Agency's Biopharmaceutical Classification System (BCS) Class 1 designation for ruxolitinib phosphate. The Agency reviewed the data and on 07/30/09 Ruxolitinib Phosphate Tablets were classified as a BCS-Class 1 drug substance.
- **Biowaiver Requests:**
 - On 07/08/10, the Applicant submitted an amendment to IND 77,456 (SN-203) requesting a waiver for the CFR requirement to provide bioavailability (BA) data for the higher strengths, 10, 15, 20, and 25 mg, which were not tested clinically. The amendment included the supportive comparative dissolution data in three media (0.1 N HCl, pH 4.5 buffer and pH 6.8 buffer) for the 5 tablet strengths of ruxolitinib phosphate. The comparative dissolution data in three media were reviewed and found acceptable. The letter dated 11/04/10 indicated that the

Agency would formally review and provide their recommendation regarding the acceptability of the biowaiver proposal under the NDA submission.

- On 01/17/11, the Applicant submitted another amendment to their IND (SN-235) requesting a waiver for the requirement of conducting a bioequivalence (BE) study comparing the oral solution/suspension vs. the oral tablets. The amendment also included an *in vitro* study protocol designed to assess the stability and degradation of the dispersed solution/suspension. The overall information provided on 01/17/11 to support this biowaiver request and the protocol for the *in vitro* stability/degradation study was formally reviewed under the NDA.

▪ ***Proposed Dissolution Method and Acceptance Criterion:***

The proposed method and acceptance criterion for the dissolution test evaluating Ruxolitinib Phosphate tablets are shown below.

USP Apparatus: II (Paddle)
Speed: 50 rpm
Dissolution medium: 900 mL of 0.1 N HCl at 37± 0.5°C
Sampling timepoints: 10, 15, 20, 30, and 60 min
Acceptance Criterion: Q= (b)(4) at 30 min

The dissolution information/data supporting the proposed dissolution method was reviewed under the IND and the method was deemed acceptable. However, the Agency informed the Applicant that the evaluation of the overall dissolution data supporting the acceptability of the proposed acceptance criterion was a review issue under the NDA.

Biopharmaceutics Review:

Since the dissolution development report and the comparative dissolution data for the five strengths of ruxolitinib phosphate IR tablets were reviewed previously under the IND, the Biopharmaceutics review for the NDA would focus on the evaluation of the data supporting: **1)** the biowaiver requests, **2)** the proposed dissolution acceptance criterion, and **3)** the *in vitro* study evaluating the stability of ruxolitinib phosphate in oral solution after passing through the NG tubes, including the Applicant's 07/07/11 response to the Agency's 06/29/11 information request. Note that the recommendation regarding the acceptability of the stability/degradation data will be provided by the CMC reviewer.

The Applicant also included the updated 24-month stability data for the 25 mg tablet strength in the 09/27/11 submission. A teleconference was held on 10/18/11 between the Agency and the Applicant to discuss the Agency's proposed dissolution acceptance criteria. The Applicant responded on 10/19/11. These responses are reviewed here.

RECOMMENDATION

ONDQA-Biopharmaceutics has evaluated the overall information supporting the approval of this submission and has the following comments:

1. The BA waiver request for the 10, 15, 20, and 25 mg higher strengths that were not tested clinically and the waiver request for a BE study comparing the oral solution/suspension vs. the oral tablets are acceptable.
2. With respect to the dissolution acceptance criterion, the dissolution data from the bio-batch and registration stability batches clearly supported a tighter value. Therefore, the following revision for the dissolution acceptance criterion was recommended:

From Q = (b)(4) at 30 minutes
To Q = (b)(4) at 30 minutes

The updated 24-month stability data submitted on 09/27/11 also support the dissolution acceptance criterion of Q = (b)(4) at 30 minutes. On 10/18/11, the Applicant agreed to implement Q = (b)(4) at 30 minutes as the specification criterion for the dissolution test of their product at release and on 10/19/11, the Applicant submitted the revised specifications for all five strengths to Section M32P51. Therefore, the final dissolution method and acceptance criterion for Ruxolitinib Phosphate Tablets are as follow:

USP Apparatus: USP II (Paddle)
Speed: 50 rpm
Dissolution Medium: 900 mL of 0.1 N HCl at 37± 0.5°C
Final Acceptance Criterion: Q = (b)(4) at 30 minutes for release (USP <711>)

Overall Assessment:

From the Biopharmaceutics viewpoint, NDA 202-192 for Jakafi (ruxolitinib phosphate) Tablets is recommended for approval.

Tien-Mien Chen, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

10/19/11

Date

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

10/19/11

Date

CC: NDA
Tien-Mien Chen, Scott Goldie

BIOPHARMACEUTICS QUALITY ASSESSMENT

1. BACKGROUND

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAK-STAT pathway has been associated with several cancers and increased proliferation and survival of malignant cells.

Ruxolitinib is indicated for the treatment of patients with myelofibrosis, including primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF), and post-essential thrombocythemia-myelofibrosis (PET-MF). The recommended dose is (b) (4) mg twice a day (BID) to 25 mg BID.

2. CURRENT SUBMISISON

On 06/03/11, Incyte submitted NDA 202-192 for Ruxolitinib Phosphate IR tablets, 5, 10, 15, 20, and 25 mg. It is an NME and the first in its class of action for the unmet medical needs. Therefore, it was designated for priority, a 6-month time review clock.

Ruxolitinib Phosphate has been developed by Incyte for five strengths, 5, 10, 15, 20, and 25 mg IR oral tablets. The TBM formulations are uncoated (b) (4)

The Applicant conducted a phase 3 clinical trials using only the 5 mg tablet strength for the treatment of myelofibrosis. The phase 3 formulation is the same as the TBM formulation.

This NDA includes: **1)** The studies/reports that have been previously reviewed by the Biopharmaceutics team under the IND and **2)** The overall dissolution data supporting the proposed dissolution acceptance criterion, and **3)** the new data for the *in vitro* study assessing the stability and degradation of the dispersed solution/suspension.

3. PREVIOUS AMENDMENTS UNDER IND 77,456

The previous IND amendments and the Agency's responses are summarized here:

- On 02/27/09, the Applicant requested (SN-082) the BCS Class 1 designation for the ruxolitinib phosphate drug substance based on the supportive data consisting of
 - (a) solubility of API (active pharmaceutical ingredient) in different pH conditions,
 - (b) permeability in caco-2 cells,
 - (c) lack of active transporter involvement in the oral absorption,
 - (d) stability of drug substance in simulated gastric and intestinal fluid,
 - (e) rapid dissolution of 5 mg and 25 mg tablets that were used in earlier clinical studies,
 - (f) linear pharmacokinetics in healthy volunteers over a dose range of 5 mg to 200 mg administered as single doses, and
 - (g) results from a ¹⁴C mass balance study in healthy volunteers that indicated near-complete oral absorption.

- On 07/30/09, the Agency reviewed the submitted data and classified ruxolitinib phosphate as a BCS Class 1 drug substance.
- On 07/08/10, the Applicant requested (SN-203) the Agency’s feedback for a biowaiver request and the review of the *in vitro* dissolution data for the 5 tablet strengths. The comparative dissolution data showed $\geq$ (b) (4) dissolved at 15 min for all 5 tablet strengths under all three dissolution conditions (pHs of 0.1 N HCl, pH 4.5 buffer and pH 6.8 buffer).
- In the 11/04/10 Advice letter, the Agency agreed with the biowaiver proposal and informed the Applicant that the recommendation regarding the acceptability of the biowaiver request will be done under the NDA.
- On 12/22/10, the Agency further agreed that it was appropriate to submit a biowaiver request for demonstrating *in vivo* BE between the intact tablet and the dispersed solution/suspension.
- On 01/17/11, the Applicant submitted (SN-235), the biowaiver request with an *in vitro* study protocol to assess the stability and degradation of the dispersed solution/suspension.
- The above biowaiver request and the *in vitro* protocol were reviewed and the Biopharmaceutics comments were conveyed to the Applicant on 05/27/11 and the Applicant responded on 07/07/11.

4. DRUG PRODUCT FORMULATIONS

The description/composition of the TBM formulations for the five commercial tablet strengths are summarized below.

Table 1. The Description/Composition of the Commercial Formulation of Ruxolitinib Phosphate IR Tablets

Component	5 mg Tablets (mg/tablet)	10 mg Tablets (mg/tablet)	15 mg Tablets (mg/tablet)	20 mg Tablets (mg/tablet)	25 mg Tablets (mg/tablet)
Tablet Formulation	(b) (4)				
Ruxolitinib Phosphate*					
Microcrystalline Cellulose, NF					
Lactose Monohydrate, NF					
Colloidal Silicon Dioxide, NF					
Hydroxypropylcellulose, NF					
Polyvinyl Pyrrolidone, USP					
Sodium Starch Glycolate, NF					
Magnesium Stearate, NF					
(b) (4)					
Total Tablet Weight					
Tablet Shape	Round	Round	Oval	Capsule-shaped	Oval
Size	7.5 mm diam.	9.3 mm diam.	0.589 x 0.278"	0.648 x 0.291"	0.689 x 0.328"
Lot Number Tested	A53228	1399-2644RD-3B	1399-2644RD-2B	1399-2493RD-Sublot 2	1399-2612RD-18KP

(b) (4)

The formulations are (b) (4)
However, only the lowest strength, 5 mg, was tested clinically.

5. DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION

The proposed dissolution methodology and acceptance criterion for the five tablet strengths are shown below.

USP Apparatus: II (Paddle)
Speed: 50 rpm
Dissolution medium: 900 mL of 0.1 N HCl at $37 \pm 0.5^\circ\text{C}$
Sampling timepoints: 10, 15, 20, 30, and 60 min
No. of Units: 12 tablets/test
Acceptance Criterion: $Q = (b) (4)$ at 30 min

The details, the individual and mean dissolution data for all five strengths are included in Appendix 1.

Review Comments:

- 1. The data supporting the proposed dissolution test was reviewed under the IND and deemed acceptable (see Dr. Tien-Mien Chen review in DARRTS).*
- 2. With respect to the acceptance criterion, the dissolution data clearly support a tighter value. Therefore, it was recommended that the acceptance criterion be revised as follows:*

*From $Q = (b) (4)$ at 30 minutes
To $Q = (b) (4)$ at 30 minutes*

- On 10/18/11, a teleconference was held to discuss the above recommendation and they agreed to implement $Q = (b) (4)$ at 30 minutes as the specification criterion for the dissolution test of their product at release.*

6. BIOWAIVER REQUESTS

Biowaiver for Higher Strengths: To support the approval of the biowaiver request for the 10, 15, 20, and 25 higher strengths, the Applicant provided the supportive comparative dissolution profile data for the five tablet strengths in three media (0.1 N HCl, pH 4.5, and pH 6.8 using USP Apparatus 2 and 50 rpm).

Figure 1. Mean Dissolution Profiles of Ruxolitinib Phosphate IR Tablets (5 Strengths) in 0.1 N HCl Medium

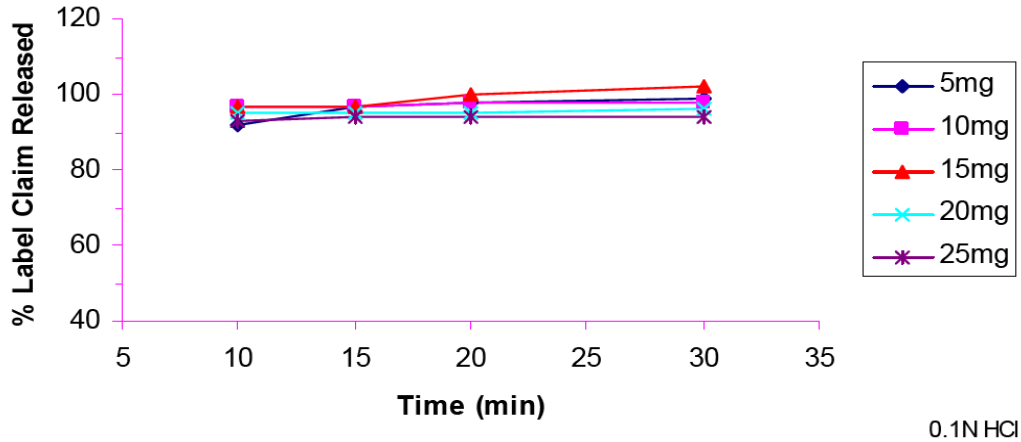


Figure 2. Mean Dissolution Profiles of Ruxolitinib Phosphate IR Tablets (5 Strengths) in pH 4.5 Buffer Medium

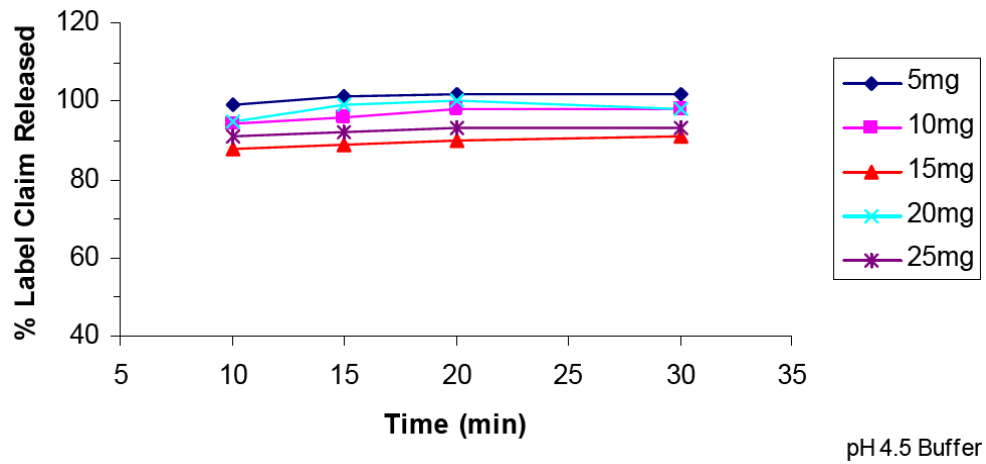
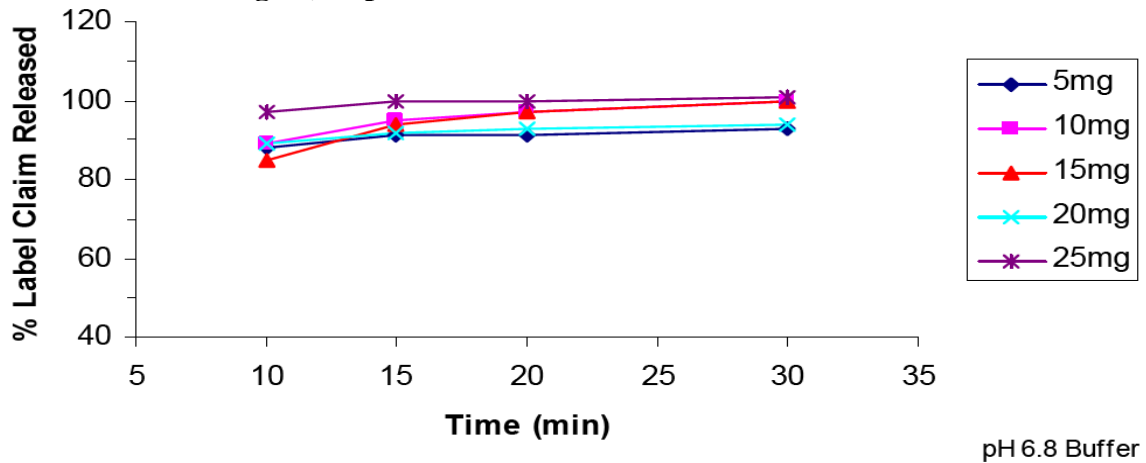


Figure 3. Mean Dissolution Profiles of Ruxolitinib Phosphate IR Tablets (5 Strengths) in pH 6.8 Buffer Medium



The above dissolution data showed $\geq 85\%$ dissolved at 15 min for all five tablet strengths under all 3 dissolution conditions (pHs of 0.1 N HCl, pH 4.5 buffer and pH 6.8 buffer).

Upon request, on 07/07/11 the following manufacturing information for the rest of the 4 strengths employed in the above dissolution testing was provided.

Table 2. The Manufacturing Information for the Above Tested Tablets in the *In Vitro* Dissolution Study

Strength (mg)	Lot Number	Manuf. Date	Manuf. Site	Blend Batch Size (kg)
10	1399-2644-RD-3B	4/28/10	(b) (4)	(b) (4)
15	1399-2644-RD-2B	4/28/10	(b) (4)	(b) (4)
20	1399-2493-RD-sublot 2	11/23/09	(b) (4)	(b) (4)
25	1399-2612-RD-18KP	3/25/10	(b) (4)	(b) (4)

Note: (b) (4)

The Applicant reported that they have been manufacturing ruxolitinib phosphate clinical supplies at (b) (4) since June 2008 (IND 77,456 SN0042, dated June 18, 2008).

Reviewer Comments:

The following issues were identified by this reviewer:

- *The four higher strengths were made at (b) (4) (a site for the phase 2 formulations).*
- *The (b) (4) is not the proposed commercial manufacturing site, DSM, (for the commercial formulation).*
- *Three out of four batches (b) (4) were manufactured (b) (4)*
- *It was also noted that for the 5 mg tablet strength, the Phase 2 formulation (No. 18424-002-00) and Phase 3/commercial formulation (No. 18424-007-00) are slightly different as shown below.*

Table 3. Composition Comparison of Ruxolitinib Phosphate 5 mg IR Tablets Formulation Nos. 18424-002-00 (Phase 2) and 18424-007-00 (Phase 3/Commercial)

Component	Formulation 18424-002-00 (mg/tablet)	Formulation 18424-007-00 (mg/tablet)
Ruxolitinib Phosphate ^a	(b) (4)	(b) (4)
Microcrystalline Cellulose, NF	(b) (4)	(b) (4)
Lactose Monohydrate, NF	(b) (4)	(b) (4)
Colloidal Silicon Dioxide, NF	(b) (4)	(b) (4)
Hydroxypropyl Cellulose, NF	(b) (4)	(b) (4)
Povidone, USP	(b) (4)	(b) (4)

Sodium Starch Glycolate, NF		(b) (4)
Magnesium Stearate, NF		
(b) (4)		
Total		

- *The Applicant, however, provided comparative dissolution data for the 5 mg tablets (Tables 4 and 5 below), demonstrating similar dissolution characteristics, i.e., ≥ 85% in 15 min and therefore, supporting the equivalence between the Phase II and Phase III formulations of the 5 mg tablets manufactured at the two different sites.*

Table 4. Dissolution Data of 5 mg Tablets of Formulation 18424-002-00 (Phase 2); Lot No. 2008H085A

Time Point (Minutes)	Lot 2008H085A	% Dissolved (0.1N HCl)	% Dissolved (pH 4.5 Buffer)	% Dissolved (pH 6.8 Buffer)
10	Mean	93	89	90
	%RSD	2.8	12.0	8.0
15	Mean	94	92	92
	%RSD	2.8	10.8	6.7
20	Mean	95	94	93
	%RSD	3.1	9.5	3.7
30	Mean	97	96	95
	%RSD	3.5	8.1	3.6

Table 5. Dissolution Data of 5 mg Tablets of Formulation 18424-007-00 (Phase 3 and Commercial); Lot No. A53228

Time Point (Minutes)	Lot A53228	% Dissolved (0.1N HCl)	% Dissolved (pH 4.5 Buffer)	% Dissolved (pH 6.8 Buffer)
10	Mean	92	99	88
	%RSD	12.0	1.8	7.2
15	Mean	97	101	91
	%RSD	5.5	1.5	5.2
20	Mean	98	102	91
	%RSD	2.4	1.3	4.7
30	Mean	99	102	93
	%RSD	1.5	1.4	3.3

- *It is also noted that the Phase 2 formulations for the four higher tablet strengths*

(b) (4)
 The comparison between the 5 and 25 mg Phase-2 tablet strengths is shown below.

Table 6. Composition of Ruxolitinib Phosphate 5 mg and 25 mg Tablets, Phase 2 Clinical Supplies

Component (mg/tablet)	Formulation # 18424-002-00 5 mg tablet	Formulation # 18424-001-00 25 mg tablet
Ruxolitinib Phosphate		(b) (4)
Microcrystalline Cellulose		
Lactose Monohydrate		
Sodium Starch Glycolate (b) (4)		
Hydroxypropyl Cellulose		
Povidone		
Colloidal Silicon Dioxide		
Magnesium Stearate (b) (4)		
Total		(b) (4)

- Since no comparative dissolution profile data between the phase 2 formulation and the Phase 3 (TBM) formulation for the 25 mg tablets were provided (to encompass the entire 5-25 mg tablet strengths range), another Information request was sent out on 09/16/11. On 09/27/11, the Applicant provided the comparative dissolution data showing the similarity of the Phase 2 and Phase 3 formulations for the 25 mg tablets below. Please see the submitted mean dissolution data and profiles in Appendix 2 for details. Finally, the issue of three out of four batches (b) (4) that were manufactured (b) (4) of a full production batch size is less of a concern.*

Figure 4. Mean Comparative Dissolution Profiles of 25 Mg Tablets; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in 0.1 N HCl Medium

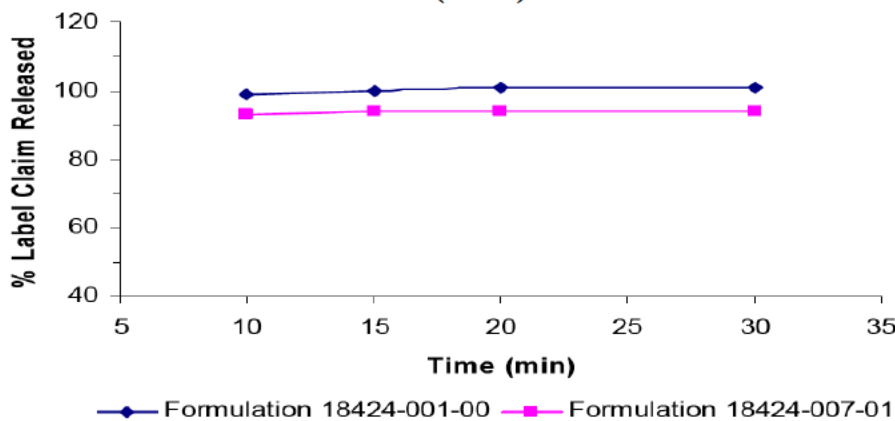


Figure 5. Mean Comparative Dissolution Profiles of 25 Mg Tablets; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in Phosphate Buffer pH 4.5 Medium

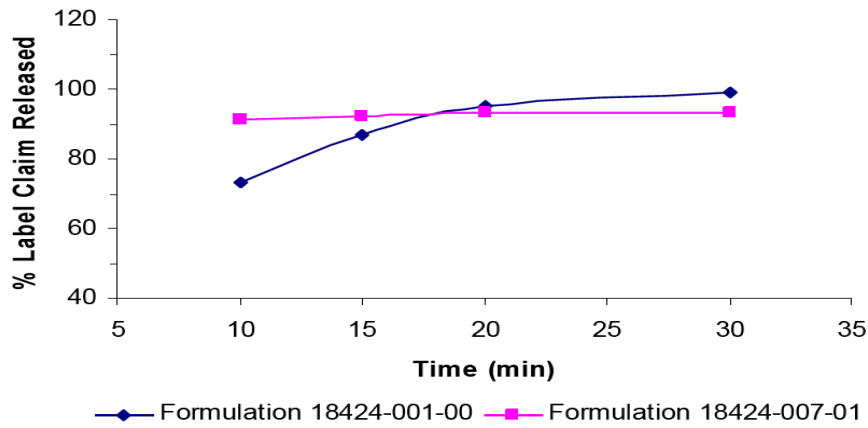
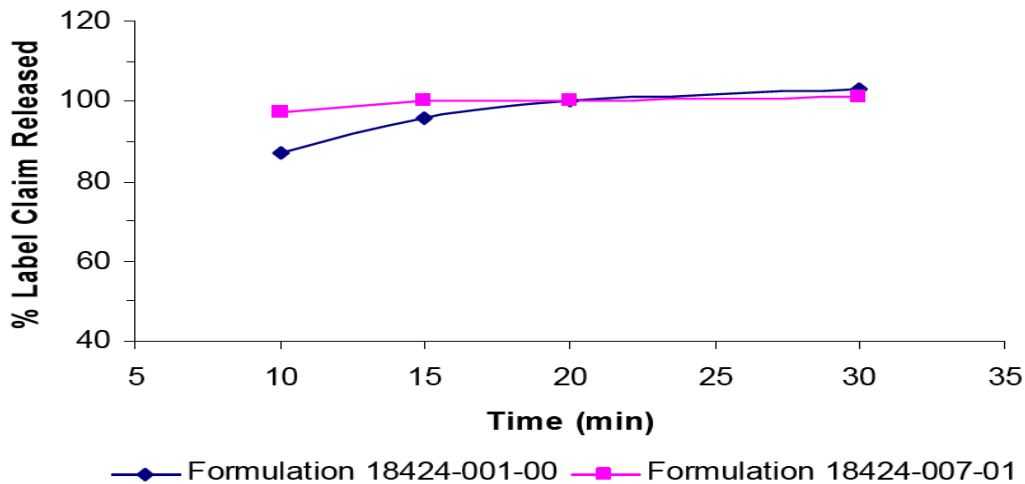


Figure 6. Mean Comparative Dissolution Profiles of 25 Mg Tablets; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in Phosphate Buffer pH 6.8 Medium



- Overall Conclusion:*** Although the above issues were identified, based on the fact that ruxolitinib phosphate has been classified as a BCS-Class 1 drug substance and the overall dissolution data support the similarity between the phase 2 and Phase 3 formulations and the fast dissolving characteristics of the product, ONDQA-Biopharmaceutics considers that the biowaiver request for Ruxolitinib 10, 15, 20, and 25 mg Tablets is appropriate and it is granted.

7. *IN VITRO* STUDY TO EVALUATE THE STABILITY and DEGRADATION OF THE DISPERSED SOLUTION/SUSPENSION

On 01/17/11, the Applicant submitted an amendment (SN-235) to the IND including: **1)** a waiver request for the requirement of conducting a bioequivalence (BE) study comparing the oral solution/suspension vs. the oral tablets, and **2)** an *in vitro* study protocol evaluating the stability and degradation of the dispersed solution/suspension. The above biowaiver request and the *in vitro* protocol were reviewed and Biopharmaceutics comments asking for additional information were conveyed to the Applicant on 05/27/11 and the Applicant responded on 07/07/11. Please see Agency's comments and the Applicant's 07/07/11 response for details.

Summary of the In Vitro Stability and Degradation Study:

The *in vitro* stability study was conducted using 6 tablets of each strength (2 tablets for each of 3 different NG tubes) at two time points, i.e., the first time point is after shaking for 10 min (immediately after tablet dispersion) and the other timepoint is upon standing for 6 hrs at ambient temperature.

The Applicant showed the above *in vitro* study results:

I. The Control Samples (After immediate preparation, at 10 min timepoint without passing through NG tubes):

Control Samples – Two control samples were prepared for both the 5 mg and 25 mg tablets produced the following results:

- The 5 mg Controls produced a mean recovery of 99.1%
- The 25 mg Controls produced a mean recovery of 98.7%

II. The NG Tube Exposure (After immediate preparation, at 10 min timepoint and after passing through NG tubes)

NG Tube Exposure – Upon exposure to three types of NasoGastric feeding tubes, two INCB018424 Phosphate Suspensions per label strength produced results as follows:

- DOBBHOFF™ (8 Fr.)
 - 5 mg suspension demonstrated a mean recovery of 92.7%
 - 25 mg suspension demonstrated a mean recovery of 95.2%
- ENTRIFLEX™ (8 Fr.)
 - 5 mg suspension demonstrated a mean recovery of 93.3%
 - 25 mg suspension demonstrated a mean recovery of 94.9%
- ARGYLE™ (18 Fr.)
 - 5 mg suspension demonstrated a mean recovery of 97.0%
 - 25 mg suspension demonstrated a mean recovery of 98.4%

III. The stability study was conducted when tablets were upon standing for 6 hrs at ambient temperature. The combined results showed the recovery results in each of the three NG tube at these two timepoints as shown below.

Tablet Sample	Recovery (% Label Claim)		
	Dobhoff Tube	Entriflex Tube	Argyle Tube
5 mg – tablet 1 ^a	(b) (4)		
5 mg – tablet 2 ^a			
5 mg – tablet 3 ^b			
5 mg – tablet 4 ^b			
Mean	93.4	93.8	97.4
%RSD	1.2	0.8	1.0
25 mg – tablet 1 ^a	(b) (4)		
25 mg – tablet 2 ^a			
25 mg – tablet 3 ^b			
25 mg – tablet 4 ^b			
Mean	95.2	94.7	98.3
%RSD	0.4	0.5	0.5

^a Initial time point (average of 2 injections)

^b 6 hour time point(average of 2 injections)

Note that the Applicant initiated the *in vitro* study on NG tubes before they received the Agency's comments requesting this *in vitro* study. ONDQA-Biopharmaceutics considers that the Applicant adequately addressed the Agency's comments and the study results and their justifications are acceptable.

For the specific details, please see the mean and individual stability/recovery data in Appendix 3 for details. Note that the recommendation regarding the acceptability of the stability/degradation data is been provided by the CMC Reviewer.

Reviewer's Comments:

- *The results for the above in vitro study on the stability of ruxolitinib phosphate in oral solution after passing through the NG tubes showed the following similarities in stability: a) Between the two timepoints (10 min and 6 hrs) and b) Between the two strengths (5 and 25 mg). The results also showed similarity in recovery after passing through the three NG tubes; a mean recovery of greater than 93% (range: 92.7 to 98.5%) was observed.*
- *Based on the BCS-Class 1 designation for ruxolitinib phosphate and the data showing stability of the dispersed solution/emulsion, the waiver request for the requirement to provide BE data comparing the dispersed solution/suspension vs. the oral tablets is acceptable.*

**NDA 202-192 (N-000) for Ruxolitinib Phosphate
IR Oral Tablets, 5, 10, 15, 20, and 25 mg**

Appendix 1

In Vitro Mean and Individual Dissolution Data

Table 1. Mean and Individual Dissolution Profiles of Ruxolitinib Phosphate IR 25 mg Tablets

Time Point	25 mg Lot# 1399-2612-RD-18 KP	(b) (4)
10 Minutes	Average	(b) (4)
	Min	
	Max	
	%RSD	
15 Minutes	Average	
	Min	
	Max	
	%RSD	
20 Minutes	Average	
	Min	
	Max	
	%RSD	
30 Minutes	Average	
	Min	
	Max	
	%RSD	

Table 2. Mean and Individual Dissolution Profiles of Ruxolitinib Phosphate IR 20 mg Tablets

Time Point	20 mg Lot# 1399-2493-RD- Sub lot-2	(b) (4)
10 Minutes	Average	(b) (4)
	Min	
	Max	
	%RSD	
15 Minutes	Average	
	Min	
	Max	
	%RSD	
20 Minutes	Average	
	Min	
	Max	
	%RSD	
30 Minutes	Average	
	Min	
	Max	
	%RSD	

Table 3. Mean and Individual Dissolution Profiles of Ruxolitinib Phosphate IR 15 mg Tablets

Time Point	15 mg Lot# 1399-2644-RD- 2B	(b) (4)	
10 Minutes	Average		(b) (4)
	Min		
	Max		
	%RSD		
15 Minutes	Average		
	Min		
	Max		
	%RSD		
20 Minutes	Average		
	Min		
	Max		
	%RSD		
30 Minutes	Average		
	Min		
	Max		
	%RSD		

Table 4. Mean and Individual Dissolution Profiles of Ruxolitinib Phosphate IR 10 mg Tablets

Time Point	10 mg Lot# 1399-2644-RD- 3B	(b) (4)	
10 Minutes	Average		(b) (4)
	Min		
	Max		
	%RSD		
15 Minutes	Average		
	Min		
	Max		
	%RSD		
20 Minutes	Average		
	Min		
	Max		
	%RSD		
30 Minutes	Average		
	Min		
	Max		
	%RSD		

Table 5. Mean and Individual Dissolution Profiles of Ruxolitinib Phosphate IR 5 mg Tablets

Time Point	10 mg Lot# 1399-2644-RD-3B	(b) (4)	
10 Minutes	Average		(b) (4)
	Min		
	Max		
	%RSD		
15 Minutes	Average		
	Min		
	Max		
	%RSD		
20 Minutes	Average		
	Min		
	Max		
	%RSD		
30 Minutes	Average		
	Min		
	Max		
	%RSD		

**NDA 202-192 (N-000) for Ruxolitinib Phosphate
IR Tablets, 5, 10, 15, 20, and 25 mg**

Appendix 2

**Mean Comparative Dissolution Data on 25 mg
Tablets Between Phase 2 and Phase 3
Formulations**

Table 1. Mean Comparative Dissolution Data of 25 Mg Tablets; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in 0.1 N HCl Medium

25 mg Tablet Strength	10 min	15 min	20 min	30 min
Phase-2 Formulation No. 18424-001-00 (Lot No. 2008H086A)	99	100	101	101
Phase-3 (TBM) Formulation No. 18424-007-01 (Lot No. 1399-2612-RD-18 KP)	93	94	94	94

Figure 1. Mean Comparative Dissolution Profiles of 25 Mg Tablets; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in 0.1 N HCl Medium

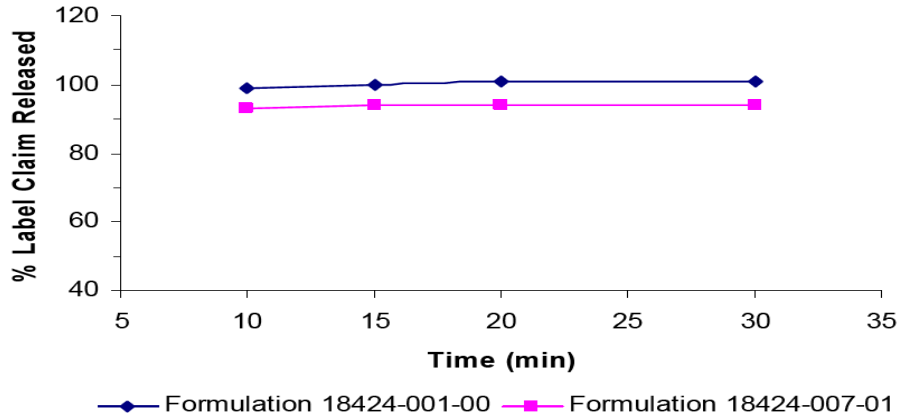


Table 2. Mean Comparative Dissolution Data of 25 Mg Tablet; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in Phosphate Buffer pH 4.5 Medium

25 mg Tablet Strength	10 min	15 min	20 min	30 min
Phase-2 Formulation No. 18424-001-00 (Lot No. 2008H086A)	73	87	95	99
Phase-3 (TBM) Formulation No. 18424-007-01 (Lot No. 1399-2612-RD-18 KP)	91	92	93	93

Figure 2. Mean Comparative Dissolution Profiles of 25 Mg Tablets; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in Phosphate Buffer pH 4.5 Medium

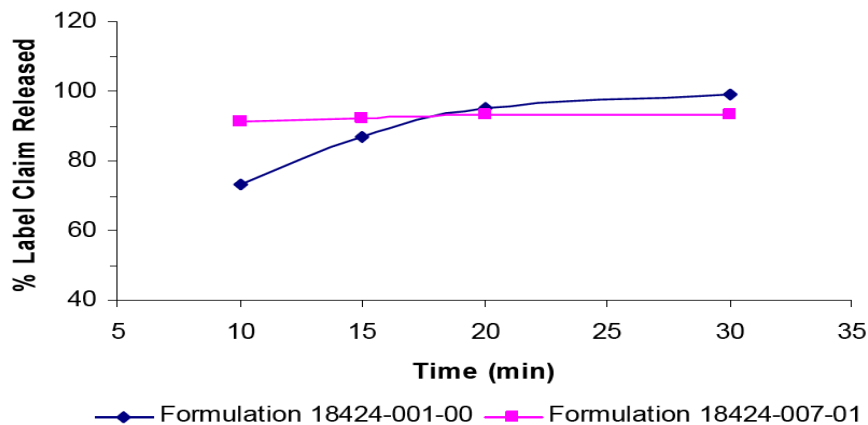
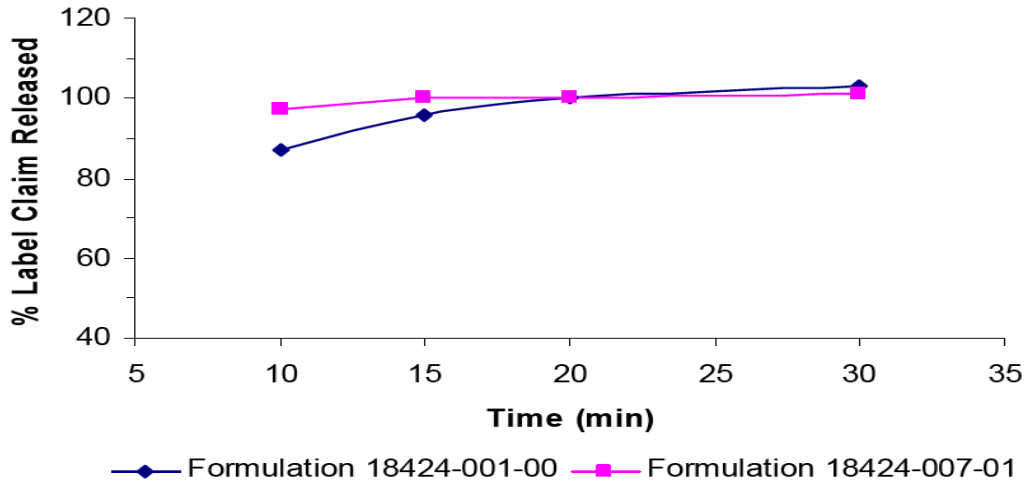


Table 3. Mean Comparative Dissolution Data of 25 Mg Tablet; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in Phosphate Buffer pH 6.8 Medium

25 mg Tablet Strength	10 min	15 min	20 min	30 min
Phase-2 Formulation No. 18424-001-00 (Lot No. 2008H086A)	87	96	100	103
Phase-3 (TBM) Formulation No. 18424-007-01 (Lot No. 1399-2612-RD-18 KP)	97	100	100	101

Figure 2-3. Mean Comparative Dissolution Profiles of 25 Mg Tablets; Phase-2 vs. Phase-3/Commercial (TBM) Formulation in Phosphate Buffer pH 6.8 Medium



**NDA 202-192 (N-000) for Ruxolitinib Phosphate
IR Tablets, 5, 10, 15, 20, and 25 mg**

Appendix 3

***In Vitro* Mean and Individual Stability/Recovery
Data on NG Tubes**

Control Samples – Two control samples were prepared for both the 5 mg and 25 mg tablets produced the following results:

- The 5 mg Controls produced a mean recovery of 99.1%
- The 25 mg Controls produced a mean recovery of 98.7%

Individual and Mean Data for Control Samples

Control Solutions: 5 mg	% Label Claim	Control Solutions: 25 mg	% Label Claim
5mg - 1	(b) (4)	25mg - 1	(b) (4)
5mg - 1		25mg - 1	
5mg - 2		25mg - 2	
5mg - 2		25mg - 2	
Mean	99.1	Mean	98.7
%RSD	0.7	%RSD	0.1

** Indicates Control Solution prepared to a final volume of 250 mL

NG Tube Exposure – Upon exposure to three types of NasoGastric feeding tubes, two INCB018424 Phosphate Suspensions per label strength produced results as follows:

- DOBBHOFF™ (8 Fr.)
 - 5 mg suspension demonstrated a mean recovery of 92.7%
 - 25 mg suspension demonstrated a mean recovery of 95.2%
- ENTRIFLEX™ (8 Fr.)
 - 5 mg suspension demonstrated a mean recovery of 93.3%
 - 25 mg suspension demonstrated a mean recovery of 94.9%
- ARGYLE™ (18 Fr.)
 - 5 mg suspension demonstrated a mean recovery of 97.0%
 - 25 mg suspension demonstrated a mean recovery of 98.4%

Nasogastric Tube Effects/Exposure on Ruxolitinib Recovery

NG Tube Effects	INJ	% Label Claim		
		Dobhoff Tube 8 Fr.	Entriflex Tube 8 Fr.	Argyle Tube 18 Fr.
5mg Sample 1	1	(b) (4)		
	2			
5mg Sample 2	1			
	2			
Mean		92.7	93.3	97.0
%RSD		0.2	0.5	1.2
25mg Sample 1	1	(b) (4)		
	2			
25mg Sample 2	1			
	2			
Mean		95.2	94.9	98.4
%RSD		0.4	0.3	0.5

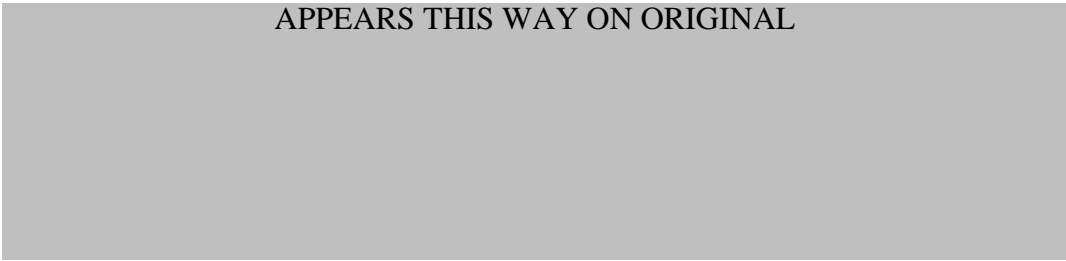
Suspension Stability - After approximately 6 hours at ambient laboratory conditions, two INCB018424 Phosphate Suspensions per label strength produced results as follows:

- DOBBHOFF™ (8 Fr.)
 - 5 mg suspension demonstrated a mean recovery of 94.1%
 - 25 mg suspension demonstrated a mean recovery of 95.0%
- ENTRIFLEX™ (8 Fr.)
 - 5 mg suspension demonstrated a mean recovery of 94.2%
 - 25 mg suspension demonstrated a mean recovery of 94.3%
- ARGYLE™ (18 Fr.)
 - 5 mg suspension demonstrated a mean recovery of 97.7%
 - 25 mg suspension demonstrated a mean recovery of 98.1%

The Recovery of the Suspension Stability Samples After 6 Hours

Suspension Stability		% Label Claim				
		INJ	Dobhoff Tube 8 Fr.	Entriflex Tube 8 Fr.	Argyle Tube 18 Fr.	
5mg Sample 1	1		(b) (4)	(b) (4)		
	2					
5mg Sample 2	1					
	2					
Mean		94.2			94.2	97.7
%RSD		1.0			0.7	0.2
25mg Sample 1	1		(b) (4)	(b) (4)		
	2					
25mg Sample 2	1					
	2					
Mean		95.0			94.3	98.1
%RSD		0.6			0.6	0.4

APPEARS THIS WAY ON ORIGINAL



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIEN MIEN CHEN
10/20/2011

ANGELICA DORANTES
10/20/2011

**CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	202192	Brand Name	Jakafi
OCP Division (I, II, III, IV, V)	5	Generic Name	Ruxolitinib Phosphate Tablets
Medical Division	DHP	Drug Class	
OCP Reviewer	Joseph Grillo	Indication(s)	Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis
OCP Team Leader	Julie Bullock	Dosage Form	Tablets
Pharmacometrics Reviewer	Jian Wang/ Satjit Brar	Dosing Regimen	(b) (4) 20 mg PO bid start based on platelet count then titrate to a maximum of 25 mg PO bid
Date of Submission	June 3, 2011	Route of Administration	Oral
Estimated Due Date of OCP Review	9/9/11	Sponsor	Incyte
Medical Division Due Date	9/23/11	Priority Classification	Priority (4 month)
PDUFA Due Date	10/3/11		

Clin. Pharm. and Biopharm. Information

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	4		
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	3		
Blood/plasma ratio:	X			
Plasma protein binding:	X	2		
In vivo Metabolite Characterization & Quant	X	3		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	1		
Patients-				
single dose:				
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	3		
In-vivo effects of primary drug:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vitro:	X	10		
Subpopulation studies -				
Weight:	X			Pop-Pk
ethnicity:	X			Pop-Pk
gender:	X			Pop-Pk
pediatrics:				
geriatrics:	X			No PK. P3 safety/efficacy
renal impairment:	X	1		
hepatic impairment:	X	1		
PD -				
Phase 1:				
Phase 2/3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:	X	2		
Population Analyses -				
Data rich:	X	1		
Data sparse:	X	2		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	X			ADME not compared to tab
alternate formulation as reference:	X	1		SR formulation
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X			Part of NHV SD
Bio-waiver request based on BCS	X			2 submitted
BCS class	X	3		
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	X			waiver
Literature References	X			4 submitted
ECG Monitoring	X	1		TQT
Biomarkers	X	1		pSTAT3 across studies
Immunogenicity Testing				
Metabolite activity	X	1		
Total Number of Studies		43		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		Biowavers submitted for 1) BE for 10 mg, 15 mg, 20 mg and 25 mg tabs 2) BE of dispersed sol/susp and tabs
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			EOP2 agreement
4	Did the sponsor submit data to allow the evaluation of	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

	Content Parameter	Yes	No	N/A	Comment
	the validity of the analytical assay?				
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			Some errors
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		Will IR
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and			X	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

	Content Parameter	Yes	No	N/A	Comment
	provided in this submission?				

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

___ Yes ___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Please provide a complete study report and raw data set in electronic format (i.e., SAS transport files) for the Nasogastric tube study summarized in Section 1.4 of module 3.2.P.8
2. Please provide a table listing the different tablet formulations used in the various human clinical studies or affirm that the to-be-marketed image was used in all studies.
3. (b) (4)
4. Please confirm that the formulation used in the food effect sub- study in study INCB 18424-131 was the to-be-marketed formulation.
5. We note in both your hepatic impairment (INCB 18424-137) and renal impairment (INCB 18424-142) studies that the fraction unbound parameter was part of your PK analysis plan yet these data are not present in your report or your raw data sets. Please provide your analysis of this parameter and the respective raw data set in electronic format (i.e., SAS transport files) for each of these studies. If this information has already been submitted please provide the location in the eCTD.
6. Please provide the raw data set in electronic format (i.e., SAS transport files) for each of the following studies:
 - a. DMB-10.43.1
 - b. DMB-10.55.1
 - c. DMB-06.168.1
 - d. IN VITRO-11.01.1
7. Please provide file definitions for the raw datasets associated with study INCB 18424-251
8. Please provide the Provide Bioanalytical Report(s) for studies DMB-10.43.1 and DMB-10.55.1

**CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

9. We noticed that you submitted the dataset for PopPK analysis and PK/PD analyses. Please submit the each PK and PD datasets for each clinical study and the programs you used to support the individual PK analysis in each study.
10. In PopPK dataset, please clarify the difference regarding the coding for the following variables:
 - a. Variable “HEPCLS”: both 2 and 3 are coded for “Mild impairment” in the Define.PDF file
 - b. Variable “CYPInd” both 3 and 4 are coded for “weak inducers” in the Define.PDF file

**CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for
NDA_BLA or Supplement 090808

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSEPH A GRILLO
07/05/2011

JULIE M BULLOCK
07/06/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202192Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 202192

PMR Description: 1838-1 Provide safety findings related to the interval of drug discontinuation in at least 75 patients previously entered on INCB-351 to determine if specific cautions are appropriate to describe discontinuation strategies.

PMR Schedule Milestones:	Final Protocol Submission:	INCB-351	
	Study/Trial Completion:	07/2009	
	Final Report Submission:	08/2012	
	Other:	10/2013	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Study INCB18424-351 and study INCB18424-352 are designed to follow patients and collect data including adverse event data for approximately 30 days after the last dose of study drug was taken after a patient was discontinued from the study. Data on patients discontinuing from ruxolitinib either from randomized treatment or after crossover to ruxolitinib from either placebo (Study -351) or best available therapy (BAT; Study -352) will be provided. Based on estimated discontinuation rates, we expect to have data for at least 70 patients who discontinued ruxolitinib by the completion date of the trials as noted above. The information regarding safety findings related to the interval of drug discontinuation will be provided in a separate report that combines this data from these studies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the post marketing study is to characterize in 150 patients from the ruxolitinib arms of the two randomized phase III studies (INCB-351 and INCB-352) the severity of symptoms of MF or splenomegaly or other adverse events accompany if the discontinuation of ruxolitinib in patients who have previously responded to the drug.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The post marketing commitment pertains to observations to be made with longer follow-up on 150 patients already entered and treated on the two randomized phase III trials INCB-351 and INCB-352, who were randomized to ruxolitinib, who responded as defined in the primary and secondary endpoints of these two trials, and then for some reason discontinued therapy.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
See answer to Question 4 above

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- X Other
See answer to Question 4 above
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Yes Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Yes Are the objectives clear from the description of the PMR/PMC?
 - Yes Has the applicant adequately justified the choice of schedule milestone dates?
 - Yes Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 202192

PMR Description: 1838-2 Provide safety findings related to the interval of drug discontinuation in at least 75 patients previously entered on INCB-352 to determine if specific cautions are appropriate to describe discontinuation strategies.

PMR Schedule Milestones:		INCB-352
	Final Protocol Submission:	05/2010
	Study/Trial Completion:	08/2012
	Final Report Submission:	10/2013
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Study INCB18424-351 and study INCB18424-352 are designed to follow patients and collect data including adverse event data for approximately 30 days after the last dose of study drug was taken after a patient was discontinued from the study. Data on patients discontinuing from ruxolitinib either from randomized treatment or after crossover to ruxolitinib from either placebo (Study -351) or best available therapy (BAT; Study -352) will be provided. Based on estimated discontinuation rates, we expect to have data for at least 150 patients who discontinued ruxolitinib by the completion date of both of the trials. The information regarding safety findings related to the interval of drug discontinuation will be provided in a separate report that combines this data from these studies.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the post marketing study is to characterize in 150 patients from the ruxolitinib arms of the two randomized phase III studies (INCB-351 and INCB-352) the severity of symptoms of MF or splenomegaly or other adverse events accompany if the discontinuation of ruxolitinib in patients who have previously responded to the drug.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The post marketing commitment pertains to observations to be made with longer follow-up on 150 patients already entered and treated on the two randomized phase III trials INCB-351 and INCB-352, who were randomized to ruxolitinib, who responded as defined in the primary and secondary endpoints of these two trials, and then for some reason discontinued therapy.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
See answer to Question 4 above

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - X Other
See answer to Question 4 above
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Yes Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Yes Are the objectives clear from the description of the PMR/PMC?
 - Yes Has the applicant adequately justified the choice of schedule milestone dates?
 - Yes Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*
-

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 202192

PMR Description:

1838-3 Collect and analyze safety information on myelosuppression for up to 144 weeks of therapy following randomization in the patients entered on INCB-351 who are continuing on therapy past 24 weeks.

PMR Schedule Milestones:

INCB-351
Final Protocol Submission: 07/2009
Study/Trial Completion: 03/2013
Final Report Submission: 12/2013
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Study INCB18424-351 and Study INCB18424-352 are currently designed to continue until the last patient remaining on study has completed the 144-week visit and the follow-up visit which occurs approximately 28 days later. We will continue to collect safety information on myelosuppression including laboratory evaluations of RBC, Hgb, platelets, WBC, and ANC as specified in the respective protocols through the completion of the studies. The projected study completion dates for Studies INCB18424-351 and INCB 18424-352 are 3/2013 and 12/2012, respectively. The final reports for both trials will be submitted by 8/2013. The final report submission providing additional safety information on myelosuppression from both trials will be by 08/2013.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the proposed PMR is to provide long term (up to 144 weeks following randomization) follow-up evaluation of patients with MF who were entered into the phase III randomized trials (INCB-351 and INCB-352), randomized to the ruxolitinib arm and to either the placebo or BAT arms, and have been chronically exposed to ruxolitinib therapy, in order to ascertain if long term administration has any consequences for production of red cells, white cells or platelets by the bone marrow.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMR will provide long term (up to 144 weeks following randomization) follow-up evaluation of patients with MF who were entered into the phase III randomized trials (INCB-351 and INCB-352), randomized to the ruxolitinib arm and to either the placebo or BAT arms, and have been chronically exposed to ruxolitinib therapy, in order to ascertain if long term administration has any consequences for production of red cells, white cells or platelets by the bone marrow.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
See answer to question 4 above

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - Yes Other
See answer to question 4 above
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Yes Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Yes Are the objectives clear from the description of the PMR/PMC?
 - Yes Has the applicant adequately justified the choice of schedule milestone dates?
 - Yes Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 202192

PMR Description:

1838-4 Collect and analyze safety information on myelosuppression for up to 144 weeks of therapy following randomization in the patients entered on INCB-352 who are continuing on therapy past 48 weeks.

PMR Schedule Milestones:

INCB-352
Final Protocol Submission: 05/2010
Study/Trial Completion: 03/2013
Final Report Submission: 12/2013
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Study INCB18424-351 and Study INCB18424-352 are currently designed to continue until the last patient remaining on study has completed the 144-week visit and the follow-up visit which occurs approximately 28 days later. We will continue to collect safety information on myelosuppression including laboratory evaluations of RBC, Hgb, platelets, WBC, and ANC as specified in the respective protocols through the completion of the studies. The projected study completion dates for Studies INCB18424-351 and INCB 18424-352 are 3/2013 and 12/2012, respectively. The final reports for both trials will be submitted by 8/2013. The final report submission providing additional safety information on myelosuppression from both trials will be by 08/2013.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the proposed PMR is to provide long term (up to 144 weeks following randomization) follow-up evaluation of patients with MF who were entered into the phase III randomized trials (INCB-351 and INCB-352), randomized to the ruxolitinib arm and to either the placebo or BAT arms, and have been chronically exposed to ruxolitinib therapy, in order to ascertain if long term administration has any consequences for production of red cells, white cells or platelets by the bone marrow.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This PMR will provide long term (up to 144 weeks following randomization) follow-up evaluation of patients with MF who were entered into the phase III randomized trials (INCB-351 and INCB-352), randomized to the ruxolitinib arm and to either the placebo or BAT arms, and have been chronically exposed to ruxolitinib therapy, in order to ascertain if long term administration has any consequences for production of red cells, white cells or platelets by the bone marrow.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
See answer to question 4 above

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - Yes Other
See answer to question 4 above
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Yes Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Yes Are the objectives clear from the description of the PMR/PMC?
 - Yes Has the applicant adequately justified the choice of schedule milestone dates?
 - Yes Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 202192

PMC Description: 1838-5 Provide longer-term efficacy and safety outcomes of current clinical trial INCB-351 to provide at least 3 year follow-up data.

PMC Schedule Milestones:	Final Protocol Submission:	INCB-351 07/2009
	Study/Trial Completion:	08/2013
	Final Report Submission:	08/2014
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Study INCB18424-351 and Study INCB18424-352 are currently designed to continue until the last patient remaining on study has completed the 144-week visit and the follow-up visit which occurs approximately 28 days later (approximately 3 years). We will continue to collect both safety and efficacy data as specified in the respective protocols through completion of the studies. The projected study completion dates for Studies INCB18424-351 and INCB 18424-352 are 3/2013 and 12/2012, respectively. The final report submission with longer-term efficacy and safety outcomes data from both studies is planned for 08/2013.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the PMC proposed is to follow each patient already entered onto the ruxolitinib or the comparator (placebo or BAT) arms of randomized phase III trials INCB-351 and INCB-352 for up to 3 years after randomization in order to collect both safety and efficacy data as specified in the protocols and to then make a final report of the findings by 08/2013.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study proposed in the PMC is to follow each patient already entered onto the ruxolitinib or the comparator (placebo or BAT) arms of randomized phase III trials INCB-351 and INCB-352 for up to 3 years after randomization in order to collect both safety and efficacy data as specified in the protocols and to then make a final report of the findings by 08/2013.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Trial is in progress

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - Yes Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Yes Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Yes Are the objectives clear from the description of the PMR/PMC?
 - Yes Has the applicant adequately justified the choice of schedule milestone dates?
 - Yes Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA #/Product Name: 202192

PMC Description: 1838-6 Provide longer-term efficacy and safety outcomes of current clinical trial INCB-352 to provide at least 3 year follow-up data.

PMC Schedule Milestones:	Final Protocol Submission:	INCB-352 05/2010
	Study/Trial Completion:	08/2013
	Final Report Submission:	08/2014
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Study INCB18424-351 and Study INCB18424-352 are currently designed to continue until the last patient remaining on study has completed the 144-week visit and the follow-up visit which occurs approximately 28 days later (approximately 3 years). We will continue to collect both safety and efficacy data as specified in the respective protocols through completion of the studies. The projected study completion dates for Studies INCB18424-351 and INCB 18424-352 are 3/2013 and 12/2012, respectively. The final report submission with longer-term efficacy and safety outcomes data from both studies is planned for 08/2013.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the PMC proposed is to follow each patient already entered onto the ruxolitinib or the comparator (placebo or BAT) arms of randomized phase III trials INCB-351 and INCB-352 for up to 3 years after randomization in order to collect both safety and efficacy data as specified in the protocols and to then make a final report of the findings by 08/2013.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study proposed in the PMC is to follow each patient already entered onto the ruxolitinib or the comparator (placebo or BAT) arms of randomized phase III trials INCB-351 and INCB-352 for up to 3 years after randomization in order to collect both safety and efficacy data as specified in the protocols and to then make a final report of the findings by 08/2013.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Yes Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Yes Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Yes Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Yes Are the objectives clear from the description of the PMR/PMC?
 - Yes Has the applicant adequately justified the choice of schedule milestone dates?
 - Yes Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY C BAIRD
11/15/2011

ROBERT C KANE
11/15/2011

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 202192

Name of Drug: Jakafi (ruxolitinib) Tablets

Applicant: Incyte Corporation

Labeling Reviewed

Submission Date: 6/3/2011

Receipt Date: 6/3/2011

Background and Summary Description

NDA 202192 provides for the treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

Conclusions/Recommendations

No deficiencies were identified in the review of this labeling.

Regulatory Project Manager

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY C BAIRD
11/09/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 202192 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Jakafi Established/Proper Name: ruxolitinib Dosage Form: Tablets Strengths: 5, 10, 15, 20, and 25 mg		
Applicant: Incyte Corporation Agent for Applicant (if applicable):		
Date of Application: June 3, 2011 Date of Receipt: June 3, 2011 Date clock started after UN:		
PDUFA Goal Date: December 3, 2011	Action Goal Date (if different):	
Filing Date: 8/2/2011	Date of Filing Meeting: 7/5/2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of patients with myelofibrosis, including thrombocythemia myelofibrosis.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☒ Fast Track ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 077456				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>		X		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required																			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears																			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].																				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>																				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm		X																		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	X			

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>		X		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			QT/IRT
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 11/3/2010 for Clinical and CMC <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): 9/2/2010 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 5, 2011

BLA/NDA/Supp #: 202192

PROPRIETARY NAME: Jakafi

ESTABLISHED/PROPER NAME: ruxolitinib

DOSAGE FORM/STRENGTH: tablets

APPLICANT: Incyte Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Amy Baird	Y
	CPMS/TL:	Janet Jamison	N
Cross-Discipline Team Leader (CDTL)	Edvardas Kaminskas, MD		
Clinical	Reviewer:	Albert Deisseroth, MD	Y
	TL:	Edvardas Kaminskas, MD	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Joseph Grillo, PhD Christine Garnett, PhD Jian Wang, PhD	Y
	TL:	Julie Bullock, PhD	Y
Biostatistics	Reviewer:	Hong Lu, PhD	Y
	TL:	Mark Rothmann, PhD	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wei Chen, PhD	Y
	TL:	Haleh Saber, PhD	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Sue Ching Lin, PhD Joyce Crich, PhD Anne Marie Russell, PhD	N
	TL:	Janice Brown, PhD	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Anthony Orenca, MD	N
	TL:	Tejashri Purohit-Sheth, MD Lauren Iacono-Connors	N
OSE/DMEPA (proprietary name)	Reviewer:	Sue Kang, PhD	N
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

APPEARS THIS WAY ON ORIGINAL

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? If yes, list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? If no, explain:	☐ YES ☐ NO
• Electronic Submission comments List comments:	☐ Not Applicable
CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? Comments: <i>If no, for an original NME or BLA application, include the reason. For example:</i> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	
• Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology (for sterile products)</u> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority:	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> ☐ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY C BAIRD
11/09/2011

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301 796 8930) or refer to OCP's intranet page <http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm>.

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center:

Division:

Mail Code: HF

Consulting Reviewer Name: Robert Becker, MD

Building/Room #: WO66, Room 5674

Phone #: 301 796 5450

Fax #:

Email Address: robertl.becker@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: Division of Hematology Products

Mail Code: HFD 160

Requesting Reviewer Name: Albert Deisseroth, MD

Building/Room #: WO22, Room 6187

Phone #: 301 796 4864

Fax #: 301 796 9845

Email Address: albert.deisseroth@fda.hhs.gov

RPM/CSO Name and Mail Code: Amy Baird, WO22, Room 1223, HFD-160

Requesting Reviewer's Concurring

Supervisor's Name: Edvardas Kaminskas, MD

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 10-25-11

Requested Completion Date: 10-31-11

Submission/Application Number: 202192
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: 6-3-11

Official Submission Due Date: 12-3-11

Name of Product:

Name of Firm:

Intended Use:

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Documents to be returned to Requesting Reviewer? Yes No

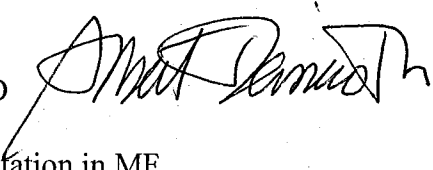
Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review Collaborative Review

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF HEMATOLOGY PRODUCTS

DATE: October 25, 2011

FROM: Albert Deisseroth MD, PhD 

SUBJECT: Assay for V617F JAK2 mutation in MF

TO: Dr. Robert Becker, CDRH

THROUGH: Edvardas Kaminskas, M.D., Deputy Division Director (Acting)

Introduction:

The Division of Hematology Products of the Office of Oncology and Hematological Products of OND CDER is in the final stages of reviewing NDA 202192 which proposes an ATP mimetic, ruxolitinib, which at nanomolar concentrations partially inhibits JAK2 by competitively inhibiting the binding of ATP to the catalytic site of JAK2. An activating mutation of JAK2 has been found in 50% of patients with MF.

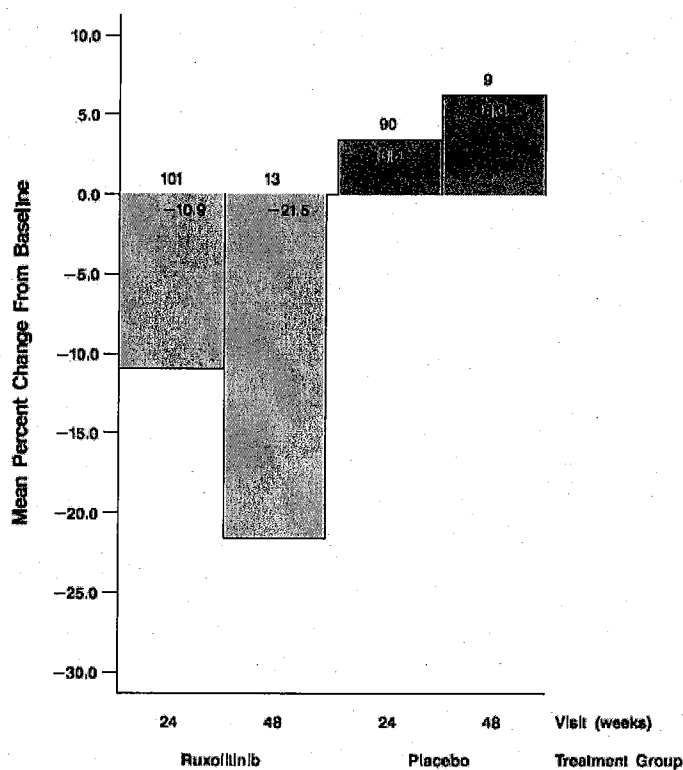
Background on the JAK2 V617F Mutation in MF (page 136 CSR INCB-351)

Recent studies have shown that an activating mutation resulting in a valine to phenylalanine substitution at residue 617 (V617F) in the pseudokinase domain of JAK2 enzyme is present in a high proportion of patients with MPNs.³³ Over expression of JAK2 V617F confers interleukin-3 (IL-3) independence to Ba/F3 cells that co-express a homodimeric type I cytokine receptor, such as the erythropoietin receptor. Transplantation of JAK2 V617F-over expressing hematopoietic cells into mice is sufficient to recapitulate some aspects of MPN disease phenotype, including increased hematocrit, splenomegaly, and decreased survival. In MPN patients, JAK2V617F mutated genotype as well as V617F allele burden (as determined by quantitative PCR) are variably associated with unique hematologic and clinical characteristics of MPNs.³⁴ In addition, following therapy with pegylated interferon in PV patients, no correlation between molecular responses as evidenced by decreased V617F allele burden and hematological responses were noted,³⁵ suggesting that V617F allele burden changes have limited utility to predict clinical response in MPNs.

Analysis of the Percentage of Peripheral Blood White Cells Positive for the V617F JAK2 Mutation at Baseline, and at 24, and 48 Weeks of Ruxolitinib Therapy (page 136 of the CSR for INCB-351):

Nonetheless, given the importance of the JAK2 V617F mutation in MPNs, the percentage of JAK2 V617F mutant allele relative to total JAK2 (wild type JAK2 plus JAK2 V617F, referred to as JAK2V617F allele burden) was assessed in this study to determine what effect, if any, JAK 1/2 inhibition had on JAK2 V617F allele burden. JAK2 V617F allele burden was measured in whole blood at Baseline and Weeks 24 and 48. As shown in Figure 22 (See below), subjects in the ruxolitinib group have a mean percent decrease at Weeks 24 and 48, whereas subjects in the placebo group have mean percent increases at both time points. For subjects in the ruxolitinib group, there was a mean percent change from V617F Baseline values of -10.9% at Week 24 (n = 101, p < 0.0001 from the rank test) and -21.5% at Week 48 (n=13, p = 0.0002 from the rank test). This is in contrast to a mean percent change from V617F Baseline values of 3.5% in the placebo group at Week 24 (n = 90, p=0.0179 from the rank test) and a non-statistically significant change in mean percent change from V617F Baseline of 6.3% at Week 48 in the placebo group (n = 9).

Figure 22 (page 137 CSR INCB 18424-351): Mean Percent Change From Baseline in Percent V617F at Weeks 24 and 48 (Observed Cases)



References on Assay for Percentage of V317F in Patients with MF

33. Guglielmelli, P et al. Identification of patients with poorer survival in primary myelofibrosis based on the burden of JAK2V617F mutated allele. *Blood*. 2009;114(8):1477-83.
- 34 Vannucchi AM et al. Clinical correlates of JAK2V617F presence or allele burden in myeloproliferative neoplasms: a critical reappraisal. *Leukemia*. 2008;22(7):1299–1307.
- 35 Kiladjian JJ et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. *Blood*. 2008;112(8):3065-72.

Statement of Problem for Dr. Robert Becker's Comment:

About 78% of the patients entered into the two randomized controlled trials of the effects of ruxolitinib treatment on patients with MF on which the marketing application for ruxolitinib for MF is based were V617F positive (therefore 22% negative). Text books usually say that the percentage of patients with MF who are positive for the V617F JAK2 mutation is 50%, and homozygosity for this mutation is found in 13% of patients with MF. A mutation of the transmembrane domain of the thrombopoietin receptor (MPLW5515) has been found in 9% of patients for MF who are negative for V617F. 30% of the patients with MF positive for the MPLW515 mutation are also positive for the JAK2 V617F mutation. Patients with MF who are negative for the JAK2 V617F and MPLW515 mutations still exhibit clonal hematopoiesis suggesting the presence of other yet undiscovered mutations that play a role in the development of MF. Many authorities feel that the clinical presentation and natural histories of patients with MF who are positive or negative for the V617F mutation are similar. It is known also that the hematopoiesis is clonal in both the V617F positive and negative patients. The phosphorylated STAT3 levels are elevated in both the V617F positive and negative patients.

The company's exploratory subgroup analysis (using quantitative PCR-see the attached Blood paper of Guglielmelli-reference 33 above) of the response to ruxolitinib in the patients positive for V617F vs those negative for V617F showed that the point estimates (based upon binomial exact method) of the percent of patients showing $\geq 35\%$ reduction in spleen volume by MRI or CAT scans was 48% in the V617F positive group and 25% in the V617F negative group (95% confidence intervals of the two groups overlapped-see page 139, Figure 23, CSR INCB-351). The company's position is that the clinical presentations, natural history of disease, and response to therapy for the V617F positive and negative

patients are indistinguishable. The company is seeking an indication for ruxolitinib in the treatment of MF irrespective of the presence or absence of the V617F mutation.

Question for Dr. Robert Becker: Given the high likelihood that there are other JAK2 mutations and mutations in other proteins which are upstream of STAT3 which are being missed or not detected by the Guglielmelli quantitative PCR assay, that could produce the symptoms of MF, Dr. Richard Pazdur wanted Dr. Becker's opinion of what requirements or commitments the FDA should be asking of the Sponsoring company (INCYTE) to work with CDRH on validating the assay they are using for the detection of V617F and for attempting to identify the other mutations upstream of STAT3 that may be playing a role in the development of MF.

blood

2009 114: 1477-1483
Prepublished online June 23, 2009;
doi:10.1182/blood-2009-04-216044

Identification of patients with poorer survival in primary myelofibrosis based on the burden of *JAK2V617F* mutated allele

Paola Guglielmelli, Giovanni Barosi, Giorgina Specchia, Alessandro Rambaldi, Francesco Lo Coco, Elisabetta Antonioli, Lisa Pieri, Alessandro Pancrazzi, Vanessa Ponziani, Federica Delaini, Giovanni Longo, Emanuele Ammatuna, Vincenzo Liso, Alberto Bosi, Tiziano Barbui and Alessandro M. Vannucchi

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/s/

AMY C BAIRD
10/25/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Label and Labeling Review

Date: October 28, 2011

Reviewer(s): Lissa C. Owens, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Carlos Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Drug Name & Strength(s): Jakafi (Ruxolitinib) Tablets
5 mg, 10 mg, 15 mg, 20 mg, and 25 mg

Application Type/Number: NDA 202192

Applicant/sponsor: Incyte Corporation

OSE RCM #: 2011-2319

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review responds to a request from the Division of Hematology Products for a review of the revised Jakafi (Ruxolitinib) Tablets 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg labels submitted on October 20, 2011 in response to the Division of Medication Error Prevention and Analysis's (DMEPA) previous comments to the Applicant. DMEPA reviewed the initial proposed label and labeling under OSE RCM #2011-2319 dated October 11, 2011.

2 MATERIALS REVIEWED

The revised label and labeling submitted on October 20, 2011 and the OSE review #2011-2319 were evaluated to assess whether the revisions adequately addresses our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised label and labeling submitted by the Applicant adequately addresses our concerns from a medication error perspective. We do not have any additional comments at this time.

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

4 REFERENCES

OSE Review #2011-2319, Label and Labeling Review for Jakafi (Ruxolitinib) Tablets 5 mg, 10 mg, 15 mg, 20 mg, 25 mg. Owens, Lissa. October 11, 2011.

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/s/

LISSA C OWENS
10/28/2011

CARLOS M MENA-GRILLASCA
10/28/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: October 27, 2011

To: Ann T. Farrell, MD, Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Medical Policy Programs

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): Jakafi (ruxolitinib)

Dosage Form and Route: Tablets, for oral administration

Application Type/Number: NDA 202192

Applicant: Incyte Corporation

OSE RCM #: 2011-3200

1 INTRODUCTION

This review is written in response to a request by the Division of Hematology Products (DHP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert for Jakafi (ruxolitinib) tablets.

On June 3, 2011, Incyte Corporation submitted original New Drug Application (NDA) 202192 for Jakafi (ruxolitinib) tablets. The proposed indication is for the treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. (b) (4)

2 MATERIAL REVIEWED

- Draft Jakafi (ruxolitinib) tablets, for oral administration Patient Package Insert (PPI) received on June 3, 2011 and revised by the review division throughout the current review cycle and received by DMPP on October 20, 2011.
- Draft Jakafi (ruxolitinib) tablets, for oral administration Prescribing Information (PI) received June 3, 2011, revised by the review division throughout the current review cycle and received by DMPP on October 20, 2011.

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. In our review of the PPI the target reading level is at or below an 8th grade 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 APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- 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 meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.

- Our annotated versions of the PPI are appended to this memo. Consult DMPP 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/

LATONIA M FORD
10/27/2011

LASHAWN M GRIFFITHS
10/27/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Direct-to-Consumer Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 27, 2011
To: Amy Baird, Regulatory Health Project Manager, DHP
From: Adora Ndu, Regulatory Review Officer, DDTCP
Subject: NDA 202192
DDTCP comments for JAKAFI™ (Ruxolitinib)
Patient Package Insert

On June 20 2011, DDTCP received a consult request from DHP to review the proposed Patient Package Insert for JAKAFI™ (Ruxolitinib).

DDTCP has reviewed the proposed label using the version of the draft PPI entitled "Ruxolitinib FDA Proposed labeling v9" and offers the following comments.

If you have any questions on the patient labeling, please contact Adora Ndu at 301-796-5114 or adora.ndu@fda.hhs.gov.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ADORA E NDU
10/27/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: 10/19/2011

To: Amy Baird, Regulatory Project Manager
Division of Hematology Products

From: James Dvorsky, Regulatory Reviewer
Division of Professional Promotion

Subject: Comments on draft labeling (Package Insert) for NDA 202192,
Ruxolitinib

In response to your labeling consult request on June 20, 2011, we have reviewed the draft Package Insert for Ruxolitinib and offer the following comments. Note that these comments are based upon the October 18, 2011 version of the label.

Section	Statement	Comment
14. Clinical Studies	(b) (4)	We do not consider this secondary endpoint substantial evidence to support promotional claims. This information could be this could be misleading in a promotional context. In addition, there were multiple other secondary endpoints not presented in the PI, thus for consistency, we recommend removing the analysis of this endpoint from the PI. However, if this section is determined essential and is retained, it is recommended to revise the title and description of Table 5. The table only presents the number (%) of patients with ≥ 50% improvement in total symptom score. The title and

		description imply that change from baseline and mean changes are presented, when this information was deleted from a previous version of the labeling.

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/s/

JAMES S DVORSKY
10/19/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: October 11, 2011

Reviewer(s): Lissa C. Owens, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Carlos Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name & Strength(s): Jakafi (Ruxolitinib) Tablets
5 mg, 10 mg, 15 mg, 20 mg, and 25 mg

Application Type/Number: NDA 202192

Applicant/sponsor: Incyte Corporation

OSE RCM #: 2011-2319

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container labels for Jakafi (NDA 202192) for areas of vulnerability that can lead to medication errors.

1.1 PRODUCT INFORMATION

Jakafi is an inhibitor of the Janus kinase family of protein tyrosine kinases (JAK's) that is used in the treatment of myelofibrosis. The recommended starting dose is dependent on platelet count starting at either 15 mg twice daily or 20 mg twice daily with dose adjustments in 5 mg twice daily increments. The maximum daily dose recommended is 50 mg (25 mg twice daily). In patients taking concomitant potent CYP3A4 inhibitors Jakafi is dosed once a day. In patients with hepatic impairment a 25% to 50% dose reduction is recommended. Jakafi will be available in the following strengths:

- 5 mg round white tablets with "INCY" on one side and "5" on the other
- 10 mg round white tablets with "INCY" on one side and "10" on the other
- 15 mg oval white tablets "INCY" on one side and "15" on the other
- 20 mg capsule-shaped white tablets with "INCY" on one side and "20" on the other
- 25 mg oval white tablets with "INCY" on one side and "25" on the other

Jakafi will be supplied in 60-count bottles to be stored at (b) (4) excursions permitted to 15° to 30°C (59° to 86°F).

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 29, 2011 – Images included in Appendix A
- Prescribing Information submitted June 3, 2011 – No image

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

The following section describes the deficiencies identified in our assessment of the labels and labeling.

3.1 CONTAINER LABELS

- a. The established name does not appear to be ½ the size of the proprietary name.
- b. The manner in which the established name and strength are expressed is inconsistent. While the strength of the ruxolitinib phosphate component is expressed as the base, the established name is expressed as a salt.
- c. The Rx Only statement competes in prominence with more relevant information, such as the established name.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels are vulnerable to confusion that could lead to medication errors. We advise the following recommendations be implemented prior to approval.

Container Label

1. Ensure the size of the established name is at least half as large as the letters comprising the proprietary name and has a prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10 (g)(2).
2. Revise the presentation of the established name to read “(Ruxolitinib) Tablets”. As currently presented as the salt form is inconsistent with the presentation of the strength statement in the base form.
3. Decrease the prominence of the ‘TM’ next to the proprietary name by using a smaller font.
4. Decrease the prominence of the color block that appears below the strength to allow for implementation of comment 1.
5. Decrease the prominence of the “Rx only” statement by un-bolding and using a smaller font.
6. Revise the storage conditions statement to read “20° to 25°C (68° to 77°F)”.
7. Revise the statement (b) (4) to read “Usual Dosage: See Prescribing Information”

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

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/s/

LISSA C OWENS
10/11/2011

CARLOS M MENA-GRILLASCA
10/11/2011

CAROL A HOLQUIST
10/11/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 15, 2011

TO: Amy Baird, Regulatory Project Manager
Albert Deisseroth, MD, Medical Officer
Division of Hematology Products

FROM: Anthony Orenca, MD, FACP
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations (*formerly* Division of Scientific Investigations)

THROUGH: Lauren Iacono-Connors, PhD
Acting Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Jean Mulinde, MD
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202192

APPLICANT: Incyte Corporation

DRUG: ruxolitinib

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority (accelerated four-month review)

INDICATIONS: For treatment of primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF) and post-essential thrombocythemia-myelofibrosis (PET-MF) (b) (4)

CONSULTATION REQUEST DATE: June 20, 2011

DIVISION ACTION GOAL DATE: October 4, 2011

PDUFA DATE: December 3, 2011

I. BACKGROUND:

Myelofibrosis (MF) may present as a *de novo* disorder (primary myelofibrosis [PMF]), or evolve from other myeloproliferative neoplasms, and can be termed either secondary MF, post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF). No drugs are approved in the United States for the treatment of MF. Hydroxyurea, androgens, prednisone, erythropoiesis-stimulating agents, and danazol have been variably used frequently with measurable effect in a few subjects. Busulfan, melphalan, and 2-chlorodeoxyadenosine, have been used in hydroxyurea-refractory subjects. Splenectomy and splenic irradiation are also performed to control spleen size; however, these measures lead to perioperative complications (up to 30%) and fatal outcomes (up to 10%). In addition, allogeneic stem cell transplantation provides a curative option although transplant-related mortality is reported in 22-27% of patients, and not a viable option for subjects greater than 60 years old.

Janus kinases (JAK) play an important role in hematopoietic cytokine receptor signaling by activating a number of signal transducers and activators of transcription (STATs) which regulate genes implicated in the proliferation and survival of malignant cells. While multiple JAK pathway abnormalities have been identified, JAK2 somatic mutations are present in approximately 55-65% of PMF and PET-MF patients, and approximately 96% of PPV-MF patients. JAK inhibitors, such as ruxolitinib, represent potential therapeutic agents.

The Applicant submitted results from Study INCB 18424-351 to support the approval of ruxolitinib for the treatment of primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF) (b) (4).

Protocol INCB 18424-351 (a.k.a. Study 351):

Study 351 was a randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ruxolitinib to placebo in subjects with PMF, PPV-MF, or PET-MF. Subjects were randomized to receive ruxolitinib or matching placebo tablets. The starting dose was determined based on baseline platelet count. Subjects with baseline platelet count greater than 200,000 per microliter began a dose regimen of 20 mg twice daily. The primary endpoint was the proportion of subjects achieving at least 35% reduction from baseline in spleen volume at Week 24 as measured by MRI (or CT scan in applicable subjects).

This product is a new molecular entity. Verification of data submitted in support of the requested new indication is considered essential by the review division. Two domestic clinical investigator sites and the sponsor were inspected in support of this application.

II. RESULTS (by protocol/site):

Name of CI/ Inspected Entity	City, State	Protocol/ Study Site	Insp. Date	EIR Received Date	Final Classification
Jason Gotlib, M.D.	Stanford, CA	Protocol INCB 18424-351 Site #23	8/15-8/25, 2011	Pending	Pending (Preliminary: NAI)
Carole B. Miller, M.D.	Baltimore, MD	Protocol INCB 18424-351 Site #46	7/25- 7/29, 2011	Pending	Pending (Preliminary: NAI)
Incyte Corporation	Wilmington, DE	SPONSOR	8/15- 8/19, 2011	Pending	Pending (Preliminary: NAI)

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Preliminary= The Establishment Inspection Report (EIR) has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATOR INSPECTIONS**1. Jason Gotlib, M.D./Site #23**

Stanford Cancer Center
875 Blake Wilbur Drive, Clinic C
Stanford, CA 95405

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from August 15-25, 2011.

A total of 19 subjects were screened, 15 were randomized and completed the study. There was no under-reporting of serious adverse events noted. An audit of records for 17 randomized study subjects was conducted.

During the inspection the following documents were evaluated: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings.

No discrepancies were noted. In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued.

d. Assessment of data integrity:

The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

2. Carole B. Miller, M.D./Site #46

St. Agnes Health Care, Inc.
900 Caton Avenue
Baltimore, MD 21229

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from July 25-29, 2011.

A total of 8 subjects were screened, randomized, and completed the study. There was no under-reporting of serious adverse events noted. An audit of all enrolled study subjects was conducted.

During the inspection the following documents were evaluated: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. Limitations of inspection

None.

c. General observations/commentary

The inspection revealed that the study was conducted adequately. Source documents, for all of the subjects that were enrolled and randomized, were verified against the case report forms and patient line listings. No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices.

d. Assessment of data integrity:

The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

SPONSOR INSPECTION**3. Incyte Corporation**

Rt. 141 & Henry Clay Road
Wilmington, Delaware 19880

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.810, from August 15-19, 2011.

Documents related to site #23 (Jason Gotlib, M.D.) and site #46 (Carole Miller, M.D.), were focused on during the inspection. During the inspection the following items were evaluated: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed FDA forms 1572, monitoring reports, drug accountability records, and training of clinical site staff and site monitors.

b. Limitations of inspection

None.

c. General observations/commentary

The Sponsor maintained adequate oversight of the clinical trial. There were no noncompliant sites and monitoring of the investigator sites was considered adequate.

No salient issues were identified. There was no evidence of under-reporting of adverse events.

d. Assessment of data integrity:

The study appears to have been conducted adequately, and the data submitted by this sponsor appear acceptable in support of the respective indication.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As part of the PDUFA-related inspections two U.S. clinical investigator sites and the Sponsor were inspected in support of this application, for Protocol INCB 18424-351. The inspections documented general adherence to Good Clinical Practices and applicable regulations governing the conduct of clinical investigations. Preliminary classifications for all three inspections conducted are No Action Indicated (NAI). The data submitted for Study INCB 18424-351 are considered reliable in support of the application.

Note: Observations noted above, for the two clinical sites and Sponsor are based on the preliminary communications from the field investigators; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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Jean Mulinde, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
09/16/2011

LAUREN C IACONO-CONNORS
09/16/2011

JEAN M MULINDE
09/16/2011

Executive CAC

Date of Meeting: September 13, 2011

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
William Taylor, Ph.D., DTOP, Alternate Member
Haleh Saber, Ph.D., DHOT, Team Leader
Wei Chen, Ph.D., DHOT, Presenting Reviewer

Author of Draft: Wei Chen

NDA 202-192

Drug Name: ruxolitinib phosphate

Sponsor: Incyte Corporation

Background: Ruxolitinib phosphate, a new molecular entity, is a small molecule inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs). A topical cream formulation of ruxolitinib phosphate is under investigation for the treatment of psoriasis (IND 77,101). Ruxolitinib phosphate capsules have been developed for the treatment of rheumatoid arthritis (IND 77,455) and myeloproliferative disorders (IND 77,456). ^{(b) (4)}
^{(b) (4)} With this NDA, the sponsor is submitting the results of a 6-month Tg.rasH2 mouse carcinogenicity study. A two-year oral rat carcinogenicity study with ruxolitinib is ongoing.

Tg.rasH2 Mouse Carcinogenicity Study

Carcinogenic assessment in Tg.rasH2 mice was conducted with daily oral (gavage) doses of 0 (0.5% methylcellulose), and 15, 45, 125 mg/kg/day ruxolitinib, in accordance with the Committee's dosing recommendation. Urethane at 1000 mg/kg was used as the positive control. An MTD was reached based on the decreased body weight and decreased weight gain at the high-dose. There were no treatment-related neoplastic lesions at doses tested.

Executive CAC Recommendations and Conclusions:

- The Committee determined that the study was adequate, noting prior FDA protocol concurrence.
- The Committee determined that the study results showed no drug related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\ /Division File, DHOT
/Haleh Saber, Ph.D., Supervisory Pharmacologist, DHOT
/Wei Chen, Ph.D., DHOT
/Amy Baird, DHOT
/ASeifried, OND-IO

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/s/

ADELE S SEIFRIED
09/14/2011

DAVID JACOBSON KRAM
09/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Drug Substance CMC Reviewer: Sue Ching Lin, CMC Reviewer
Drug Product CMC Reviewer: Joyce Crich, CMC Review
Janice Brown, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: SueChing.Lin@fda.hhs.gov and Joyce.Crich@fda.hhs.gov
Phone: (301)-Sue Ching: 301-796-1403 Joyce: 301-796-3882

Fax.: (301)-CMC Reviewer's FAX number

Through: Sarah Pope Miksinski, Chief Branch 2
Phone: (301)-796-1436

and

Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 202192

Name of Product: Ruxolitinib Phosphate Tablets

Applicant: Incyte Corporation

Applicant's Contact Person: Ronald C. Falcone, Ph.D.

Address: Route 141 & Henry Clay Road, Building 336, Wilmington, DE 19880

Telephone: 301-498-6700 Fax: 301-425-2734

Date NDA Received by CDER: **6/3/2011**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP:

Special Handling Required: Yes

DATE of Request: **September 8, 2011**

DEA Class: N/A

Requested Completion Date: **10/21/2011**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **12/3/2011**

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the

laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA # (b) (4)
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P. (1 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg tablets)
Specifications/Methods for New Drug Substance(s)				3.2.S.4.1, pg. 1
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.1.
Supporting Data for Accuracy, Specificity, etc.				3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				
Other:				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
IC/018424/011	Identification: HPLC Retention Time	3.2.P.5.3	0	Drug Product Identity test
IC/018424/011	Assay	3.2.P.5.3	0	Drug Product Potency
IC/018424/004	Assay	3.2.S.4.1	0	Drug Substance Potency
IC/018424/001	Chiral Purity	3.2.S.4.1	0	Drug Substance Chiral Purity and Related Substance test
IC/018424/029 and IC/018424/004.02	Related Substance	3.2.S.4.1	0	ID and Assay of Related Substance (b) (4) and INCB018424

Additional Comments: Ruxolitinib is supplied as 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg tablets. The recommended starting dose of ruxolitinib is 15 mg given orally twice daily for patients with a platelet count between 100,000 and 200,000/ μ L and 20 mg twice daily for patients with an initial platelet count of > 200,000/ μ L. The highest human therapeutic dose is 25 mg bid orally..

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)

6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

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09/08/2011

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Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	202,192
Brand Name	Ruxolitinib
Generic Name	INCB018424
Sponsor	Incyte Corporation
Indication	Myelofibrosis
Dosage Form	Tablets
Drug Class	JAK inhibitor
Therapeutic Dosing Regimen	10-25 mg b.i.d.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	25 mg b.i.d. or 100 mg q.d. for multiple dosing 200 mg as single dose (highest single dose tested) was well tolerated.
Submission Number and Date	29 June 2011
Review Division	DDOP / HFD 150

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of INCB018424 (25-mg single dose and 200-mg single dose) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between INCB018424 (25-mg single dose and 200-mg single dose) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

In this randomized, partially blinded, four-period crossover study, 50 healthy subjects received INCB018424 25-mg single dose, INCB018424 200-mg single dose, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for INCB018424 (25 mg and 200 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
INCB018424 25 mg	24	2.2	(-0.5, 4.9)
INCB018424 200 mg	12	2.2	(0.0, 4.4)
Moxifloxacin 400 mg*	1.5	10.4	(7.4, 13.5)

* Multiple endpoint adjustment of 3 time points was applied.

The suprathreshold dose (200-mg single dose) produces mean $C_{\max}$ values 7.6-fold the mean $C_{\max}$ for the therapeutic dose (25-mg single dose). Given the low accumulation ratio observed with b.i.d. dosing (9%), rapid terminal half-life (3.2 h), and reported steady-state $C_{\max}$ for 50 mg b.i.d. (2710 nM which is 1.8-fold the 25-mg single-dose $C_{\max}$ from the current study), the $C_{\max}$ observed following a single dose INCB018424 25 mg is an acceptable representation of steady-state $C_{\max}$ with 25-mg b.i.d. dosing. The concentrations for the suprathreshold dose are above those for the predicted worst case scenario (drug interaction with a potent CYP3A4 inhibitor such as ketoconazole). For such patients a 30% increase in INCB018424 $C_{\max}$ was observed in addition to a 48% reduction in clearance. Predicted steady-state $C_{\max}$ for INCB018424 25 mg b.i.d. in these patients is 1.7-fold the steady-state $C_{\max}$ in patients not administered a potent CYP3A4 inhibitor for the same INCB018424. This exposure is within the concentration range studied in the TQT study and showed no detectable prolongations of the QT-interval.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

The sponsor proposed the following language in the package insert.

12.4 Thorough QT Study

(b) (4)

2.2 QT-IRT PROPOSED LABEL

QT-IRT recommends the following label language. Our recommendations are suggestions only. We defer final decisions regarding labeling to the review division.

Section 12.2 Pharmacodynamics

The effect of single dose ruxolitinib 25 mg and 200 mg on QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 47 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the

largest placebo adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 200 mg is adequate to represent the high exposure clinical scenario.

3 BACKGROUND

3.1 PRODUCT INFORMATION

INCB018424 phosphate is an inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases that is in development for the treatment of primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (PPV-MF) and post essential thrombocythemia myelofibrosis (PET-MF).

INCB018424 Phosphate tablets are also under development for the treatment of patients with rheumatoid arthritis under IND 77,455.

3.2 MARKET APPROVAL STATUS

Ruxolitinib is not approved for marketing in any country .

3.3 PRECLINICAL INFORMATION

From eCTD, Pharmacology Written Summary

“The in vitro effects of ruxolitinib on ionic currents in voltage-clamped human embryonic kidney cells (HEK293) that stably express the human ether-à-go-go-related gene (hERG) were determined. Ruxolitinib was evaluated in a GLP study at 10, 100 and 300 µM [INCYTE-DMB- 06.187.1]. All experiments were performed at physiological temperature (35 ± 2°C). Ruxolitinib inhibited hERG current by (mean ± SEM): 3.8 ± 0.2% at 10 µM (n = 3), 40.3 ± 1.6% at 100 µM (n = 3) and by 74.1 ± 0.2% at 300 µM (n = 3) versus 0.6 ± 0.5% (n = 3) for the vehicle control. hERG inhibition at 100 µM and 300 µM of ruxolitinib was significant (P < 0.05), when compared to vehicle control values. The IC50 for the inhibitory effect of ruxolitinib on the hERG potassium current was 131.6 µM. The Cmax at the highest proposed therapeutic dose in humans (25 mg bid) is 1.48 µM (0.049 µM unbound). Therefore, the risk of meaningful inhibition of hERG in humans given ruxolitinib appears to be nonexistent. Additionally, in a study to assess the effects of ruxolitinib on heart rate corrected QT intervals in healthy subjects compared with moxifloxacin [INCB 18424-138], ruxolitinib at a dose of 200 mg did not cause prolongation of ventricular repolarization.

“In order to evaluate the cardiovascular system effects of ruxolitinib, the compound was administered as a single oral dose (gavage) at dosage levels of 0, 3, 10 or 30 mg/kg to four male beagle dogs in a GLP study [T06-10-01]. Only male animals were selected because toxicokinetic parameters were similar in male and female dogs [T06-09-07]. Dosing was conducted according to a Latin square design such that each radiotelemetry-implanted dog received each treatment once, with a 3-4 day washout period between doses. Each treatment group was represented on each day of testing. Heart rate (derived from arterial waveforms), arterial blood pressure (systolic, diastolic, calculated mean, and pulse pressure), body temperature, and ECG were collected for a 30-second period every 10 minutes for at least 24 hrs following dosing.

“All animals survived to study termination. Clinical observations were conducted at 5 and 24 hrs post-dose. After administration of 30 mg/kg ruxolitinib, injected sclera of one or both eyes was noted in 3 out of 4 animals at the 5 hrs post-dose observation timepoint. Emesis was noted after administration of 30 mg/kg ruxolitinib at 5 hrs post-dose in 2 out of 4 animals. These clinical observations (injected sclera and emesis) were considered to be test-article related but not adverse.

“Administration of ruxolitinib at a dose of 30 mg/kg (the highest dose tested) resulted in significantly lower pulse pressure, as well as lower systolic, diastolic, and calculated mean arterial pressure (up to 53%, 41%, 31%, and 33%, respectively) when compared to the control group. These changes peaked at approximately 2-3 hrs post-dose after which mean arterial blood pressure values began to recover. Although arterial blood pressure continued to recover, lower values were noted for up to 24 hrs in the 30 mg/kg dose group compared to the control group. Mean arterial pressure is presented in Figure 3. Systolic, diastolic, and pulse pressures demonstrated similar profiles. Hemodynamic changes after administration of ruxolitinib at a dose of 30 mg/kg were considered adverse.”

3.4 PREVIOUS CLINICAL EXPERIENCE

From ISS

“The proportion of subjects treated with ruxolitinib with normal ECG evaluations at Baseline who subsequently developed abnormal ECG findings was low in the Phase 3 studies. In both Phase 3 studies, a higher proportion of subjects in the ruxolitinib group had a sitting systolic blood pressure ≥ 160 mmHg or an increase from Baseline $\geq 25\%$ compared with the comparator group, the majority of which were single episodes. In Study INCB 18424-351, a higher proportion of subjects in the ruxolitinib group had a sitting diastolic blood pressure ≥ 95 mmHg compared with the placebo group, all of which were single episodes. A similar pattern was seen in Study CINC424A2352 (see Section 6.1). Mean systolic and diastolic blood pressure in the ruxolitinib groups remained similar to Baseline levels throughout the study.

“Overall, there do not seem to be clinically significant changes in ECGs or blood pressure in subjects treated with ruxolitinib. A small decrease in median heart rate (approximately 8 bpm) was noted in subjects treated with ruxolitinib in Study INCB 18424-351 and this may be associated with lower levels of circulating inflammatory cytokines in these subjects. This is discussed in further detail in the Study INCB 18424-351 CSR.”

“For the identification and evaluation of common AEs that are potentially related to ruxolitinib, INCB 18424-351 is considered the most informative study, as it is randomized, double-blinded, and placebo-controlled. The most frequently reported AE by MedDRA preferred term in the Phase 3 Population was thrombocytopenia, which was reported by 39.2% of ruxolitinib-treated subjects, 9.3% of subjects in the placebo group, and 9.6% of subjects in the BAT group. Anemia was the second most frequently reported AE and occurred in 35.5% of ruxolitinib-treated subjects as compared with 13.9% in placebo-treated subjects and 12.3% in subjects in the BAT group.

Table 2: Common Adverse Events (≥1% Incidence in the Total Ruxolitinib Group) with Greater Frequency in the Ruxolitinib Group as Compared with Placebo and/or BAT in the Phase 3 Population

Preferred Term	Study INCB 18424-351			Study CINC424A2352			Total
	Ruxolitinib (N=155)	Placebo (N=151)	Difference	Ruxolitinib (N=146)	BAT (N=73)	Difference	Ruxolitinib (N=301)
Thrombocytopenia	53 (34.2)	14 (9.3)	24.9	65 (44.5)	7 (9.6)	34.9	118 (39.2)
Anemia	48 (31.0)	21 (13.9)	17.1	59 (40.4)	9 (12.3)	28.1	107 (35.5)
Hemoglobin decreased	22 (14.2)	6 (4.0)	10.2	4 (2.7)	2 (2.7)	0	26 (8.6)
Headache	23 (14.8)	8 (5.3)	9.5	15 (10.3)	3 (4.1)	6.2	38 (12.6)
Contusion	22 (14.2)	8 (5.3)	8.9	3 (2.1)	1 (1.4)	0.7	25 (8.3)
Dizziness	23 (14.8)	10 (6.6)	8.2	10 (6.8)	4 (5.5)	1.4	33 (11.0)
Platelet count decreased	15 (9.7)	4 (2.6)	7	10 (6.8)	2 (2.7)	4.1	25 (8.3)
Weight increased	10 (6.5)	2 (1.3)	5.1	14 (9.6)	0	9.6	24 (8.0)
Flatulence	8 (5.2)	1 (0.7)	4.5	2 (1.4)	0	1.4	10 (3.3)
Cardiac murmur	11 (7.1)	5 (3.3)	3.8	6 (4.1)	2 (2.7)	1.4	17 (5.6)
Pyrexia	17 (11.0)	11 (7.3)	3.7	20 (13.7)	7 (9.6)	4.1	37 (12.3)
Chills	8 (5.2)	3 (2.0)	3.2	3 (2.1)	0	2.1	11 (3.7)
Procedural pain	5 (3.2)	0	3.2	2 (1.4)	1 (1.4)	0	7 (2.3)
Hematocrit decreased	7 (4.5)	2 (1.3)	3.2	0	1 (1.4)	-1.4	7 (2.3)
Hematoma	4 (2.6)	0	2.6	12 (8.2)	3 (4.1)	4.1	16 (5.3)
Hematuria	4 (2.6)	0	2.6	2 (1.4)	1 (1.4)	0	6 (2.0)
Wheezing	5 (3.2)	1 (0.7)	2.6	0	0	0	5 (1.7)
Red blood cell count decreased	4 (2.6)	0	2.6	0	0	0	4 (1.3)
Urinary tract infection	11 (7.1)	7 (4.6)	2.5	10 (6.8)	2 (2.7)	4.1	21 (7.0)
Arthralgia	17 (11.0)	13 (8.6)	2.4	18 (12.3)	5 (6.8)	5.5	35 (11.6)
Pneumonia	13 (8.4)	9 (6.0)	2.4	3 (2.1)	5 (6.8)	-4.8	16 (5.3)
Pain in extremity	19 (12.3)	15 (9.9)	2.3	17 (11.6)	3 (4.1)	7.5	36 (12.0)
Vomiting	19 (12.3)	15 (9.9)	2.3	13 (8.9)	1 (1.4)	7.5	32 (10.6)
Diarrhea	36 (23.2)	32 (21.2)	2	34 (23.3)	8 (11.0)	12.3	70 (23.3)
Palpitations	4 (2.6)	1 (0.7)	1.9	7 (4.8)	1 (1.4)	3.4	11 (3.7)
Neutropenia	4 (2.6)	1 (0.7)	1.9	5 (3.4)	1 (1.4)	2.1	9 (3.0)

Preferred Term	Study INCB 18424-351			Study CINC424A2352			Total
	Ruxolitinib (N=155)	Placebo (N=151)	Difference	Ruxolitinib (N=146)	BAT (N=73)	Difference	Ruxolitinib (N=301)
Chest pain	7 (4.5)	4 (2.6)	1.9	1 (0.7)	4 (5.5)	-4.8	8 (2.7)
Influenza like illness	3 (1.9)	0	1.9	2 (1.4)	0	1.4	5 (1.7)
Meniscus lesion	4 (2.6)	1 (0.7)	1.9	1 (0.7)	0	0.7	5 (1.7)
Tooth abscess	3 (1.9)	0	1.9	1 (0.7)	0	0.7	4 (1.3)
Balance disorder	4 (2.6)	1 (0.7)	1.9	0	0	0	4 (1.3)
Cardiomegaly	4 (2.6)	1 (0.7)	1.9	0	0	0	4 (1.3)
Dry eye	4 (2.6)	1 (0.7)	1.9	0	0	0	4 (1.3)
Fluid overload	4 (2.6)	1 (0.7)	1.9	0	0	0	4 (1.3)
Blast cells present	3 (1.9)	0	1.9	0	0	0	3 (1.0)
Excoriation	3 (1.9)	0	1.9	0	0	0	3 (1.0)
Myocardial infarction	3 (1.9)	0	1.9	0	0	0	3 (1.0)
Insomnia	18 (11.6)	15 (9.9)	1.7	9 (6.2)	5 (6.8)	-0.7	27 (9.0)
Cystitis	2 (1.3)	0	1.3	8 (5.5)	3 (4.1)	1.4	10 (3.3)
Herpes zoster	3 (1.9)	1 (0.7)	1.3	7 (4.8)	0	4.8	10 (3.3)
Bradycardia	3 (1.9)	1 (0.7)	1.3	4 (2.7)	0	2.7	7 (2.3)
Fluid retention	3 (1.9)	1 (0.7)	1.3	4 (2.7)	0	2.7	7 (2.3)
Blood urea increased	2 (1.3)	0	1.3	4 (2.7)	0	2.7	6 (2.0)
Post procedural hemorrhage	3 (1.9)	1 (0.7)	1.3	3 (2.1)	1 (1.4)	0.7	6 (2.0)
Neutrophil count increased	3 (1.9)	1 (0.7)	1.3	2 (1.4)	0	1.4	5 (1.7)
Productive cough	3 (1.9)	1 (0.7)	1.3	2 (1.4)	0	1.4	5 (1.7)
Skin infection	3 (1.9)	1 (0.7)	1.3	2 (1.4)	0	1.4	5 (1.7)
Muscular weakness	4 (2.6)	2 (1.3)	1.3	1 (0.7)	0	0.7	5 (1.7)
Atioventricular block first degree	2 (1.3)	0	1.3	2 (1.4)	0	1.4	4 (1.3)
Toothache	2 (1.3)	0	1.3	2 (1.4)	1 (1.4)	0	4 (1.3)
Hypoesthesia	3 (1.9)	1 (0.7)	1.3	1 (0.7)	0	0.7	4 (1.3)
Tinnitus	3 (1.9)	1 (0.7)	1.3	1 (0.7)	0	0.7	4 (1.3)

Source: ISS, Table 25.

“There were 28 on-study deaths in the Phase 3 population: 20 deaths in Study INCB 18424-351 (9 in the ruxolitinib group and 11 in the placebo group) and 8 deaths in Study INC424A2352 (4 in the ruxolitinib group and 4 in the BAT group).

Table 3: Electrocardiogram Abnormalities in the Phase 3 Population

	INCB 18424-351		INCB 18424-352		Total
	Ruxolitinib (N=155)	Placebo (N=151)	Ruxolitinib (N=146)	BAT (N=73)	Ruxolitinib (N=301)
Patient-years of exposure	106.63	88.31	132.07	52.77	238.70
QTcF (msec)					
New > 450	10 (6.8)	7 (4.9)	6 (4.4)	1 (1.7)	16 (5.6)
New > 480	0	5 (3.4)	1 (0.7)	2 (3.2)	1 (0.3)
New > 500	3 (1.9)	1 (0.7)	0	0	3 (1.0)
Increase from Baseline > 30	18 (11.6)	21 (14.1)	19 (13.4)	8 (12.5)	37 (12.5)
Increase from Baseline > 60	1 (0.6)	6 (4.0)	0	0	1 (0.3)
QTcB (msec)					
New > 450	19 (13.8)	18 (14.4)	15 (11.1)	4 (7.0)	34 (12.5)
New > 480	0	7 (4.8)	2 (1.4)	3 (4.8)	2 (0.7)
New > 500	2 (1.3)	4 (2.7)	0	2 (3.2)	2 (0.7)
Increase from Baseline > 30	13 (8.4)	23 (15.4)	20 (14.1)	6 (9.4)	33 (11.1)
Increase from Baseline > 60	3 (1.9)	6 (4.0)	2 (1.4)	0	5 (1.7)
HR (bpm)					
Increase from Baseline > 25% and > 100 bpm	2 (1.3)	4 (2.7)	5 (3.5)	2 (3.1)	7 (2.3)
Decrease from Baseline > 25% and < 50 bpm	3 (1.9)	1 (0.7)	3 (2.1)	0	6 (2.0)
PR (bpm)					
Increase from Baseline > 25% and > 200 msec	5 (3.3)	1 (0.7)	8 (5.7)	1 (1.6)	13 (4.5)
QRS (msec)					
Increase from Baseline > 25% and > 110 msec	0	7 (4.7)	2 (1.4)	0	2 (0.7)

Source: ISS, Table 54”

Reviewer’s comment: No syncope, seizures or ventricular arrhythmias were reported. From the 28 deaths reported in phase 3 studies, two had cardiac arrest as main cause of death. Both cases were confounded, one by the normal disease progression and the other by pneumonitis.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of INCB018424’s clinical pharmacology.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 77,456.

The sponsor submitted the study report INCB 18424-138 for INCB018424, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

An Assessment of Heart Rate Corrected QT Intervals in Healthy Subjects Dosed with

Single Doses of INCB018424 Compared with Moxifloxacin

4.2.2 Protocol Number

INCB 18424-138

4.2.3 Study Dates

Date first patient enrolled: 05 October 2009

Date last patient completed: 25 November 2009

4.2.4 Objectives

4.2.4.1 Primary

- To confirm a lack of effect of INCB018424 on the heart rate corrected QT interval

4.2.4.2 Secondary

- To determine the safety and tolerability of INCB018424 in healthy adult subjects when administered orally and to determine the pharmacokinetics of INCB018424 in the blood plasma of adult healthy subjects

4.2.5 Study Description

4.2.5.1 Design

This will be a randomized, 4-way crossover study evaluating the effects of placebo, 25 mg INCB018424, 200 mg INCB018424, and 400 mg moxifloxacin on the heart-rate corrected QT interval in healthy subjects. The study was double-blind with regard to INCB018424 and placebo and open-label for moxifloxacin. The total duration of subject participation in the study from screening through discharge was approximately 64 days. Fifty subjects were planned to be enrolled.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The study was double-blind with regard to INCB018424 and placebo and open-label for moxifloxacin (positive control).

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Treatment A: INCB018424 25 mg (1 active and 7 placebo tablets)

Treatment B: INCB018424 200 mg (8 active tablets)

Treatment C: Placebo (8 tablets)

Treatment D: Moxifloxacin 400 mg (1 tablet)

Single doses of INCB018424, placebo, and moxifloxacin were administered to each subject according to the randomization scheme in 1 of 8 treatment sequences (Group 1: ABCD, BDAC, CADB, and DCBA; Group 2: BCAD, CDBA, ABDC, and DACB). Two groups of subjects were randomized using different William squares. Subjects were divided equally between the 2 groups.

Table 4: William Square for Group 1 (top) and Group 2 (bottom)

	Period 1	Period 2	Period 3	Period 4
Sequence 1	A	B	C	D
Sequence 2	B	D	A	C
Sequence 3	C	A	D	B
Sequence 4	D	C	B	A

	Period 1	Period 2	Period 3	Period 4
Sequence 1	B	C	A	D
Sequence 2	C	D	B	A
Sequence 3	A	B	D	C
Sequence 4	D	A	C	B

4.2.6.2 Sponsor’s Justification for Doses

“For myelofibrosis, the highest dose being evaluated in Phase 3 studies is 25 mg b.i.d. Therefore, this study evaluated the highest likely clinical dose to be evaluated in Phase 3 (25 mg) and a suprathapeutic dose of 200 mg, which should produce plasma concentrations well above those for the highest potential clinical dose, even in the presence of a potent CYP3A4 inhibitor.”

(Source: INCB018424 study report, Section 9.4.4, Pg 29)

Reviewer’s Comment: INCB018424 was administered 25 mg b.i.d. clinically but was evaluated as a single dose in this TQT study. However, given the low accumulation ratio with b.i.d. dosing (9%), rapid terminal half-life (3.2 h), and reported steady-state C_{max} from other studies using 50 mg b.i.d. (2710 nM which is 1.8-fold the 25-mg single-dose C_{max} from the current study), the C_{max} observed following a single dose INCB018424 25 mg for this TQT study is an acceptable representation of steady-state C_{max} with 25 mg b.i.d.

Drug-drug interaction studies indicated a 30% increase in C_{max} when coadministered with ketoconazole, in addition to a 48% reduction in clearance. Predicted steady-state

C_{max} for INCB018424 25 mg b.i.d. in these patients is 1.7-fold the steady-state C_{max} with the 25-mg single dose. This exposure is within the concentration range from the 200-mg supratherapeutic dose studied in the TQT study.

The hepatic impairment study indicated a decrease a 8%, 22% and 15% decrease in C_{max} for patients with mild, moderate, and severe hepatic impairment, respectively, compared to normal patients. Concurrently, clearance decreased by 47%, 22%, and 39% for patients with mild, moderate, and severe hepatic impairment, respectively, compared to normal patients. Each of these scenarios would result in a lower increase in C_{max} compared to the drug-drug interaction results from ketoconazole. As such, the ketoconazole exposures are an appropriate high exposure scenario for assessing QT prolongation.

4.2.6.3 Instructions with Regard to Meals

Study drug was administered orally followed by 240 mL water and was taken following an overnight fast of at least 10 hours. Subjects then abstained from water for 1 hour post-dose. Subjects remained fasting and sitting or semi-recumbent for 3 hours post-dose, at which point a meal was served.

(Source: INCB018424 study report, Section 9.4.4, Pg 29)

Reviewer's Comment: Administration with a high fat meal decreased INCB018424 by 24%. As such, doses were administered orally after at least a 10 h fast from food to ensure maximum INCB018424 exposure.

4.2.6.4 ECG and PK Assessments

On Day 1 of Period 1, triplicate ECG readings were obtained from 12-lead Holter monitors at 90, 60, and 30 minutes before administration. On Days 8, 15 and 22, 12-lead Holter monitoring began approximately 30 to 60 minutes before administration. On Days 1, 8, 15, and 22, triplicate 12-lead ECG readings were obtained from 12-lead Holter monitors at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours after each dose.

Venous blood samples were collected to measure plasma concentrations of INCB018424 and moxifloxacin at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours post-dose for each period.

Reviewer's Comment: The PK and ECG assessments are adequate to capture QT at peak concentration of INCB018424 ($T_{max} \sim 1.5$ h) and potential delayed effects up to 24 h postdose.

4.2.6.5 Baseline

The average of triplicate ECG readings obtained from 12-lead Holter monitors at 90, 60, and 30 minutes before administration at each period was used as baseline.

4.2.7 ECG Collection

A (b) (4) provided standardized digital Holter recorders, protocol specific training manuals and all other accessories that are required to perform continuous

12-lead ECG data recording. A representative from the (b) (4) was responsible for training the Investigator and his/her research staff to insure a comprehensive understanding of the ‘step-by-step’ procedures that must be performed to obtain and transmit the ECG data.

A ‘true’ 12-lead Holter recorder was used to capture ECG data. A flashcard was used to collect the ECG data. All ECG data collected during the monitoring period was transmitted to the (b) (4) where it will be extracted and analyzed in digital format.

4.2.8 Sponsor’s Results

4.2.8.1 Study Subjects

Fifty subjects were enrolled in the study. Forty-seven (94%) subjects completed all 4 treatment periods. One subject discontinued because of an AE (headache and vomiting), which was judged not related to study drug. Two subjects withdrew consent.

Table 5: Summary of Demographics and Baseline Characteristics

Variable	Total (N=50)
Age (yrs)	
Mean (± SD)	33 (± 11.95)
Min, Max	18, 55
Gender - n (%)	
Male	25 (50.0)
Female	25 (50.0)
Ethnicity - n (%)	
Hispanic or Latino	2 (4.0)
Not Hispanic or Latino	48 (96.0)
Race - n (%)	
White	40 (80.0)
Black	1 (2.0)
Asian	5 (10.0)
American Indian or Alaska Native	4 (8.0)
Native Hawaiian	0
Height (cm)	
Mean (± SD)	170.28 (± 9.536)
Min, Max	146.3, 190.2
Weight (kg)	
Mean (± SD)	69.35 (± 10.418)
Min, Max	50.3, 89.6
BMI (kg/m ²)	
Mean (± SD)	23.84 (± 2.404)
Min, Max	19.5, 28

Source: CSR, Table 6

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

“The primary analysis was performed using a repeated-measure, mixed-effects, linear model that included fixed effects of treatment sequence, study treatment, study period, ECG time point, and treatment-by-ECG time point interaction. The within-subject correlation was modeled over time using an AR(1) covariance structure.

“The response variable for the above model, QTcF, was the change from the Day 1 predose baseline.

“All 4 treatments were included in the analysis, although only the 2 INCB018424 doses and placebo were used for testing the primary hypothesis. All inferences were based on the least square means estimated from this model.

“For each time point, the mean difference between each INCB018424 dose and placebo is presented, along with a 1-sided 95% upper confidence bound on the difference. The upper bound was calculated with reference to the Student’s t distribution. Primary attention was placed on the largest time-matched upper confidence bound of the QTcF difference between each INCB018424 dose and placebo for each of the comparisons made using the model stated above.”

The largest observed mean difference from placebo in baseline-corrected QTcF for the 25 mg dose was 1.69 ms at 2 hours after administration, and the largest upper bound of the confidence interval was 5.15 ms at this same time. The largest observed mean difference from placebo for the 200 mg dose is 3.28 ms at 12 hours after administration, and the largest upper bound of the confidence interval is 6.62 ms at this same time. Therefore, the primary hypothesis was rejected and the study is deemed negative for QT interval prolongation.

Reviewer’s Comments: Please see the reviewer’s analysis in section 5.2.1.

4.2.8.2.2 Assay Sensitivity

The assay sensitivity of the study was assessed by placing a 1-sided lower 99% confidence bound on the mean differences between moxifloxacin and placebo at 1, 2, 3, 4, and 6 hours postdose. The lower bound was above 5 ms at 3 of these times (1, 2, and 3 hours after administration), and the overall trend of the moxifloxacin response was as expected (with a rapid rise and gradual return to near baseline by the end of 24 hours), demonstrating that the study had assay sensitivity.

Reviewer’s Comments: The reviewer used 95% C.I. while adjusted for three time points; the analysis is in section 5.2.1.

4.2.8.2.3 Categorical Analysis

The numbers of subjects with QTcF intervals >450 ms, >480 ms, and >500 ms are summarized in Table 23 to 25 of the ECG Report. Three subjects on INCB018424 200 mg (Subjects 2, 18, 27) and 2 each on placebo (Subjects 2 and 18) and INCB018424 25 mg (Subjects 2 and 33) had 1 or more QTcF intervals > 450 ms. None of the subjects on either INCB018424 dose or on placebo had a QTcF interval > 480 ms at any time point evaluated. Thus, the outlier analysis confirmed the findings for the central tendency.

The number of subjects with increases from the Day 1 pre-dose baseline in QTcF intervals > 30 ms and > 60 ms are summarized in Table 26 and 27 of the ECG Report. One subject on placebo (Subject 18) had a single increase in QTcF > 30 ms, and none of the subjects on either INCB018424 dose had such an increase at any time point evaluated. None of the subjects had an increase from the Day 1 pre-dose baseline in QTcF > 60 ms at any time point evaluated.

4.2.8.2.4 Additional Analyses

Heart rate:

“Results for changes in heart rate are shown in the ECG Report along with 2-sided 95% confidence intervals on the mean differences from placebo. All changes in heart rate were minimal and without clinical relevance. The data indicate that only small increases over placebo were seen, maximally 3.71 (CI 1.38 to 6.04) bpm in the INCB018424 200-mg treatment arm compared to placebo at 1.5 hours. This was actually a -0.20 bpm change compared with the baseline value for the 200-mg dose group, but as the placebo group decreased by -3.90 bpm at that time point, this was an increase in heart rate compared with placebo.”

PR and QRS:

“The number of subjects with a QRS interval > 110 ms that was also a 25% increase over the Day 1 predose baseline and the number with a PR interval >200 ms that was also a 25% increase over the Day 1 predose baseline are summarized in Table 28 and 29 of the ECG Report.

None of the subjects met either criterion at any time point evaluated. Small decreases (not placebo-corrected) were seen in QRS intervals at all time points with the exception of a mean QRS increase of 0.2 ms at 4 hours for the INCB018424 200-mg treatment. Small increases (not placebo-corrected) were seen in PR intervals with a maximum increase of 6.3 ms at 1 hour for the INCB018424 200-mg treatment. Similar changes were seen following placebo dosing. Neither finding is considered clinically relevant.”

4.2.8.3 Safety Analysis

No subjects had a TEAE of syncope, seizure, ventricular tachycardia, or ventricular fibrillation. No subject died during the study. No SAEs occurred during the study.

One subject discontinued because of TEAEs of headache and vomiting. These events occurred on Day -1 of Period 2 following administration of placebo in Period 1 and were judged as unrelated to study drug.

The most frequently reported treatment-related TEAE was headache, which occurred in 8 (16%) subjects overall (see Table 14.3.1.8). It was also the most frequently reported TEAE within any treatment group. Treatment-related headache was reported by 3 (6.4%) subjects in the INCB018424 25 mg group, 2 (4.2%) subjects in the INCB018424 200 mg group, 1 (2.0%) subjects in the placebo group, and 2 (4.2%) subjects in the moxifloxacin 400 mg group. Other treatment-related TEAEs reported were dizziness (2 subjects, 4%), diarrhea (1 subject, 2%), abdominal discomfort (1 subject, 2%), dysgeusia (1 subject, 2%), flatulence (1 subject, 2%), nausea (1 subject, 2%), and vertigo (1 subject, 2%).

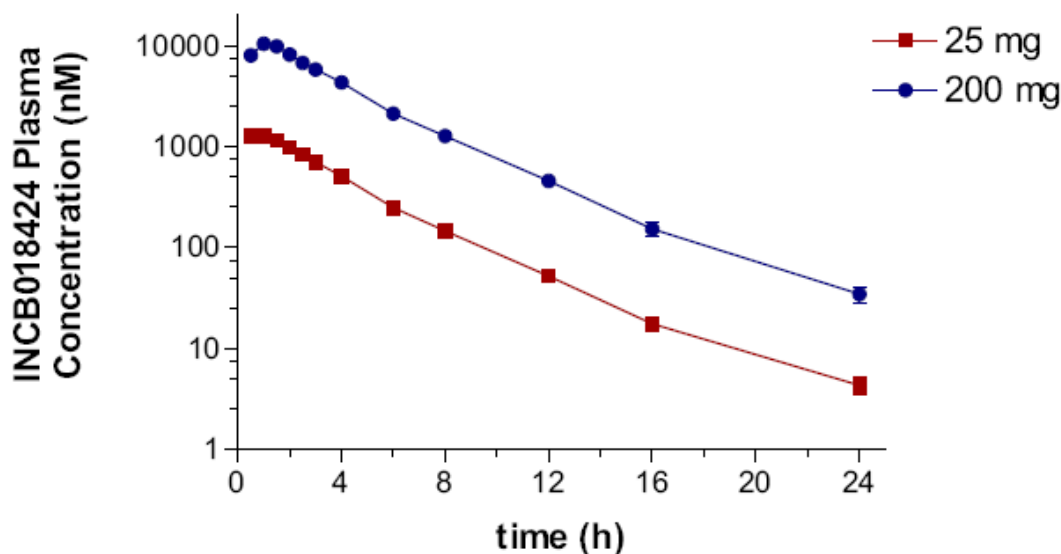
4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Figure 1 presents the mean INCB018424 plasma concentrations for individual subjects receiving 25 mg and 200 mg of INCB018424. INCB018424 pharmacokinetic parameters (C_{max} and AUC_{0-24}) for individual subjects receiving 25 mg and 200 mg of INCB018424

are summarized in Table 6. C_{max} and AUC values in the thorough QT study were 7.6- and 8.1-fold those following administration of single dose 200-mg INCB018424 compared with single dose 25-mg INCB018424.

Figure 1: INCB018424 Plasma Concentration (Mean) in Healthy Subjects Receiving a Single Dose of 25 or 200 mg INCB018424



(Source: INCB018424 study report, Section 11.2, Figure 1, Pg 44)

Table 6: Summary of INCB018424 Pharmacokinetic Parameters

Dose (mg)	n	C_{max} (nM)	T_{max} (h)	$t_{1/2}$ (h)	AUC _{0-t} (nM·h)	AUC _{0-∞} (nM·h)	CL/F (L/h)	V_z/F (L)
25	47	1510 ± 400	0.96 ± 0.5	2.6 ± 0.9	5290 ± 1640	5320 ± 1680	16.8 ± 5.01	59.1 ± 11.4
		1460	0.86	2.5	5060	5080	16.1	58.0
200	48	11500 ± 3120	1.1 ± 0.4	2.7 ± 0.55	42800 ± 14300	43000 ± 14500	16.9 ± 5.45	62.6 ± 15.0
		11100	1.1	2.6	40600	40700	16.0	60.9

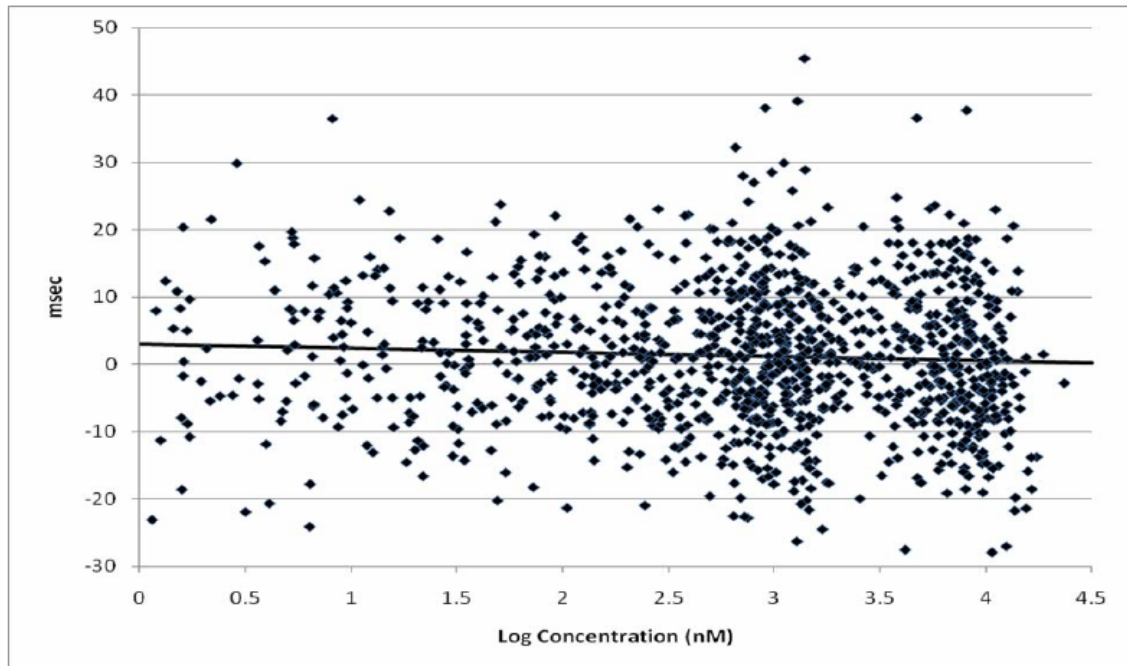
Parameter values are mean ± SD and geometric mean.

(Source: INCB018424 study report, Section 11.2, Table 8, Pg 44)

4.2.8.4.2 Exposure-Response Analysis

The relationship between the placebo-subtracted differences in changes from the Day 1 pre-dose baseline in QTcF intervals and $\log_{10}$ INCB018424 plasma concentration was assessed. A scatter plot of $\Delta\Delta\text{QTcF}$ versus $\log_{10}$ INCB018424 plasma concentration is shown in Figure 2, along with the fitted regression line. The linear regression had an intercept of 3.0 and a slope of -0.6 (p-value = 0.372). The non-statistically significant slope indicates that there was no relationship between changes in QTcF and $\log_{10}$ INCB018424 plasma concentration.

Figure 2: Time-Matched Differences From Placebo in Changes From Day 1 Predose Baseline in QTcF vs. Log INCB018424 Concentration



(Source: INCB018424 study report, Section 11.4, Table 8, Pg 51)

Reviewer's Analysis: A plot of $\Delta\Delta\text{QTcF}$ vs .INCB018424 concentrations is presented in Figure 5.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor only provided two fixed corrections, QTcF and QTcB, so we evaluated the appropriateness of the correction methods. Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

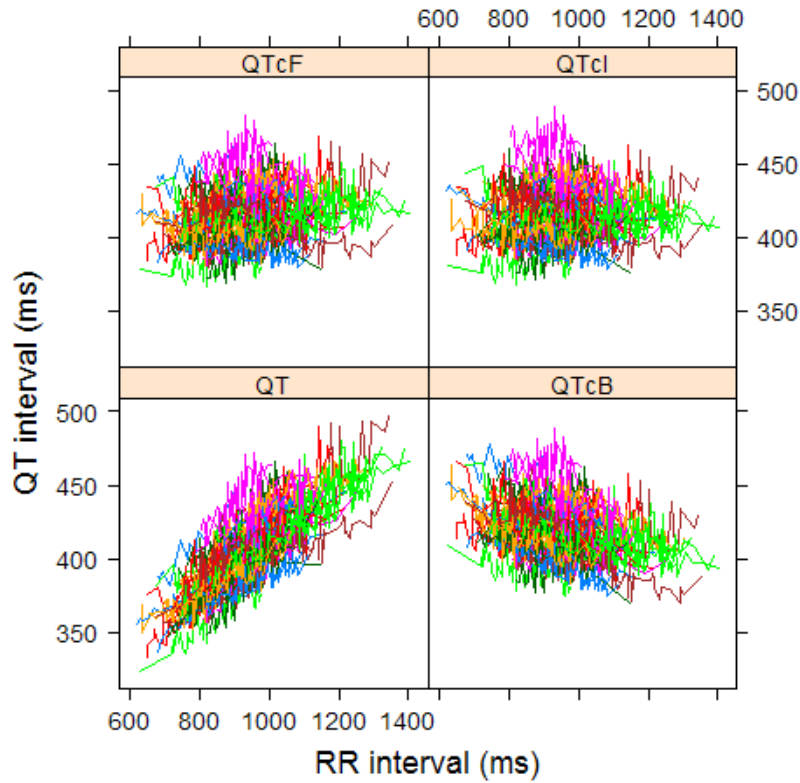
QTcB usually overcorrect, we confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 7, it also appears that QTcF is the better correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 7: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	Treatment									
	INCB018424 200 mg		INCB018424 25 mg		Moxifloxacin 400 mg		Placebo		All	
Method	N	MSSS	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	48	0.0050	47	0.0029	48	0.0037	49	0.0037	50	0.0030
QTcF	48	0.0033	47	0.0020	48	0.0052	49	0.0021	50	0.0020

The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for INCB018424

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes time point, sequence, and period as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 8: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = INCB018424 25 mg

	INCB018424 25 mg Δ QTcF	Placebo Δ QTcF	$\Delta\Delta$ QTcF	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-0.9	-0.1	-0.8	(-3.4, 1.8)
1	-1.4	-0.5	-0.9	(-3.4, 1.5)
1.5	-0.3	-0.3	0.0	(-2.3, 2.3)
2	-0.2	-1.5	1.3	(-1.0, 3.6)
2.5	1.6	1.2	0.4	(-1.9, 2.6)
3	1.1	0.6	0.5	(-2.3, 3.3)
4	-5.8	-5.6	-0.2	(-2.5, 2.1)
6	-9.8	-9.7	-0.1	(-2.3, 2.1)
8	-5.9	-5.9	0.0	(-2.1, 2.2)
12	-6.7	-7.3	0.6	(-1.7, 2.8)
16	1.0	0.5	0.5	(-1.7, 2.7)
24	-2.6	-4.8	2.2	(-0.5, 4.9)

Table 9: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = INCB018424 200 mg

	INCB018424 200 mg Δ QTcF	Placebo Δ QTcF	$\Delta\Delta$ QTcF	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-3.2	-0.1	-3.1	(-5.7, -0.6)
1	-4.4	-0.5	-3.9	(-6.3, -1.5)
1.5	-2.3	-0.3	-1.9	(-4.2, 0.4)
2	-3.1	-1.5	-1.6	(-3.9, 0.7)
2.5	-0.7	1.2	-1.9	(-4.1, 0.4)
3	1.2	0.6	0.6	(-2.2, 3.4)
4	-5.7	-5.6	-0.0	(-2.4, 2.3)
6	-9.5	-9.7	0.2	(-2.0, 2.4)
8	-4.9	-5.9	1.0	(-1.1, 3.2)
12	-5.1	-7.3	2.2	(-0.0, 4.4)
16	2.1	0.5	1.6	(-0.6, 3.8)
24	-4.6	-4.8	0.2	(-2.5, 2.9)

The largest upper bounds of the 2-sided 90% CI for the mean difference between INCB018424 25 mg and placebo, and between INCB018424 25 mg and placebo were 4.9 ms and 4.4 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in following table. The largest unadjusted 90% lower confidence interval is 8.1 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 7.4 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 10: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group = Moxifloxacin 400 mg

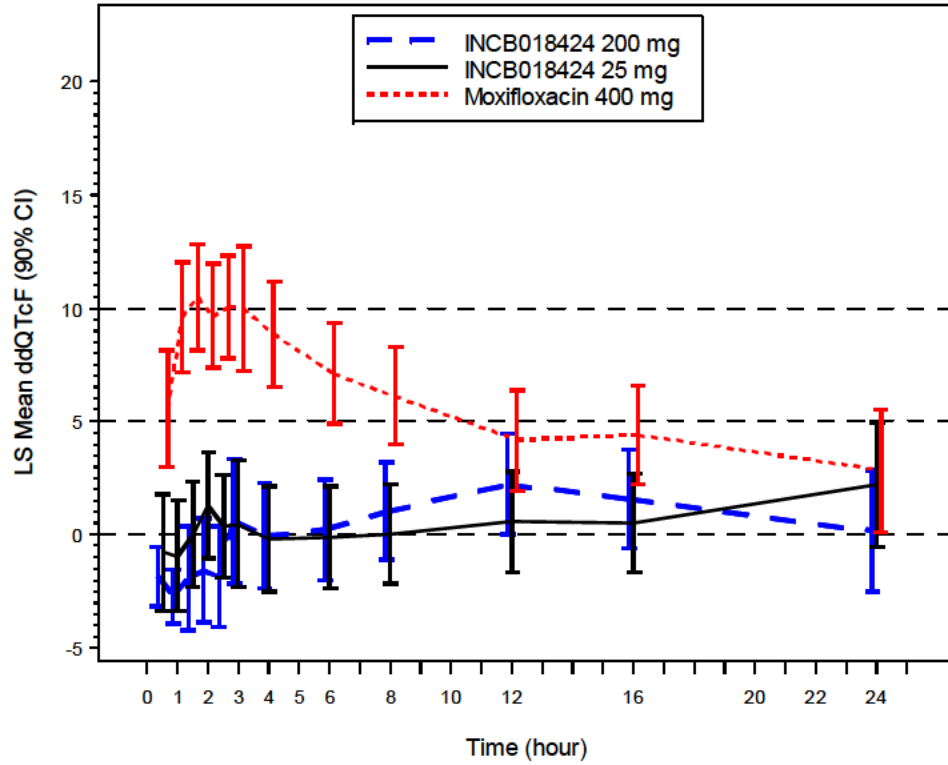
	Moxifloxacin 400 mg Δ QTcF	Placebo Δ QTcF	$\Delta\Delta$ QTcF	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	5.5	-0.1	5.6	(2.2, 8.9)
1	9.1	-0.5	9.6	(6.5, 12.7)
1.5	10.1	-0.3	10.4	(7.4, 13.5)
2	8.2	-1.5	9.6	(6.6, 12.6)
2.5	11.3	1.2	10.1	(7.1, 13.0)
3	10.6	0.6	10.0	(6.4, 13.6)
4	3.2	-5.6	8.8	(5.8, 11.8)
6	-2.6	-9.7	7.1	(4.2, 10.0)
8	0.2	-5.9	6.1	(3.3, 8.9)
12	-3.1	-7.3	4.2	(1.3, 7.0)
16	4.9	0.5	4.4	(1.6, 7.2)
24	-1.9	-4.8	2.8	(-0.7, 6.3)

* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

Figure 4: Mean and 90% CI $\Delta\Delta Q_{TcF}$ Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.4 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms and above 480 ms. No subject's QTcF was above 500 ms.

Table 11: Categorical Analysis for QTcF

Treatment Group	Total N		Value $\leq$ 450 ms		450 ms<Value $\leq$ 480 ms		480 ms<Value $\leq$ 500 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	50	2272	48 (96.0%)	2200 (96.8%)	2 (4.0%)	72 (3.2%)	0 (0.0%)	0 (0.0%)
INCB018424 200 mg	48	575	45 (93.8%)	561 (97.6%)	3 (6.3%)	14 (2.4%)	0 (0.0%)	0 (0.0%)
INCB018424 25 mg	47	562	45 (95.7%)	556 (98.9%)	2 (4.3%)	6 (1.1%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	48	571	39 (81.3%)	529 (92.6%)	8 (16.7%)	41 (7.2%)	1 (2.1%)	1 (0.2%)
Placebo	49	586	46 (93.9%)	575 (98.1%)	3 (6.1%)	11 (1.9%)	0 (0.0%)	0 (0.0%)

Table 12 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 12: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Value $\leq$ 30 ms		30 ms<Value $\leq$ 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
INCB018424 200 mg	48	575	47 (97.9%)	572 (99.5%)	1 (2.1%)	3 (0.5%)
INCB018424 25 mg	47	562	47 (100%)	562 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	48	571	47 (97.9%)	570 (99.8%)	1 (2.1%)	1 (0.2%)
Placebo	47	564	46 (97.9%)	563 (99.8%)	1 (2.1%)	1 (0.2%)

5.2.2 HR Analysis

The same statistical analysis was performed based on heart rate. The point estimates and the 90% confidence intervals are presented in Table 13 and Table 14. The largest upper limits of 90% CI for the HR mean differences between INCB018424 25 mg and placebo and INCB018424 200 mg and placebo are 2.3 bpm and 4.9 bpm, respectively.

Table 13: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group = INCB018424 25 mg

Time/(hr)	INCB018424 25 mg Δ HR	Placebo Δ HR	$\Delta\Delta$ HR	
	Mean (bpm)	Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
0.5	-1.6	-2.5	0.9	(-0.2, 2.1)
1	-1.1	-1.9	0.8	(-0.4, 1.9)
1.5	-2.3	-3.2	0.9	(-0.2, 2.0)
2	-0.7	-1.7	1.0	(-0.2, 2.1)
2.5	-2.2	-2.7	0.6	(-0.5, 1.6)
3	-0.9	-1.2	0.3	(-0.9, 1.5)
4	6.9	7.8	-0.9	(-2.2, 0.5)
6	7.4	8.2	-0.8	(-2.3, 0.8)
8	2.1	2.7	-0.6	(-2.0, 0.7)
12	8.5	8.0	0.5	(-1.0, 2.0)
16	-1.0	-1.8	0.8	(-0.7, 2.3)
24	3.3	2.6	0.7	(-0.7, 2.2)

Table 14: Analysis Results of Δ HR and $\Delta\Delta$ HR for Treatment Group = INCB018424 200 mg

	INCB018424 200 mg Δ HR	Placebo Δ HR	$\Delta\Delta$ HR	
Time/(hr)	Mean (bpm)	Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
0.5	-0.2	-2.5	2.3	(1.2, 3.5)
1	1.4	-1.9	3.2	(2.1, 4.3)
1.5	0.6	-3.2	3.8	(2.7, 4.9)
2	1.9	-1.7	3.6	(2.4, 4.7)
2.5	-0.2	-2.7	2.5	(1.5, 3.6)
3	1.2	-1.2	2.4	(1.3, 3.6)
4	7.6	7.8	-0.2	(-1.5, 1.1)
6	7.4	8.2	-0.7	(-2.3, 0.8)
8	2.5	2.7	-0.2	(-1.6, 1.1)
12	8.5	8.0	0.5	(-1.0, 2.0)
16	-1.4	-1.8	0.4	(-1.1, 1.9)
24	2.7	2.6	0.1	(-1.3, 1.6)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 15 and Table 16. The largest upper limits of 90% CI for the PR mean differences between INCB018424 25 mg and placebo and INCB018424 200 mg and placebo are 4.6 ms and 6.1 ms, respectively.

The categorical analysis results for PR are presented in Table 17.

**Table 15: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group = INCB018424
25 mg**

	INCB018424 25 mg ΔPR	Placebo Δ PR	$\Delta\Delta$ PR	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	1.8	1.0	0.8	(-1.1, 2.7)
1	2.7	0.0	2.7	(0.9, 4.4)
1.5	2.0	-0.4	2.4	(0.3, 4.6)
2	1.4	-0.3	1.7	(-0.4, 3.8)
2.5	1.2	-1.2	2.4	(0.4, 4.4)
3	1.5	-1.2	2.6	(0.6, 4.6)
4	-0.9	-0.8	-0.1	(-2.0, 1.8)
6	-4.1	-4.7	0.5	(-1.2, 2.3)
8	-3.2	-4.4	1.2	(-0.8, 3.2)
12	-1.0	-1.8	0.8	(-1.0, 2.7)
16	2.8	1.4	1.4	(-0.7, 3.6)
24	0.0	-1.5	1.5	(-0.7, 3.8)

**Table 16: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group = INCB018424
200 mg**

	INCB018424 200 mg Δ PR	Placebo Δ PR	$\Delta\Delta$ PR	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	3.6	1.0	2.6	(0.7, 4.5)
1	4.3	0.0	4.2	(2.5, 6.0)
1.5	3.6	-0.4	4.0	(1.9, 6.1)
2	2.8	-0.3	3.1	(1.0, 5.2)
2.5	2.1	-1.2	3.3	(1.3, 5.3)
3	2.3	-1.2	3.5	(1.5, 5.5)
4	-2.1	-0.8	-1.3	(-3.2, 0.6)
6	-5.3	-4.7	-0.7	(-2.4, 1.1)
8	-4.1	-4.4	0.3	(-1.7, 2.3)
12	-2.5	-1.8	-0.7	(-2.5, 1.2)
16	2.7	1.4	1.3	(-0.8, 3.5)
24	0.9	-1.5	2.4	(0.2, 4.6)

Table 17: Categorical Analysis for PR

Treatment Group	Total		Value≤200 ms		Value>200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	50	2272	48 (96.0%)	2200 (96.8%)	2 (4.0%)	72 (3.2%)
INCB018424 200 mg	48	575	47 (97.9%)	567 (98.6%)	1 (2.1%)	8 (1.4%)
INCB018424 25 mg	47	562	45 (95.7%)	547 (97.3%)	2 (4.3%)	15 (2.7%)
Moxifloxacin 400 mg	48	571	45 (93.8%)	558 (97.7%)	3 (6.3%)	13 (2.3%)
Placebo	49	586	47 (95.9%)	574 (98.0%)	2 (4.1%)	12 (2.0%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 18 and Table 19. The largest upper limits of 90% CI for the PR mean differences between INCB018424 25 mg and placebo and INCB018424 200 mg and placebo are 2.6 ms and 3.2 ms, respectively. There are no subjects who experienced QRS interval greater than 110 ms in both treatment groups.

Table 18: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group = INCB018424 25 mg

	INCB018424 25 mg Δ QRS	Placebo Δ QRS	$\Delta\Delta$ QRS	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	0.1	-0.3	0.4	(-0.4, 1.1)
1	-0.4	-0.7	0.3	(-0.6, 1.2)
1.5	0.0	-0.6	0.6	(-0.3, 1.5)
2	0.3	-0.8	1.1	(0.2, 1.9)
2.5	-0.4	-0.8	0.4	(-0.5, 1.4)
3	-0.6	-0.8	0.2	(-0.7, 1.1)
4	1.1	0.9	0.1	(-0.7, 0.9)
6	-0.6	-1.7	1.0	(0.1, 2.0)
8	-0.4	-0.9	0.4	(-0.6, 1.4)
12	0.3	-1.4	1.6	(0.7, 2.6)
16	1.4	0.4	1.0	(-0.2, 2.1)
24	-0.7	-0.8	0.1	(-0.8, 1.1)

Table 19: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group = INCB018424 200 mg

	INCB018424 200 mg Δ QRS	Placebo Δ QRS	$\Delta\Delta$ QRS	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-0.1	-0.3	0.2	(-0.5, 1.0)
1	-0.3	-0.7	0.4	(-0.5, 1.3)
1.5	-0.7	-0.6	-0.1	(-1.0, 0.7)
2	-0.8	-0.8	-0.0	(-0.9, 0.8)
2.5	-0.1	-0.8	0.8	(-0.2, 1.8)
3	-0.0	-0.8	0.7	(-0.2, 1.6)
4	1.6	0.9	0.7	(-0.1, 1.5)
6	-0.2	-1.7	1.4	(0.5, 2.4)
8	-0.0	-0.9	0.8	(-0.2, 1.8)
12	0.9	-1.4	2.2	(1.3, 3.2)
16	1.3	0.4	0.9	(-0.2, 2.0)
24	-0.1	-0.8	0.7	(-0.2, 1.7)

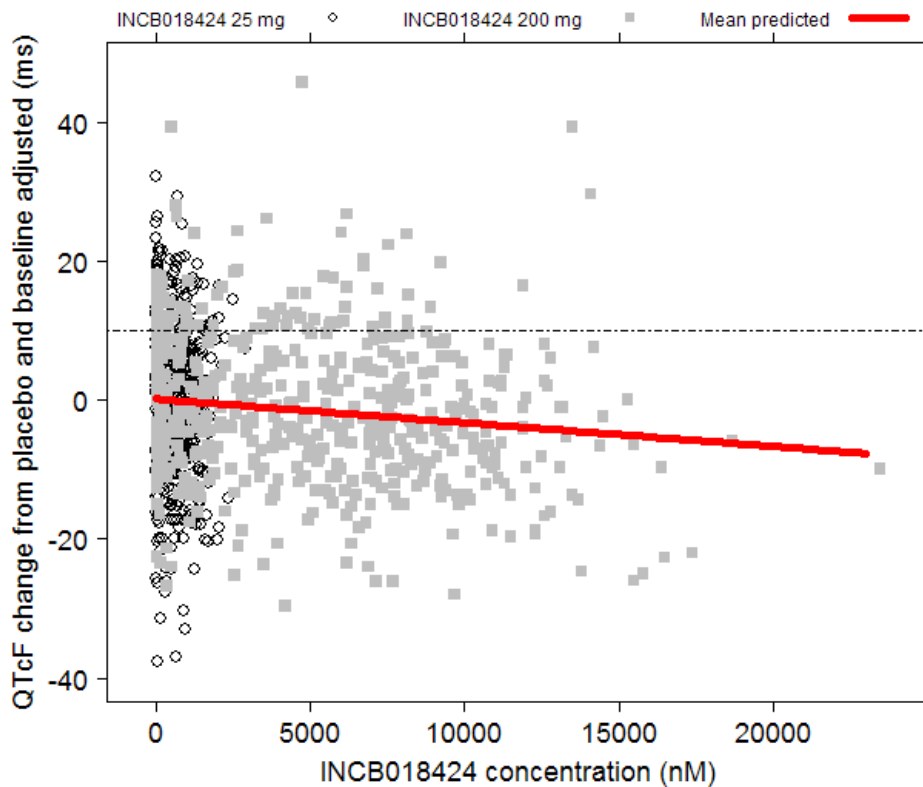
Table 20: Categorical Analysis for QRS

Treatment Group	Total		Value≤100 ms		100 ms<Value≤110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	50	2272	45 (90.0%)	2164 (95.2%)	5 (10.0%)	108 (4.8%)
INCB018424 200 mg	48	575	42 (87.5%)	540 (93.9%)	6 (12.5%)	35 (6.1%)
INCB018424 25 mg	47	562	43 (91.5%)	534 (95.0%)	4 (8.5%)	28 (5.0%)
Moxifloxacin 400 mg	48	571	45 (93.8%)	546 (95.6%)	3 (6.3%)	25 (4.4%)
Placebo	49	586	45 (91.8%)	570 (97.3%)	4 (8.2%)	16 (2.7%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The exposure-response relationship between $\Delta\Delta\text{QTcF}$ and INCB018424 concentrations is visualized in Figure 5 with no evident increase in $\Delta\Delta\text{QTcF}$ with increasing exposure of INCB018424.

Figure 5: $\Delta\Delta$ QTcF vs. INCB018424 Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. According to ECG warehouse statistics less than 1.5% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Two subjects had a PR slightly >200 ms at baseline.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology

Therapeutic dose	10 - 25 mg BID	
Maximum tolerated dose	25 mg BID or 100 mg QD for multiple dosing 200 mg as single dose (highest single dose tested) was well tolerated.	
Principal adverse events	Reversible thrombocytopenia Reversible leukopenia	
Maximum dose tested	Single Dose	200 mg
	Multiple Dose	50 mg BID or 100 mg QD in healthy volunteers 50 mg BID or 200 mg QD in myelofibrosis patients
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean C_{max} = 7.10 μ M (CV% = 19%) Mean $AUC_{0-\infty}$ = 30.7 μ M*h (CV% = 8.6%)
	Multiple Dose	Mean C_{max} : 4.89 μ M (CV% = 22%) for 100 mg QD 2.71 μ M (CV% = 36%) for 50 mg BID Mean AUC_{0-24h} : 17.1 μ M*h (CV% = 27%) for 100 mg QD 17.0 μ M*h (CV% = 31%) for 50 mg BID
Range of linear PK	5 - 200 mg, oral	
Accumulation at steady state	BID doses, Mean $AUC_{0-\tau}$ accumulation = 9.0% (CV% = 6.4%) QD dose, no $AUC_{0-\tau}$ accumulation observed	
Metabolites	Parent compound is the predominant entity in circulation. The mean plasma C_{max} and AUC values for total radioactivity (INCB018424 + metabolites) were ~ 2-fold higher than for INCB018424, suggesting metabolites represent ~ 50% of the circulating drug-related material. Two hydroxylated metabolites in plasma (INCB027598 and INCB025264) were identified as the major metabolites (30% and 14% of parent based on AUC_{0-24}). Other INCB018424-related peaks were < 10% of INCB018424 levels and consisted of mono- and di-hydroxylated and ketone metabolites. Further work to investigate minor metabolites in human plasma is ongoing. The table below shows the activity (IC_{50} values) for the major circulating metabolites in JAK1, 2 and 3 enzyme assays, as well as cell-based assays measuring IL-6 induced proliferation in INA-6 cells (INA6) and IL6 induced	

Metabolites (Cont'd)	STAT3 phosphorylation in human whole blood (hWBA Stat3p). To quantify the pharmacodynamic contribution of parent AND all the active metabolites in circulation, a whole blood pStat3 assay has been established and was used to characterize the single and multiple dose pharmacodynamics of INCB018424.						
		% parent (based on AUC)	JAK1 (nM)	JAK2 (nM)	JAK3 (nM)	INA6 (μ M)	hWBA Stat3p (μ M)
	INCB018424	100	1.9	0.4	6.3	0.2	0.28
	INCB025264 (M16)	14	12	2.5	31	1.1	0.23
INCB027598 (M18)	30	15	2.8	29	1.0	1.5	
Absorption	Absolute/Relative Bioavailability	INCB018424 has characteristics of BCS Class I compound (high solubility and high permeability) with an estimated 95% of orally administered dose absorbed. A formal relative bioavailability study has not been conducted. The mean pharmacokinetic parameters following single oral dose of 25 mg INCB018424 solution in sterile water (study INCB 18424-134, a mass balance and metabolite profile study) were generally similar to that observed with 25 mg tablets (Study INCB 18424-131, a single dose study in healthy volunteers). Results from these two separate clinical studies indicate INCB018424 tablets exhibit near-complete relative oral bioavailability.					
	T _{max}	• Parent - Median T_{max} 1.5 h (range 0.5 - 6.0 h) • Metabolites – Median T_{max} 2.0 h (range 1.0 - 6.0 h)					
Distribution	Vd/F or Vd	Mean Vd/F = 90 L (CV% = 29%)					
	% bound	Mean % bound 96.7% (CV% = 18%)					
Elimination	Route	• Primary route is metabolic biotransformation ($\geq$ 95% of dose). 73.61 $\pm$ 10.18% and 21.92 $\pm$ 5.95% of drug-related material excreted in urine and feces, respectively • Excretion of parent drug in urine and feces combined contribute to < 1% of dose					
	Terminal t _{1/2}	• Mean t_{1/2} 3.2 h (CV% = 28%) • After a single oral dose of ¹⁴C-INCB018424, the terminal half-life of total drug-related material in plasma (INCB018424 + metabolites) was 5.8 h (CV = 13%). No plasma metabolites observed after 12 h post-dose.					
	CL/F or CL	Mean Cl/F = 20.5 L/h (CV% = 31%)					

Intrinsic Factors	Clinical pharmacology studies to specifically evaluate the role of these intrinsic factors have not been conducted. However, covariate analysis was performed using data from Phase 1 studies and the results are summarized below.	
	Age	Age had no significant effect on INCB018424 PK in the range of 18 to 54 years old.
	Sex	No significant difference in PK parameters was observed between male and female subjects after the PK parameters were normalized to body weight.
	Race	No significant difference in PK observed between African-Americans and Caucasians. The ratios (90% CI) of dose normalized exposures between African-Americans and Caucasians were 1.13 (1.00, 1.27) for $AUC_{0-\infty}$ and 0.91 (0.79, 1.05) for C_{max} .
Extrinsic Factors	Hepatic & Renal Impairment	A PK study in hepatic function impaired subjects (Study INCB 18424-137) is underway and will be completed by the end of 2009. A study was conducted in patients with varying degrees of renal impairment (Study INCB 18424-142) and the preliminary data indicates that INCB018424 C_{max} and AUC were essentially unchanged ranging from 79-116% and 93-122%, respectively, as compared to the corresponding values observed in normal healthy subjects.
	Drug interactions	1. Study INCB 18424-133, DDI with potent and moderate CYP3A4 inhibitors: mean increase in INCB018424 C_{max} and AUC was 32% and 91%, respectively, with the coadministration of ketoconazole, and mean increase in INCB018424 C_{max} and AUC was 8.0% and 27%, respectively, with the coadministration of erythromycin. 2. Study INCB 18424-135, DDI with potent CYP3A4 inducer: mean reduction in INCB018424 C_{max} and AUC was 52% and 71%, respectively, following the pretreatment of rifampin. There was no clinically relevant effect on pharmacodynamic activity (IL-6 induced STAT3 phosphorylation) likely secondary to a concomitant increase in active metabolites. 3. Study INCB 18424-136, DDI with methotrexate: mean increase in both INCB018424 C_{max} and AUC was 8% ($p > 0.05$), with the coadministration of methotrexate, not felt to be

Extrinsic Factors (Cont'd)	Drug interactions (Cont'd)	clinically significant. No significant change in the pharmacokinetics of methotrexate and 7-hydroxy methotrexate following administration of INCB018424.
	Food Effects	Administration with high-fat meal moderately decreased INCB018424 mean C_{max} by 24% and slightly increased INCB018424 mean AUC by 4%.
Expected High Clinical Exposure Scenario	The worst case scenario is in the setting of concomitant use of potent CYP3A4 inhibitors. Co-administration of INCB018424 with ketoconazole, a potent CYP3A4 inhibitor, caused a 1.3-fold increase in maximum plasma INCB018424 concentrations and 1.9-fold increase in INCB018424 exposure (ie, AUC). Thus the C_{max} for a 25 mg BID dose in the presence of a potent CYP3A4 inhibitor would be 1.56 μ M, compared with 7.10 μ M for the 200 mg single dose proposed in the TQT Study INCB 18424-138. The AUC for a 25 mg BID dose in the presence of a potent CYP3A4 inhibitor would be 17.2 μ M*h, compared with 30.7 μ M*h for the 200 mg single dose proposed in Study INCB 18424-138. Therefore, with concomitant dosing of potent CYP inhibitors such as ketoconazole, a dose reduction of ~ 50% for INCB018424 is warranted.	

6.2 SCHEDULE OF TREATMENT ASSESSMENTS

Assessment	Screening Phase	Treatment Phase (Periods 1, 2, 3, and 4)			End-of-Treatment/ CRU Discharge	Follow-up or Early Termination
	Visit Day (Range): Day -28 to -2	Check-in Days -1, 7, 14, and 21	Days 1, 8, 15, and 22	Days 2, 9, 16, and 23	Days 2, 9, 16, and 23	Day 36 ± 3
Informed consent	X					
Inclusion/exclusion criteria	X	X ^a				
Medical history	X					
Prior/concomitant medications	X	X	X	X	X	X
Height and body weight	X					
Comprehensive physical examination	X				X	X
Targeted physical assessment		X	X			
Vital signs ^b	X	X	X	X		X
Clinical safety laboratories ^c	X	X		X		X
Urinalysis ^c	X					X
Hepatitis and HIV screen ^c	X					
FSH (postmenopausal females only) ^c	X					
Pregnancy test (female subjects only) ^c	X	X				X
Drug screen ^d	X	X				
12-lead electrocardiograms ^e	X	X				X
Holter monitoring ^e			X	X		
Confined to CRU ^f		X	X	X		
Discharge from CRU					X	
Randomization ^g			X ^a			
Study medication dosing ^h			X			
Plasma pharmacokinetic sampling ⁱ			X	X		
Adverse event assessment ^j	X	X	X	X	X	X

^a Only for Period 1.

^b Vital signs (oral temperature; heart rate; respiratory rate; and automated, seated blood pressure and pulse) were obtained at screening; check-in; and on Day 1 prior to dosing and at approximately 1, 2, 3, 6, and 24 hours post-dose for each dosing period.

^c See [Appendix 2 of the Protocol](#) for a list of laboratory analytes. A serum pregnancy test was obtained at screening and follow-up/ET. A urine pregnancy test was obtained at check-in for each dosing period.

^d See [Appendix 2 of the Protocol](#) for a list of drugs-of-abuse. Alcohol screen was not included at screening. Alcohol screen was included at check-in for each dosing period.

^e Standard ECGs were performed at screening, check-in for each dosing period, and follow-up. Triplicate 12-lead ECG readings were obtained from 12-lead Holter monitors predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours post-dose for each dosing period. On Day 1 only, triplicate 12-lead ECG readings were obtained from 12-lead Holter monitors at 90, 60, and 30 minutes prior to dosing.

^f Subjects were admitted to the CRU on the day prior to dosing for Periods 1, 2, 3, and 4, then discharged the day after dosing.

^g Study drug randomization occurred on Day 1 or Day -1 consistent with site procedures for Period 1 only.

^h Study drug was administered according to the randomization schedule.

ⁱ Blood samples for PK analysis were collected predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours post-dose (after ECG readings from Holter monitors were completed).

^j Adverse events were assessed at least when vital signs were taken.

Abbreviations: CRU=clinical research unit; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus.

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DSI CONSULT: Request for Clinical Inspections

Date: June 14, 2011

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Lauren Iacono-Connors, Acting Team Leader
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Albert Deisseroth, MD, Clinical Reviewer, Division of Hematology Products
Ann Farrell, MD, Acting Director, Division of Hematology Products

From: Amy Baird, Regulatory Product Manager, Division of Hematology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 202192

Applicant/ Applicant contact information (to include phone/email): Incyte Corporation
Ronald Falcone, PhD
VP, Regulatory Affairs
Rt 141 & Henry Clay Road
E336
Wilmington, DE 19880-0336
Tele: 302-498-6846
Email: rfalcone@incyte.com

Drug Proprietary Name: Ruxolitinib Phosphate Tablets

NME or Original BLA (Yes/No): NME

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

PDUFA: 12/3/11

Action Goal Date: 10/4/11

Inspection Summary Goal Date: 8/22/11

DSI Consult

version: 5/08/2008

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Stanford Cancer Center 875 Blake Wilbur Drive, Clinic C Stanford, CA 95405 PI: Jason Gotlib, MD, MS TEL: 650-736-1253 FAX: (650)724-5203 EMAIL:jason.gotlib@stanford.edu	INCB 18424-351	15	Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis
St. Agnes Health Care, Inc. 900 Caton Avenue Baltimore, MD 21229 PI: Carole B. Miller, MD TEL: 410-369-2090 FAX: (410) 368-3517 EMAIL: cmiller@stagnes.org	INCB 18424-351	8	Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis

III. Site Selection/Rationale

Proposal for DSI Inspections for NDA 202192

There are two randomized phase III trials:

- a. INCB 18424-351 (Conducted in the USA, Canada and Australia)
- b. CINC424A2352 (Conducted in Europe)

In the US trial, INCB 18424-351, 309 patients were entered and randomized in 89 sites:

- USA entered 237 patients in 68 sites
- Canada entered 24 patients in 6 sites
- Australia entered 48 patients in 48 sites

I am proposing a site visit at Site #23, because it was the top of all the clinical sites for accrual at an academic center, and a site visit at Site #46, because it was the third highest accruing center and appears to be a proprietary health care facility.

Site#	Name of PI	Institution	Number of Patients
023	Jason Gotlib	Stanford U Stanford, CA	15
046	Carole Miller	St. Agnes Health Care, Inc. Baltimore, MD	8

Rationale for DSI Audits

For the US phase III trial, I am proposing a site visit at Site #23, because it was the top of all the clinical sites for accrual at an academic center, and a site visit at Site #46, because it was the third highest accruing center and appears to be a proprietary health care facility.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

Page 4-Request for Clinical Inspections

Should you require any additional information, please contact Amy Baird, Regulatory Project Manager, at 301-796-4969 or Albert Deisseroth, MD, Clinical Reviewer, at 301-796-4864.

Concurrence: (as needed)

_____ Medical Reviewer
_____ Division Director

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06/16/2011

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06/20/2011

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06/20/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202192Orig1s000

PROPRIETARY NAME REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Proprietary Name Review

Date: September 6, 2011

Reviewer: Lissa C. Owens, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Carlos Mena-Grillasca RPh, Team Leader
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

Drug Name & Strength(s): Jakafi (Ruxolitinib Phosphate) Tablets
5 mg, 10 mg, 15 mg, 20 mg, and 25 mg

Application Type/Number: NDA 202192

Sponsor: Incyte Corporation

OSE RCM #: 2011-2318

***** This document contains proprietary and confidential information that should not be released to the public.*****

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Jakafi, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A, respectively.

1.1 BACKGROUND

This review responds to a request from the Sponsor, Incyte Corporation, dated June 10, 2011 for a promotional and safety assessment of the proposed proprietary name, Jakafi. The Sponsor submitted an external study in support of their proposed proprietary name.

1.2 PRODUCT INFORMATION

Jakafi is an inhibitor of the Janus kinase family of protein tyrosine kinases (JAK's) that is used in the treatment of myelofibrosis. The recommended starting dose is dependent on platelet count starting at either 15 mg twice daily or 20 mg twice daily with dose adjustments in 5 mg twice daily increments. The maximum daily dose recommended is 50 mg (25 mg twice daily). In patients taking concomitant potent CYP3A4 inhibitors Jakafi is dosed once a day. In patients with hepatic impairment a 25% to 50% dose reduction is recommended. Jakafi will be available in 5 mg, 10 mg, 15 mg, 20 mg and 25 mg tablets. Jakafi will be supplied in 60-count bottles to be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1, 2.2, and 2.3 identify specific information associated with the methodology for the proposed proprietary name, Jakafi.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter 'J' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.^{1,2}

To identify drug names that may look similar to Jakafi, the DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (six letters), upstrokes (two, capital letter 'J' and lower case 'k'), one down strokes (lower case 'f'), cross strokes (one, lower case 'f'), and dotted (one, lower case i). Additionally, several letters in Jakafi

¹ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

² Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

may be vulnerable to ambiguity when scripted (See Appendix B). As a result, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Jakafi.

When searching to identify potential names that may sound similar to Jakafi, the DMEPA staff search for names with similar number of syllables (three), stresses (JA-ka-fi, ja-KA-fi or ja-ka-FI), and placement of vowel and consonant sounds (See Appendix B). The Sponsor's intended pronunciation (jak' ah fee) was also taken into consideration, as it was included in the Proprietary Name Review Request. Moreover, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

2.2 PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, an inpatient medication order, outpatient and verbal prescription was communicated during the FDA prescription studies. (See Appendix C for samples and results).

2.3 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT

For this product, the Applicant submitted an external evaluation of the proposed proprietary name. The Division of Medication Error Prevention and Analysis conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in DMEPA's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in the usual practice settings. After the Safety Evaluator has determined the overall risk associated with the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether the Division's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, the Division of Medication Error Prevention and Analysis provides a detailed explanation of these differences.

3 RESULTS

The following sections describe the findings from our database searches, expert panel discussion, prescription analysis studies and safety evaluator risk assessment.

3.1 DATA BASE AND INFORMATION SOURCES

The DMEPA safety evaluator searches yielded a total of 12 names as having some similarity to the name Jakafi.

Eleven of the twelve names were thought to look like Jakafi. They are: Tikosyn, Jinteli, Tekral, Tekamlo, Tykerb, (b) (4) Noxafil, Jenloga, Javavi, Tokelu, and Totect. The remaining name was thought to look and sound similar to Jakafi: Jakafi.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of August 1, 2011.

3.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Jakafi.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.3 PRESCRIPTION ANALYSIS STUDIES

A total of 39 practitioners responded to the prescription analysis studies and none of the responses overlap with existing marketed products. Twenty-two participants interpreted the name correctly, all in the written prescription studies. All the participants in the verbal study misinterpreted the name. Most of the written responses in the verbal study misinterpreted the letter 'J' as the letters 'Ch' and the ending letter 'i' as the letters 'ee'. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.4 EXTERNAL STUDY

The proprietary name risk assessment submitted by Incyte, found the proposed proprietary name acceptable. In the external name risk assessment submitted by the Sponsor, ^{(b) (4)} identified and evaluated a total of 2 drug names: Jalyn and Jantoven. These two names were added to the safety evaluator's assessment.

3.5 SAFETY EVALUATOR SEARCHES

Independent searches by the primary Safety Evaluator did not identify any additional names which were thought to look or sound similar to Jakafi and represent a potential source of drug name confusion. Thus, we identified a total of 14 names as having some similarity to the proposed proprietary name.

One of the 14 names "Jakafi" was eliminated since it was identified on the U.S. Patent and Trademark Office website registered to the Applicant for this product. Thus, a total of 13 names moved forward for evaluation: 2 identified in the External Study submitted by the Applicant and 11 identified in section 3.1 above.

3.6 Comments from the Division of Hematology (DHP)

3.6.1 Initial Phase of Review

In response to the OSE, June 29, 2011 e-mail, DHP forwarded concerns about the proposed name and the use of the pathway, 'JAK' in the name at the initial phase of the name review.

3.6.2 Midpoint of Review

DMEPA notified DHP via e-mail that we found the proposed name, Jakafi, acceptable on August 26, 2011. Per e-mail correspondence from DHP on September 2, 2011, they indicated that they had no objections to the proposed proprietary name, Jakafi.

4 DISCUSSION

This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered their comments accordingly.

4.1 PROMOTIONAL ASSESSMENT

DDMAC had no concerns with the proposed name, Jakafi, from a promotional perspective. However, the division was concerned that the use of the “JAK” pathway in the proprietary name was misleading. DDMAC was made aware of the concern and they changed their opinion and objected to the name Jakafi on July 13, 2011. Before DMEPA issued the denial letter, the sponsor learned of DDMAC’s concern with their proposed name and on July 22, 2011 submitted via email background information in support of their proposed name. This information was later officially submitted as an amendment to the initial request for name review.

On August 1, 2011, DMEPA, DDMAC, and DHP met to discuss DDMAC’s evaluation of the Sponsor’s background package in support of their proposed proprietary name Jakafi. At the meeting DDMAC communicated that they re-evaluated their objection and changed their position based on the applicant’s submission. DDMAC stated, “DDMAC does not feel that it has an appropriate regulatory basis to uphold an objection to the proposed proprietary names from a promotional perspective based only on the fact that the proposed site of drug activity is embedded within the names. Therefore, upon further consideration, DDMAC does not have any objections to the proposed proprietary names, (b) (4) and Jakafi, from a promotional perspective”.

DMEPA and DHP concurred with DDMAC’s final promotional evaluation of the proposed proprietary name Jakafi.

4.2 SAFETY ASSESSMENT

DMEPA identified 13 names for their potential similarity in sound and spelling to the proposed name, Jakafi. We did not identify any other aspects of the name that would be considered as a potential source for error.

Three of the thirteen potentially similar names did not undergo failure mode and effect analysis (FMEA) for the following reasons: No additional information in our internal databases and common drug references, proposed proprietary name that was denied, and the name of a medical condition (see Appendix D).

Failure mode and effects analysis (FMEA) was applied to determine if the proposed proprietary name could potentially be confused with the remaining 10 names and lead to medication errors. This analysis determined that the name similarity between Jakafi and

all of the identified names was unlikely to result in medication error for the reasons presented in Appendix E.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Jakafi, is not vulnerable to name confusion that could lead to medication errors, nor is it considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proposed proprietary name, Jakafi, for this product at this time. DMEPA will notify the Applicant of this determination via letter.

If any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

If you have further questions or need clarifications, please contact Sue Kang, OSE Project Manager, at 301-796-4216.

5.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Jakafi, and have concluded that the name is acceptable.

The proposed proprietary name must be re-reviewed 90 days before approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your June 10, 2011 submission are altered the name must be resubmitted for review. The conclusions upon re-review are subject to change.

6 REFERENCES

1. ***Micromedex Integrated Index*** (<http://csi.micromedex.com>)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO***
(<http://factsandcomparisons.com>)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

DARRTS is a government database used to organize Applicant and Applicant submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

7. ***Electronic online version of the FDA Orange Book***
(<http://www.fda.gov/cder/ob/default.htm>)

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. ***U.S. Patent and Trademark Office*** (<http://www.uspto.gov>)

USPTO provides information regarding patent and trademarks

Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

10. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Stat!Ref (www.statref.com)

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (<http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml>)

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (www.lexi.com)

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.³

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.⁴ DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and

³ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

⁴ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

monitoring the impact of the medication.⁵ DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Applicant’s intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	- Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication - Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters	Names may look similar when scripted, and lead to drug name confusion in written communication

⁵ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

		Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, the DMEPA staff also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten

prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

4. Comments from the OND review Division or Generic drugs

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division responsible for the application for their comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND or OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to concur/not concur with DMEPA's final decision.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁶ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

⁶ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?”

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

- a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that

could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Applicant can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Applicants have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Applicant and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Applicants' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. . (See Section 4 for limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in Name, Jakafi	Scripted may appear as	Spoken may be interpreted as
Capital 'J'	'T', 'Z', 'I', and 'Y'	'G', Ch
lower case 'a'	'c', 'ce,' 'ci,' 'd', 'e', 'o' or 'u'	Any vowel
lower case 'k'	"n', 'x', 'h', 'la'	'c' or 'g'
lower case 'f'	't'	'v'
lower case 'i'	Any vowel	'ee'. 'y' and any vowel

Appendix C: FDA Prescription Study for Jakafi

Figure 1. Jakafi Study Samples (conducted on June 24, 2011)

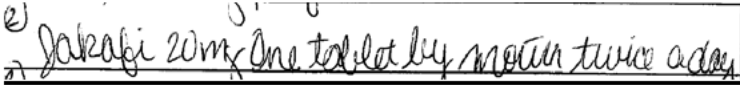
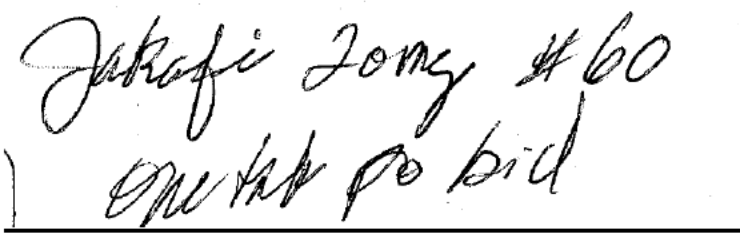
HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
<u>Medication Order</u> 	Jakafi 20 mg One tablet by mouth twice a day #30
<u>Outpatient Rx</u> 	

Table 1: Responses to Prescription Study

Outpatient Prescription	Inpatient Medication Order	Voice Prescription
Jakafi	Jakafi	Chicoffe
Jarafi	Jakafi	Chacoffee
Jakafi	Jakafi	Chicoffee
Jakafi	Jakafi	Chicoffe
Jakafi	Jakafi	Chicofee
Jarofic	Jakafi	Jicoffy
Jakafi	Jakafi	Chickoffee
Jakafic	Jakafi	Chicoffee
Jakafic	Jakafi	Chicaphi
Jakafi	Jakafi	Jacafe
Jakafi	Jakafi	Chicoffee
Jakafi	Jakafi	Jecoffee
	Jakafi	
	Jakafi	
	Jakafi	

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Proprietary Name	Active Ingredient	Noted Similarity to Jakafi	Failure preventions
Javavi	Not Listed	Look	Found on POCA as a proprietary name entered to the database by a Safety Evaluator. However, the name is not in the Proposed Names List. Therefore it seems to be a typo. No additional information was available elsewhere (i.e. L: drive, AIMS, or in common drug references).
Tokelu	None	Look	Found on Micromedex. It is another name for the medical condition 'Tinea imbricata'.
(b) (4)			

Appendix E: Products with orthographic, phonetic and/or multiple differentiating product characteristics minimize the risk for medication errors

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Failure Mode of name confusion prevented by the combination of stated product characteristics as well as orthographic and/or phonetic differences as described.
Jakafi (Ruxolitinib Phosphate)		5 mg, 10 mg, 15 mg, 20 mg, and 25 mg Tablets	15 to 25 mg twice a day	
Tekamlo (Aliskeren hemifumarate and Amlodipine besylate) <i>Orthographic similarities: The letters 'J' and 'T' when scripted can look similar. Both names have an upstroke letter, 'k' in the third position.</i>	Look	150 mg/5 mg, 150 mg/10 mg, 300 mg/5 mg, 300 mg/ 10 mg Tablets	One tablet once a day	Orthographic differences: The ending letters of Jakafi, 'afi' and the ending letters of Tekamlo, 'mlo' help to differentiate between the two names.
Tikosyn (Miglustat) <i>Orthographic similarities: The letters 'J' and 'T' when scripted can look similar. Both names have an upstroke letter, 'k' in the third position.</i>	Look	0.125 mg, 0.25 mg, 0.5 mg Capsules	0.125 mg to 0.5 mg twice a day	Orthographic differences: When scripted the ending of Jakafi 'afi' looks different than Tikosyn, 'syn'.
Jalyn (Dutasteride and Tamsulosin hydrochloride) <i>Orthographic similarities: They both begin with the same letter string 'Ja' followed by an upstroke 'k' in Jakafi and 'l' in Jalyn.</i>	Look	0.5 mg/0.4 mg Capsule	One capsule once a day	Strength: Multiple strengths vs. Single strength Orthographic differences: The ending letters of Jakafi, 'afi' and the ending letters of Jalyn, 'lyn' help to differentiate between the two names.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Failure Mode of name confusion prevented by the combination of stated product characteristics as well as orthographic and/or phonetic differences as described.
Jakafi (Ruxolitinib Phosphate)		5 mg, 10 mg, 15 mg, 20 mg, and 25 mg Tablets	15 to 25 mg twice a day	
Jinteli (Norethindrone and Ethinyl estradiol) <u>Orthographic similarities:</u> Both begin with similar letter strings 'Ja' and 'Ji' which when scripted may look similar. Both share the common letters, 'J,' and 'i'	Look	1 mg/0.05 mg Tablets	One tablet once a day	Strength: Multiple strengths vs. Single strength Orthographic differences: Jakafi has an upstroke letter 'k' in the third position vs. Jinteli which does not. Jakafi has one dotted letter 'i' vs. Jinteli which has two dotted letter 'i'.
Tekral (Diphenhydramine and Pseudoephedrine hcl) <u>Orthographic similarities:</u> The letters 'J' and 'T' when scripted can look similar. Both names have an upstroke letter, 'k' in the third position	Look	100 mg/120 mg Tablets	One tablet every 12 hours	Strength: Multiple strengths vs. Single strength Orthographic differences: The ending letters of Jakafi, 'afi' and the ending letters of Tekral, 'ral' help to differentiate between the two names. Jakafi has a downstroke letter 'f' in the 5 th position vs. Tekral which does not have any downstroke letters. Jakafi has a dotted letter 'i' vs. Tekral which has no dotted letters.
Tykerb (Lapatinib) <u>Orthographic similarities:</u> The letters 'J' and 'T' when scripted can look similar. Both names have an upstroke letter, 'k' in the third position	Look	250 mg Tablets	Five to Six tablets once a day	Strength: Multiple strengths vs. Single strength Dose: One tablet vs. Multiple tablets Orthographic differences The ending letters of Jakafi, 'afi' and the ending letters of Tykerb, 'erb' help to differentiate between the two names. Jakafi has a downstroke letter 'f' in the 5 th position vs. Tykerb which has a downstroke letter 'y' in the 2 nd position. Jakafi has a dotted letter 'i' vs. Tykerb which has no dotted letters.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Failure Mode of name confusion prevented by the combination of stated product characteristics as well as orthographic and/or phonetic differences as described.
Jakafi (Ruxolitinib Phosphate)		5 mg, 10 mg, 15 mg, 20 mg, and 25 mg Tablets	15 to 25 mg twice a day	
Noxafil (Posaconazole) <i>Orthographic similarities: Both share the common letters, 'a', 'f', and 'i'</i>	Look	40 mg/ml Suspension	100 mg to 400 mg two to three times a day	Dosage Form: Tablet vs. Suspension Dosage: Tablet vs. XX ml Orthographic differences: Jakafi has an upstroke letter 'k' in the 3 rd position vs. Noxafil which does not.
Jenloga (Clonidine Hydrochloride) <i>Orthographic similarities: They both begin with similar letter strings 'Ja' and 'Je' that when scripted look similar</i>	Look	0.1 mg Tablets	0.1 mg to 0.6 mg in twice a day	Strength: Multiple strengths vs Single strength Orthographic differences: The ending letters of Jakafi, 'kafi' and the ending letters of Jenloga, 'loga' help to differentiate between the two names. Jakafi has one dotted letter 'i' vs. Jenloga which has no dotted letters.
Jantoven (Warfarin) <i>Orthographic similarities: They both begin with the same letter string 'Ja'. Both share the common letters, 'J' and 'a'</i>	Look	1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg Tablets	Varies per patient	Orthographic differences: Jakafi has 6 letters and may appear shorter when scripted vs. Jantoven which has 8 letters The ending letters of Jakafi, 'kafi' and the ending letters of Jantoven, 'oven' help to differentiate between the two names. Jakafi has a dotted letter 'i' vs. Jantoven which has no dotted letters.
Totect (Dexrazoxane) <i>Orthographic similarities: The letters 'J' and 'T' when scripted can look similar.</i>	Look	500 mg powder for Injection	Day one: 1000 mg/m2 Day two: 1000 mg/m2 Day three: 500 mg/m2	Route of Administration: Oral vs. Intravenous Orthographic differences: The ending letters of Jakafi, 'afi' and the ending letters of Totect, 'ect' help to differentiate between the two names. Jakafi has one dotted letter 'i' vs. Totect which has no dotted letters. Jakafi has a downstroke letter 'f' in the 5 th position vs. Totect which has no downstroke letters. Jakafi contains no cross stroke letters vs. Totect which has two cross stroke letter 't'

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISSA C OWENS
09/06/2011

CARLOS M MENA-GRILLASCA
09/06/2011

CAROL A HOLQUIST
09/06/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202192Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 202192

SUPPL #

HFD # 160

Trade Name Jakafi

Generic Name ruxolitinib

Applicant Name Incyte Corporation

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 for new molecular entity and 7 years for orphan drug designation

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

YES

!

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====
Name of person completing form: Amy Baird
Title: Regulatory Project Manager
Date: November 9, 2011

Name of Office/Division Director signing form: Edvardas Kaminskas, M.D.
Title: Deputy Director, Division of Hematology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

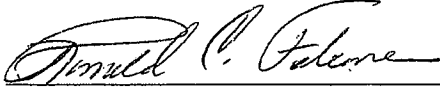
AMY C BAIRD
11/15/2011

EDVARDAS KAMINSKAS
11/16/2011

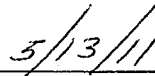
1.3. Administrative Information

3. DEBARMENT CERTIFICATION

Incyte Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Ronald C. Falcone, Ph.D.
Vice President, Regulatory Affairs
Incyte Corporation



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 202192 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Jakafi Established/Proper Name: ruxolitinib Dosage Form: tablets		Applicant: Incyte Corporation Agent for Applicant (if applicable):
RPM: Amy Baird		Division: CDER/OHOP/DHP
NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)		505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. If no listed drug, explain. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ Other (explain) <u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☐ No changes ☐ Updated Date of check: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.
❖ Actions • Proposed action • User Fee Goal Date is <u>12/3/2011</u> • Previous actions (<i>specify type and date for each action taken</i>)		☒ AP ☐ TA ☐ CR ☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): 1P ☒ Fast Track ☐ Rx-to-OTC full switch ☐ Rolling Review ☐ Rx-to-OTC partial switch ☒ Orphan drug designation ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Press Release

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	☒ No ☐ Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)	☒ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire _____
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist³	11-22-2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 11-16-2011
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	N/A

³ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	10-3-2011
❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.	9/7/2011 9/6/2011
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☐ RPM ☒ DMEPA 10/28/2011 ☒ DRISK 10/27/2011 ☒ DDMAC 10/19/2011 ☐ SEALD ☐ CSS ☒ Other reviews DDTCP 10/27/2011
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PerRC <u>N/A</u> • If PerRC review not necessary, explain: <u>Application granted orphan designation</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☐ Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	☒ Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	☒ No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg 11-3-2010
• EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☐ None 11-16-2011
Division Director Summary Review (<i>indicate date for each review</i>)	☒ None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 11-15-2011
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 11-15-2011
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	11-15-2011
• Clinical review(s) (<i>indicate date for each review</i>)	11-4-2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None

⁵ Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	☐ None requested 9/16/2011
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ None
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☐ None
Statistical Team Leader Review(s) (indicate date for each review)	☒ None
Statistical Review(s) (indicate date for each review)	☐ None 9/19/2011
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology review(s) (indicate date for each review)	☐ None 10/27/2011
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☐ None 10/27/2011
• Supervisory Review(s) (indicate date for each review)	☐ None 10/27/2011
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None 10/27/2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☐ No carc 9/16/2011
❖ ECAC/CAC report/memo of meeting	☐ None Mtg 9/13/2011 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	☐ None 10/21/2011
• Branch Chief/Team Leader Review(s) (indicate date for each review)	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	☐ None 10/20/2011 (2 reviews)
❖ Microbiology Reviews	☐ Not needed 8/23/2011
☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	10/20/2011
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	☐ Completed ☐ Requested ☒ Not yet requested ☐ Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

AMY C BAIRD
11/22/2011

Baird, Amy

From: Baird, Amy
Sent: Monday, October 24, 2011 10:26 AM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - FDA PMR/PMC Request

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

The Division of Hematology Products has determined that additional postmarketing information is required. Below are the PMR/PMCs for both efficacy and safety. We require Incyte's written agreement to commit to fulfill these requests as part of the FDA's review of your application. We encourage you to enhance the description further to improve the final product's data and evidence to be obtained. We may identify additional PMR/PMCs later in our review.

1.
NDA #/Product Name: NDA 202192 Ruxolitinib
PMC Description: Commit to provide longer-term efficacy and safety outcomes of current clinical trials (INCB-351 and INCB-352) to provide at least 3 year follow-up data

PMR/PMC Schedule Milestones: Preliminary Protocol Submission MM/YYYY
Final Protocol Submission: MM/YYYY
Study/Trial Completion: MM/YYYY
Final Report Submission: MM/YYYY
Other: MM/YYYY

2.
NDA #/Product Name: NDA 202192 Ruxolitinib
PMR Description: Commit to provide safety findings related to the interval of drug discontinuation in at least 150 patients previously entered onto to INCB-351 and INCB-352 to determine if specific cautions are appropriate to describe discontinuation strategies.

PMR/PMC Schedule Milestones: Preliminary Protocol Submission MM/YYYY
Final Protocol Submission: MM/YYYY
Study/Trial Completion: MM/YYYY
Final Report Submission: MM/YYYY
Other: MM/YYYY

3.
NDA #/Product Name: NDA 202192 Ruxolitinib
PMR Description: Submit a protocol/plan to provide safety information on myelosuppression for up to 144 weeks of therapy following randomization in patients entered on INCB-351 and INCB-352 who are continuing on therapy past 24 and 48 weeks respectively

PMR/PMC Schedule Milestones: Preliminary Protocol Submission MM/YYYY
Final Protocol Submission: MM/YYYY
Study/Trial Completion: MM/YYYY
Final Report Submission: MM/YYYY

Other:

MM/YYYY

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
10/24/2011

Baird, Amy

From: Baird, Amy
Sent: Tuesday, October 18, 2011 12:33 PM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - OSE Completed Review of Container Label

Importance: High

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

The FDA's Office of Surveillance and Epidemiology has completed the review of the proposed labels for Jakafi and have the following comments. Please attempt to provide revised labels NLT COB October 21, 2011.

Container Label

1. Ensure the size of the established name is at least half as large as the letters comprising the proprietary name and has a prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10 (g)(2).
2. Revise the presentation of the established name to read "(Ruxolitinib) Tablets". As currently presented as the salt form is inconsistent with the presentation of the strength statement in the base form.
3. Decrease the prominence of the 'TM' next to the proprietary name by using a smaller font.
4. Decrease the prominence of the color block that appears below the strength to allow for implementation of comment 1.
5. Decrease the prominence of the "Rx only" statement by un-bolding and using a smaller font.
6. Revise the statement "Dosage and Use: See Package Insert" to read "Usual Dosage: See Prescribing Information".

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
10/18/2011



NDA 202192

INFORMATION REQUEST

Incyte Corporation
Attention: Ronald Falcone, Ph.D.
Vice President, Regulatory Affairs
Experimental Station
Rt. 141 & Henry Clay Road, E336
Wilmington, DE 19880-0336

Dear Dr. Falcone:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for JAKAFI™ (ruxolitinib) tablets.

We also refer to your September 27, 2011 submission, containing Chemistry, Manufacturing and Controls (CMC) information in response of an information request dated September 16, 2011.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

For container labeling:

1. Revise the drug name from “JAKAFI™ (ruxolitinib phosphate) tablets” to “JAKAFI™ (ruxolitinib) tablets”, as the strengths of the drug product are based on the ruxolitinib free base.
2. Revise the storage condition on container labels as follows:
Store at room temperature 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].
3. Revise the name in the Structured Product Labeling (SPL) to “ruxolitinib tablets” from “ruxolitinib phosphate tablets”.

For drug product container/closure system.

4. Provide USP <671> test results. Also, ensure the inner seal is removed prior to testing. Refer to Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, May 1999 (Section III.D). We note that in your 27-Sep-2011 response to comments No. 5 (b) under drug product in Agency's information request of 16-Sept-2011, USP <661> test results were provided, but USP <671> test results were not included.

Follow up comments for the Response to Information Request #3 dated 27-Sep-2011.

5. Provide in a tabular format the batch number and batch size for all the common blends from which subsequent batches of tablets across five different strengths were manufactured in section 3.2.P.5.4 in Tables 3, 4, and 5 with the phase 3/commercial formulation. In your response, you did not specify the batch number and batch size for (b) (4)

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Project Manager, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
10/04/2011

Baird, Amy

From: Baird, Amy
Sent: Monday, October 03, 2011 10:56 AM
To: Ronald Falcone
Subject: NDA 202192 Ruxolitinib - FDA Pharm/Tox Request for Information

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the Pharmacology/Toxicology review team, please provide a response to the following requests for information.

1. Indicate whether the impurities (b) (4) were present in the 26-week Tg.rasH2 carcinogenicity study.

2. What were the levels of these impurities if they were present in the carcinogenicity study.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
10/03/2011



NDA 202192

**METHODS VALIDATION
MATERIALS RECEIVED**

Incyte Corporation
Attention: Ronald C. Falcone, Ph.D.
Route 141 & Henry Clay Road
Building 336
Wilmington, DE 19880

Dear Ronald C. Falcone, Ph.D.:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ruxolitinib Phosphate Tablets, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg and to our 9/13/2011 letter requesting sample materials for methods validation testing.

We acknowledge receipt on 9/28/2011, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
09/28/2011

Baird, Amy

From: Baird, Amy
Sent: Thursday, September 22, 2011 3:34 PM
To: Ronald Falcone
Subject: NDA 202192 Jakafi - FDA Clinical Pharmacology Request

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the Clinical Pharmacology review team, please provide a response to the following requests for information NLT COB September 28, 2011.

- We note your clinical pharmacology highlights report states "After a single oral dose of 14C-INCB018424, the terminal $t_{1/2}$ of total drug-related material (ruxolitinib + metabolites) in plasma was 5.8 h (CV = 13%) (Study [INCB 18424-134]);" however we are unable to find this analysis in the report for Study [INCB 18424-134]. Please provide the location of this information or submit this analysis.
- It appears that sample stability following long term frozen storage for assay's DMB-07.111.1 and DMB-10.14.1 was not reported. Please confirm whether or not this was assessed. If it was please provide the location of this information or submit it.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
09/22/2011



NDA 202192

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Incyte Corporation
Attention: Ronald C. Falcone, Ph.D
Vice President, Regulatory Affairs
Rt. 141 & Henry Clay Road
Building 336
Wilmington, Delaware 19880-0336

Dear Dr. Falcone:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ruxolitinib Phosphate Tablets.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by (b)(4)¹. The pervasiveness and egregious nature of the violative practices by (b)(4) has led FDA to have significant concerns that the bioanalytical data generated at (b)(4) from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented (b)(4) and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by (b)(4) (b)(4) during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

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(

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by [REDACTED]^{(b)(4)} during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Janet Jamison, Regulatory Project Manager, at (301) 796-2313.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Research and Evaluation

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/s/

ANN T FARRELL
09/16/2011



NDA 202192

INFORMATION REQUEST

Incyte Corporation
Attention: Ronald C. Falcone, Ph.D.
Vice President, Regulatory Affairs
Rt. 141 & Henry Clay Road, E336
Wilmington, DE 19880-0336

Dear Dr. Falcone:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ruxolitinib Phosphate Tablets.

We also refer to your June 3, 2011, July 8, 2011, August 1, 2011, August 30, 2011 submissions, containing Chemistry, Manufacturing, and Control section of your NDA.

We are reviewing the Chemistry, Manufacturing, and Control section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

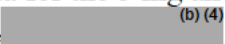
Drug Substance

1. For all proposed starting materials, provide the following information in Section 3.2.S.2.3:
 - (a) A detailed description of the impurity profile.
 - (b) Data from purging studies as generated by using impurities in the proposed starting materials, at levels higher than those proposed in the starting material specifications. The data should adequately demonstrate the ability of the manufacturing process to remove and control impurities that may be present in the proposed starting materials at the desired levels in the drug substance.
 - (c) Justification of the starting material specifications based on the results from purging studies.
 - (d) Change control strategies for any potential revisions to the manufacture of the proposed starting materials including the vendor's reporting of any changes in starting material specifications or control.

2. For the specification for Intermediate (b) (4) (Section 3.2.S.2.4), establish acceptance criteria and incorporate specifications for assay and achiral purity. Include a justification for the proposed limits.

3. Include testing for residue on ignition in the drug substance specification. Your justification for omitting this test, as provided in Section 3.2.S.4.5, is not acceptable.
4. For the drug substance specification (Table 1, Section 3.2.S.4.1), designate only one analytical procedure (either IC/018424/024 or IC/018424/033) as the regulatory method for the determination of phosphate content. The other method can be designated as an alternate method. Revise and submit the drug substance specification accordingly.
5. In Section 3.2.S.6 for the drug substance packaging materials, provide specific 21 CFR citations indicating compliance with 21 CFR requirements for direct food contact.

Drug Product

1. Provide in a tabular format the formulation number and composition for Batch 1399-2644-RD-3B (10 mg), Batch 1399-2644-RD-2B (15 mg), Batch 1399-2493-RD-sublot 2 (20 mg) and Batch 399-2612-R-18KP (25 mg) for studies described in section 3.2.P.2.2.1.2.
2. In addition to the 5 mg tablet strength (Tables 3 and 4; Module 3.2.P.2, page 5), provide similar comparative multipoint dissolution profile data (mean, individual, and plots) for the 25 mg tablet strength manufactured using formulation 18424-001-00 and formulation 18424-007-00 in order to encompass the entire tablet strengths.
3.  (b) (4)
4. Submit data demonstrating that  (b) (4)
5. Provide the following for the container/closure system:
 - (a) Confirmation that all packaging components (in section 3.2.P.7.1) conform to appropriate CFR food additive regulations. Provide specific 21 CFR references for each component.
 - (b) USP <661> and <671> testing results.
6. Provide test results from identification, assay, and degradation product analysis for the nasogastric tube compatibility study and for the tablet (aqueous suspension) stability study to support the proposed maximum hold period.
7. Provide an explanation for the decrease in dissolution (5 min, 15 min, and 30 min) for certain lots [e.g., Lot A51341B (25 mg) and Lot A51342B (25 mg)].
8. Provide comparative data for the 5 mg and 25 mg tablets that indicates the correlation between tablet hardness,  (b) (4) and dissolution at different time points of the stability studies.

If you have any questions, call Tu-Van Lambert, Product Quality Regulatory Health Project Manager, at (301) 796-4246.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
09/16/2011



NDA 202192

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Incyte Corporation
Attention: Ronald C. Falcone, Ph.D.
Route 141 & Henry Clay Road
Building 336
Wilmington, DE 19880

Dear Ronald C. Falcone, Ph.D.:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ruxolitinib Phosphate Tablets, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg.

We will be performing methods validation studies on Ruxolitinib Phosphate Tablets, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg, as described in NDA 202192.

In order to perform the necessary testing, we request the following sample materials and equipments:

Sample

30 -- Ruxolitinib Phosphate Tablets, 5 mg/ tablet
300 mg - INCB018424 Phosphate Drug Substance

Standards

500 mg - INCB018424 Phosphate Reference Standard

(b) (4)

(b) (4)

Equipment

- 1 - Zorbax Eclipse XDB-C18, 3.5 μ m, 4.6 x 150 mm
- 1 - Zorbax SB-C18, 3.5 μ m, 4.6 mm x 150 mm
- 1 - Chiralcel OD, 10 μ m, 250 x 4.6 mm

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
09/13/2011

Baird, Amy

From: Baird, Amy
Sent: Thursday, September 08, 2011 2:14 PM
To: Ronald Falcone
Subject: NDA 202192 Ruxolitinib - FDA Pharm/Tox Requests

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the pharmacology/toxicology review team, please provide a response to the following requests for information.

We note that you have not provided the complete data for the Ames tests conducted with the impurities. For evaluation of the mutagenicity potential of the 6 impurities with structural aler (b) (4) please submit the study reports of Ames tests with detailed information, such as the basis for selection of concentrations and the number of colonies under the conditions tested.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
09/08/2011



NDA 202192

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Incyte Corporation
Rt. 141 & Henry Clay Road
Building E336
Wilmington, Delaware 19880-0336

ATTENTION: Ronald C. Falcone, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Falcone:

Please refer to your New Drug Application (NDA) dated June 3, 2011, received June 3, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ruxolitinib Phosphate Tablets, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg.

We also refer to your June 10, 2011, correspondence, received June 10, 2011, and your August 4, 2011, amendment, received August 4, 2011, requesting review of your proposed proprietary name, Jakafi. We have completed our review of the proposed proprietary name, Jakafi and have concluded that it is acceptable.

The proposed proprietary name, Jakafi, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your June 10, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Amy Baird at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
09/07/2011

Baird, Amy

From: Baird, Amy
Sent: Friday, August 26, 2011 4:18 PM
To: Ronald Falcone; 'Neil Wummer'
Subject: NDA 020192 Ruxolitinib - Request regarding Container Labels

Ron and Neil,

Please refer to the NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis." We also refer to your submission dated August 28, 2011, which provided a clearer image of the container labels.

There seems to be some discrepancy as to which carton and container labels are the correct version that Incyte will be using to market the product. For instance...

[Redacted content]

In order to confirm which are the correct labels, please officially submit a letter confirming the correct color of the labels and also provide another copy of these labels. Please do not make reference to any previous submissions in your response.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
08/26/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, August 17, 2011 11:36 AM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - FDA Request for Better Resolution Carton/Container Labels

Ron,

Please refer to the NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis." We also refer to your submission dated August 5, 2011, providing a response to the FDA August 3, 2011, e-mail requesting better quality images of the container/carton labels.

The FDA team has reviewed your August 5, 2011, submission and still find the images difficult to read. Please provide mock-ups of the proposed container/carton labels as an electronic submission to your NDA, but also provide a paper copy of the labels directly to myself via courier. Please send the paper copy to the address below.

Amy Baird
Food and Drug Administration
10903 New Hampshire Ave.
WO #22, Room 1223
Silver Spring, MD 20993

Regards,

[Amy Baird](#)
[Regulatory Project Manager](#)
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
08/17/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, August 03, 2011 2:52 PM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - Labeling Request

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the FDA review team, provide responses to the following requests for information.

The images of the container labels submitted in both the Proprietary Name Request dated June 10, 2011, and in the original NDA submission are not legible. Can you please submit a better quality/readable images of the container labels. Perhaps a better resolution image or mock up samples?

Please submit this NLT COB August 8, 2011.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
08/03/2011



NDA 202192

FILING COMMUNICATION

Incyte Corporation
Attention: Ronald C. Falcone, Ph.D.
Vice President, Regulatory Affairs
Route 141 & Henry Clay Road
Building 336
Wilmington, DE 19880-0336

Dear Dr. Falcone:

Please refer to your New Drug Application (NDA) dated June 3, 2011, received June 3, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Ruxolitinib Phosphate Tablets.

We also refer to your amendments dated June 10, July 8 and 12, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is December 3, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 4, 2011.

We request that you submit the following information:

1. Regarding Study 352, provide a one record per subject dataset including primary, secondary endpoints, patient demographics and disposition.
2. Your submission includes two proposed comparability protocols for an alternate drug substance and drug product manufacturer. Identify the proposed alternate drug substance and drug product manufacturer.
3. Your CP for an alternate drug substance manufacturer states “There will be no major manufacturing process modifications; no changes in acceptance criteria and no major changes to analytical methods for starting materials, intermediates, reagents and solvents involved. The scale of the drug substance manufacture will be comparable with the approved commercial scale. Equipment changes will be limited to those needed to accommodate the site change.” A similar statement is included in your drug product CP. Revise your CP to fully describe all CMC changes for both manufacturers.
4. In your CP for the alternate drug substance manufacturer, specify the manufacturing process that will be used at the alternate manufacturing site. Your submission states that “Incyte may elect to file for an alternate site to manufacture the ruxolitinib phosphate drug substance using only [REDACTED] (b) (4) initially. In this case, the request to qualify the site for [REDACTED] (b) (4) will follow at a later date.”
5. Revise your drug substance CP to include drug substance characterization analysis.
6. Your request for a proposed reporting category of a CBE-0 is not acceptable.
7. Each proposed CP is a stand alone submission. Revise your CP’s to include all changes and acceptance criteria for each specified test to demonstrate equivalence between pre- and post-change material.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Acting Director
Division of Hematology Drug Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
08/02/2011

Baird, Amy

From: Baird, Amy
Sent: Monday, August 01, 2011 2:36 PM
To: 'Ronald Falcone'
Subject: RE: NDA 202192 Ruxolitinib - FDA CMC, Clinical Pharmacology, and Biometrics requests

Ron,

Thank you for the email below.

Per the request of the FDA review team, please identify the name of the dataset (one dataset) that is one record per patient and includes primary endpoint, secondary endpoints, patient demographics and disposition for Study 352. This dataset should be similar in structure to 'ASEFF2.xpt' for Study 351.

Thanks,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

From: Ronald Falcone [mailto:rfalcone@incyte.com]
Sent: Friday, July 29, 2011 10:01 AM
To: Baird, Amy
Subject: RE: NDA 202192 Ruxolitinib - FDA CMC, Clinical Pharmacology, and Biometrics requests

Dear Amy,

In response to your email of July 27, 2011, which contained requests from CMC, Clinical Pharmacology, and Biometrics regarding the review of NDA 202192, I have attached responses. Incyte plans to provide the formal eCTD response in the near future.

Please let me know if you have questions.

Kind Regards,
Ron

Ron C Falcone, PhD
Vice President, Regulatory Affairs
Incyte Corporation
E400/6220A
Rt 141 & Henry Clay Rd
Wilmington, DE 19880

Work: 302-498-6846
Mobile: 610-457-2258

From: Baird, Amy [mailto: Amy.Baird@fda.hhs.gov]
Sent: Wednesday, July 27, 2011 11:28 AM
To: Ronald Falcone
Subject: NDA 202192 Ruxolitinib - FDA CMC, Clinical Pharmacology, and Biometrics requests

Ron,
Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the FDA review team, please provide responses to the following requests for information.

Chemistry, Manufacturing, and Controls (CMC)

1. Your submission includes two proposed comparability protocols for an alternate drug substance and drug product manufacturer. Identify the proposed alternate drug substance and drug product manufacturer.
2. Your CP for an alternate drug substance manufacturer states "There will be no major manufacturing process modifications; no changes in acceptance criteria and no major changes to analytical methods for starting materials, intermediates, reagents and solvents involved. The scale of the drug substance manufacture will be comparable with the approved commercial scale. Equipment changes will be limited to those needed to accommodate the site change." A similar statement is included in your drug product CP. Revise your CP to fully describe all CMC changes for both manufacturers.
3. In your CP for the alternate drug substance manufacturer, specify the manufacturing process that will be used at the alternate manufacturing site. Your submission states that "Incyte may elect to file for an alternate site to manufacture the ruxolitinib phosphate drug substance using only (b) (4) initially. In this case, the request to qualify the site for (b) (4) will follow at a later date."
4. Revise your drug substance CP to include drug substance characterization analysis.
5. Your request for a proposed reporting category of a CBE-0 is not acceptable.
6. Each proposed CP is a stand alone submission. Revise your CP's to include all changes and acceptance criteria for each specified test to demonstrate equivalence between pre- and post-change material.

Biometrics

For Study 352, provide a one record per subject dataset including primary, secondary endpoints, patient demographics and disposition.

Clinical Pharmacology

We note that in the dataset recently provided for study DMB-10.55.1 the reported exposure (aucinf, AUClast, Cmax) for the parent compound (INCB018424) for each subject differs from that reported for the same subjects in Study INCB 18424-137 (see attached). Please provide the following: a rationale for this discrepancy, whether a similar discrepancy should be expected for other metabolite studies evaluated as part of the DMB-10.55.1 study, and how the sponsor believes the metabolite to parent ratios reported in DMB-10.55.1 should be interpreted in light of this discrepancy.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager

Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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AMY C BAIRD
08/01/2011

Baird, Amy

From: Baird, Amy
Sent: Monday, August 01, 2011 2:26 PM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - FDA Clinical Request for Information

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the FDA review team, provide responses to the following requests for information. Please provide the response NLT August 12, 2011.

Please provide the following information in a list of all patients on INCB-351 and INCB-352 who achieved a $\geq 35\%$ reduction of spleen volume (for each patient individually) on the ruxolitinib arms:

1. Date of initiation of ruxolitinib therapy, patient identification number from NDA 202192.
2. Date of achievement of $\geq 35\%$ reduction of spleen volume
3. Interval between the time of achievement of $\geq 35\%$ reduction of spleen volume and the time of data lock for the submission of NDA 202192 on June 3, 2011 (if the patient had not progressed by the time of data lock).
4. Interval between the time of achievement of $\geq 35\%$ reduction of spleen volume and the time of a regrowth of the spleen volume by 25% from the nadir (if that occurred) if that occurred before the data lock before the June 3, 2011 submission of the NDA 202192.

Please provide similar information for INCB-351 patients on the ruxolitinib arm who achieved a reduction of Total Symptom Score $\geq 50\%$ (for each patient individually).

1. Date of initiation of ruxolitinib therapy, patient identification number from NDA 202192 and the patient identification number from NDA 202192.
2. Date of achievement of a reduction by $\geq 50\%$ of the Total Symptom Score
3. Interval between the time of achievement of reduction by $\geq 50\%$ of the Total Symptom Score and the time of data lock for the submission of NDA 202192 on June 3, 2011 (if the patient had not progressed by the time of data lock).
4. Interval between the time of achievement of $\geq 50\%$ of the Total Symptom Score and the time of progression if that occurred before the time of data lock prior to the June 3, 2011 of the NDA 202192, along with the criteria used to define progression of symptoms after achieving a reduction of $\geq 50\%$ of the Total Symptom Score.

Please do not hesitate to contact me should you have any questions.

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
08/01/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, July 27, 2011 11:28 AM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - FDA CMC, Clinical Pharmacology, and Biometrics requests

Attachments: study137vsdmb10551.pdf

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the FDA review team, please provide responses to the following requests for information.

Chemistry, Manufacturing, and Controls (CMC)

1. Your submission includes two proposed comparability protocols for an alternate drug substance and drug product manufacturer. Identify the proposed alternate drug substance and drug product manufacturer.
2. Your CP for an alternate drug substance manufacturer states "There will be no major manufacturing process modifications; no changes in acceptance criteria and no major changes to analytical methods for starting materials, intermediates, reagents and solvents involved. The scale of the drug substance manufacture will be comparable with the approved commercial scale. Equipment changes will be limited to those needed to accommodate the site change." A similar statement is included in your drug product CP. Revise your CP to fully describe all CMC changes for both manufacturers.
3. In your CP for the alternate drug substance manufacturer, specify the manufacturing process that will be used at the alternate manufacturing site. Your submission states that "Incyte may elect to file for an alternate site to manufacture the ruxolitinib phosphate drug substance using only (b) (4) initially. In this case, the request to qualify the site for (b) (4) will follow at a later date."
4. Revise your drug substance CP to include drug substance characterization analysis.
5. Your request for a proposed reporting category of a CBE-0 is not acceptable.
6. Each proposed CP is a stand alone submission. Revise your CP's to include all changes and acceptance criteria for each specified test to demonstrate equivalence between pre- and post-change material.

Biometrics

For Study 352, provide a one record per subject dataset including primary, secondary endpoints, patient demographics and disposition.

Clinical Pharmacology

We note that in the dataset recently provided for study DMB-10.55.1 the reported exposure (aucinf, AUClast, Cmax) for the parent compound (INCB018424) for each subject differs from that reported for the same subjects in Study INCB 18424-137 (see attached). Please provide the following: a rationale for this discrepancy, whether a similar discrepancy should be expected for other metabolite studies evaluated as part of the DMB-10.55.1 study, and how the sponsor believes the metabolite to parent ratios reported in DMB-10.55.1 should be interpreted in light of this discrepancy.



study137vsdmb105
51.pdf (11 KB)...

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
07/27/2011

Baird, Amy

From: Baird, Amy
Sent: Tuesday, July 12, 2011 10:44 AM
To: 'Ronald Falcone'
Subject: RE: NDA 202192 ruxolitinib - FDA Clinical Pharmacology Request

Ron,

Thank you for your email below which provides a response to the FDA Clinical Pharmacology requests.

Per the Clinical Pharmacology review team, please provide a response to the following:

Please clarify if the phrase "data was not generated" in your response 3.5.1 should be taken to mean the samples were not collected all, collected but not bioanalyzed, or bioanalyzed but not incorporated into the statistical/PK analysis plan.

While we note your argument regarding the importance of protein binding, we are not persuaded by it. If the raw data for unbound concentrations in the renal and hepatic studies exist please submit it in SAS transport format with additional variables that would allow a summary by impairment class and merging with other data sets to include other pertinent variables that have already been submitted.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

From: Ronald Falcone [mailto:rfalcone@incyte.com]
Sent: Thursday, July 07, 2011 2:52 PM
To: Baird, Amy
Subject: RE: NDA 202192 ruxolitinib - FDA Clinical Pharmacology Request

Dear Amy,

In response to your email of June 29, 2011, which contained requests from the Clinical Pharmacology review team, Incyte will provide a full eCTD response with all requested data sets by Tuesday July 12. In advance of the full formal submission, I have attached 2 pdf files: the 1st file provides textual responses to questions (raw data sets for questions #1 and #8 will accompany the eCTD response); the 2nd file contains the study report (CMC 11.11.1) for the nasogastric tube study, which was requested in question #1.

Please let me know if I can be of further assistance.

Kind regards,
Ron

Ron C Falcone, PhD

Vice President, Regulatory Affairs
Incyte Corporation
E400/6220A
Rt 141 & Henry Clay Rd
Wilmington, DE 19880

Work: 302-498-6846
Mobile: 610-457-2258

From: Baird, Amy [mailto:Amy.Baird@fda.hhs.gov]
Sent: Wednesday, June 29, 2011 1:08 PM
To: Ronald Falcone
Subject: NDA 202192 ruxolitinib - FDA Clinical Pharmacology Request

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the clinical pharmacology review team, please provide a response to the following requests for information within 10 business days. If this information has already been submitted, please provide the location within the eCTD.

1. Please provide a complete study report and raw data set in electronic format (i.e., SAS transport files) for the Nasogastric tube study summarized in Section 1.4 of module 3.2.P.8
2. Please provide a table listing the different tablet formulations used in the various human clinical studies or affirm that the to-be-marketed image was used in all studies.
3.  (b) (4)
4. Please confirm that the formulation used in the food effect sub- study in study INCB 18424-131 was the to-be-marketed formulation.
5. We note in both your hepatic impairment (INCB 18424-137) and renal impairment (INCB 18424-142) studies that the fraction unbound parameter was part of your PK analysis plan yet these data are not present in your report or your raw data sets. Please provide your analysis of this parameter and the respective raw data set in electronic format (i.e., SAS transport files) for each of these studies. If this information has already been submitted please provide the location in the eCTD.
6. Please provide the raw data set in electronic format (i.e., SAS transport files) for each of the following studies:
 - a. DMB-10.43.1
 - b. DMB-10.55.1
 - c. DMB-06.168.1

d. IN VITRO-11.01.1

- 7. Please provide file definitions for the raw datasets associated with study INCB 18424-251
- 8. Please provide the Provide Bioanalytical Report(s) for studies DMB-10.43.1 and DMB-10.55.1
- 9. We noticed that you submitted the dataset for PopPK analysis and PK/PD analyses. Please submit the each PK and PD datasets for each clinical study and the programs you used to support the individual PK analysis in each study.
- 10. In PopPK dataset, please clarify the difference regarding the coding for the following variables:
 - e. Variable "HEPCLS": both 2 and 3 are coded for "Mild impairment" in the Define.PDF file
 - f. Variable "CYPInd" both 3 and 4 are coded for "weak inducers" in the Define.PDF file

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
 Regulatory Project Manager
 Division of Hematology Products, CDER, FDA
 10903 New Hampshire Ave
 WO #22, Room 1223
 Silver Spring, MD 20993
 Telephone: 301-796-4969
 Facsimile: 301-796-9845
 Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
07/12/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, June 29, 2011 3:23 PM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - FDA CMC Request

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the CMC review team, please provide a response to the following requests for information within 14 business days.

1. Under Module 3.2.P.2.2, Section 2.1.2.2 (p.5), you provided the dissolution data of the 5 representative batches, 5 mg (Lot A53228), 10 mg (Batch 1399- 2644-RD-3B), 15 mg (Batch 1399-2644-RD-2B), 20 mg (Batch 1399-2493-RD-sublot 2), and 25 mg (Batch 399-2612-R-18KP) tablets strengths in three dissolution media, 0.1 N HCl, and pH 4.5 and pH 6.8 buffer.

You reported that the 5 mg (the reference drug product and the Phase-3 biobatch), 10 mg, 15 mg, 20 mg, and 25 mg strengths exhibit rapid (b) (4) of the drug dissolved in < 15 min in each of the three dissolution media) and similar dissolution profiles. However, the lot/batch manufacturing information on the 4 higher strengths could not be located in the NDA (except for the size of the 5 mg biobatch A53228; M3.2.P.8.1, Table 4, p.4).

Therefore, please provide the needed information (manufacturing date, site, and batch size) on the 4 higher strengths for review so that the proposed specifications ($Q = \text{span style="background-color: #cccccc; color: #000000;">(b) (4)$ at 30 min) using the proposed dissolution method, USP 2 (paddle) with 50 rpm in 0.1 N HCl medium can be evaluated.

2. You requested the Agency's review on your IND amendment (SN-235) dated 01/17/11 for the CMC investigational study protocol entitled:

"Evaluation of Stability and Dosing of Ruxolitinib Phosphate (INCB018424 Phosphate) Tablets as Suspension to Support Nasogastric Administration"

The Agency reviewed the protocol and forwarded the comments to you on 05/27/11. Please respond to the Agency's comments and provide your justifications for the results of the above *in vitro* stability study (already submitted in the NDA) to support the Nasogastric administration of your product.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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AMY C BAIRD
06/29/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, June 29, 2011 1:08 PM
To: 'Ronald Falcone'
Subject: NDA 202192 ruxolitinib - FDA Clinical Pharmacology Request

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the clinical pharmacology review team, please provide a response to the following requests for information within 10 business days. If this information has already been submitted, please provide the location within the eCTD.

1. Please provide a complete study report and raw data set in electronic format (i.e., SAS transport files) for the Nasogastric tube study summarized in Section 1.4 of module 3.2.P.8
2. Please provide a table listing the different tablet formulations used in the various human clinical studies or affirm that the to-be-marketed image was used in all studies.
3.  (b) (4)
4. Please confirm that the formulation used in the food effect sub- study in study INCB 18424-131 was the to-be-marketed formulation.
5. We note in both your hepatic impairment (INCB 18424-137) and renal impairment (INCB 18424-142) studies that the fraction unbound parameter was part of your PK analysis plan yet these data are not present in your report or your raw data sets. Please provide your analysis of this parameter and the respective raw data set in electronic format (i.e., SAS transport files) for each of these studies. If this information has already been submitted please provide the location in the eCTD.
6. Please provide the raw data set in electronic format (i.e., SAS transport files) for each of the following studies:
 - a. DMB-10.43.1
 - b. DMB-10.55.1
 - c. DMB-06.168.1
 - d. IN VITRO-11.01.1
7. Please provide file definitions for the raw datasets associated with study INCB 18424-251
8. Please provide the Provide Bioanalytical Report(s) for studies DMB-10.43.1 and DMB-10.55.1
9. We noticed that you submitted the dataset for PopPK analysis and PK/PD analyses. Please submit the each PK and PD datasets for each clinical study and the programs you used to support the individual PK analysis in each study.
10. In PopPK dataset, please clarify the difference regarding the coding for the following variables:
 - a. Variable "HEPCLS": both 2 and 3 are coded for "Mild impairment" in the Define.PDF file
 - b. Variable "CYPInd" both 3 and 4 are coded for "weak inducers" in the Define.PDF file

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird

Regulatory Project Manager

Division of Hematology Products, CDER, FDA

10903 New Hampshire Ave

WO #22, Room 1223

Silver Spring, MD 20993

Telephone: 301-796-4969

Facsimile: 301-796-9845

Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
06/29/2011

REQUEST FOR CONSULTATION

TO (Office/Division): **QT/IRT Team Interdisciplinary Review Team**
Attention: **Devi Kozeli**

FROM (Name, Office/Division, and Phone Number of Requestor): **Amy Baird, Division of Drug Oncology Products**

DATE
6-29-2011

IND NO.

NDA NO.
202192

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
6-3-2011

NAME OF DRUG
Ruxolitinib

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
8-29-2011

NAME OF FIRM: **Incyte Corporation**

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END-OF-PHASE 2a MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ END-OF-PHASE 2 MEETING	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ RESUBMISSION	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ SAFETY / EFFICACY	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE / ADDITION	☐ PAPER NDA	☐ OTHER (SPECIFY BELOW):
☐ MEETING PLANNED BY	☐ CONTROL SUPPLEMENT	

II. BIOMETRICS

☐ PRIORITY P NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END-OF-PHASE 2 MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER (SPECIFY BELOW):
☐ OTHER (SPECIFY BELOW):	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILITY STUDIES	☐ PROTOCOL - BIOPHARMACEUTICS
☐ PHASE 4 STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: NDA 202192 Ruxolitinib is a new NDA submitted with the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Within the NDA submission are the study results of the trial entitled "An Assessment of Heart Rate Corrected QT Intervals in Healthy Subjects Dosed with Single Doses of INCB018424 Compared with Moxifloxacin." Please review. Below is a link to the NDA submission.

\\CDSESUB1\EVSPROD\NDA202192\202192.ENX

MOR: Dr. Albert Deisseroth
Clin Pharm: Dr. Joseph Grillo
RPM: Amy Baird

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

AMY C BAIRD
06/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO (*Division/Office*): **New Drug Microbiology Staff**

***E-mail to:* CDER OPS IO MICRO**

***Paper mail to:* WO Bldg 51, Room 4193**

FROM: Tu-Van Lambert, Product Quality RPM, Office of New Drug Quality Assessment, WO 21 Room 2625, (301) 796-4246
PROJECT MANAGER (*if other than sender*):

REQUEST DATE
June 29, 2011

IND NO.

NDA NO.
202192

TYPE OF DOCUMENT
Electronic new NDA

DATE OF DOCUMENT
June 3, 2011

NAMES OF DRUG
Ruxolitinib phosphate tablets

PRIORITY CONSIDERATION
Priority (very)

PDUFA DATE
December 3, 2011

DESIRED COMPLETION DATE
September 3, 2011

NAME OF APPLICANT OR SPONSOR: Incyte Corporation

GENERAL PROVISIONS IN APPLICATION

☐ 30-DAY SAFETY REVIEW NEEDED	☐ CBE-0 SUPPLEMENT
☐ NDA FILING REVIEW NEEDED BY: <u>August 1, 2011</u>	☐ CBE-30 SUPPLEMENT
☐ BUNDLED	☐ CHANGE IN DOSAGE, STRENGTH / POTENCY
☒ DOCUMENT IN EDR	

COMMENTS / SPECIAL INSTRUCTIONS:

Micro reviewer requested to review micro and chirality tests that have been removed from the NDA from what was included in referenced IND 077456. Clinical requests this NDA to be a super priority NDA review.

Link to application: \\Cdsesub1\evsprod\nda202192

SIGNATURE OF REQUESTER Tu-Van Lambert

REVIEW REQUEST DELIVERED BY (Check one):

DARRTS EDR E-MAIL MAIL HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

EDR E-MAIL MAIL HAND

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/s/

TU-VAN L LAMBERT
06/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**	
TO: CDER-DDMAC-RPM		FROM: (Name/Title, Office/Division/Phone number of requestor) Amy Baird, Regulatory Project Manager, Division of Hematology Products, 301-796-4969	
REQUEST DATE 6/20/2011	IND NO.	NDA/BLA NO. 202192	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG Ruxolitinib Phosphate Tablets	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) 9/9/2011
NAME OF FIRM: Incyte		PDUFA Date: 12/4/2011	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) ☒ PACKAGE INSERT (PI) ☒ PATIENT PACKAGE INSERT (PPI) ☒ CARTON/CONTAINER LABELING ☐ MEDICATION GUIDE ☐ INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION ☒ ORIGINAL NDA/BLA ☐ IND ☐ EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ PLR CONVERSION	
REASON FOR LABELING CONSULT ☒ INITIAL PROPOSED LABELING ☐ LABELING REVISION			
EDR link to submission:			
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.			
COMMENTS/SPECIAL INSTRUCTIONS: Mid-Cycle Meeting: 8/4/2011 Labeling Meetings: 8/11/2011, 8/17/2011, 8/18/2011, 8/22/2011, 8/31/2011, 9/1/2011, 9/7/2011, 9/8/2011, 9/16/2011 Wrap-Up Meeting: 9/19/2011 Below is the EDR link to the original submission: \\CDSESUB1\EVSPROD\NDA202192\202192.ENX			
SIGNATURE OF REQUESTER			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND	

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/s/

AMY C BAIRD
06/20/2011

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/s/

AMY C BAIRD
06/20/2011

Baird, Amy

From: Baird, Amy
Sent: Monday, June 20, 2011 2:08 PM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - Sponsor NDA Presentation

Ron,

The FDA review team would like Incyte to give an NDA presentation for Ruxolitinib (very similar to an Advisory Committee presentation). The information below will help Incyte in the preparation of the presentation.

The possible dates for scheduling the presentation are 7/8, 7/15, 7/18, 7/22, or 7/25 (if the presentation falls on a Monday Incyte would present in the morning and if on a Friday presentation would be in the afternoon). Also, you will need to provide a copy of the presentation a couple of days prior to the scheduled meeting. The presentation would be attended by the Office Director, Division Director, and the remaining review team members, but also is open for all Divisions to attend (all Divisions under the Office of Oncology Drug Products).

Regards,
Amy

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

OODP's General Advice for Application Orientation Presentation Meetings

Within 45 days after arrival of a new NDA, original BLA or efficacy supplement, FDA may hold an Application Orientation Presentation meeting with you for purposes of orienting the review team to the content and format of the application. Preferably, the meeting would take place as soon as possible once the application has been submitted so that the review team can become familiar with your application.

Below are comments, which are intended to help in your presentation preparation. This list is not inclusive of all issues that you should consider in preparing for your presentation, but highlights areas of interest to OODP. These are general comments and we acknowledge that individual applications have unique characteristics. We also acknowledge that information needed to support a new NDA or original BLA will differ from an efficacy supplement. If you believe some comments are inapplicable to your

application or you believe that other information is relevant, adjust your presentation accordingly.

Application Orientation Presentation meetings are generally one hour in length, including time for discussion and Q & A (approximately 35-40 minutes of presentation and 25-20 minutes for discussion). The primary focus of the presentation should be on clinical (with clinical sections presented first) with highlights of other sections to follow (i.e., 1-2 slides for remaining sections).

Administrative:

1. Sponsor attendees
2. Presentation outline or Agenda. Should list sections included in submission.

Background and Application Specifics:

3. Proposed indication(s) and current indication(s), if efficacy supplement. Dosing recommendation from proposed labeling.
4. Drug/biologic characteristics, including what makes the drug/biologic unique, mechanism of action.
5. Listing of registration trial(s), to support marketing/licensing application, as well as Phase 1 and Phase 2 trials to support application.
6. Statement of whether you plan to seek approval under 21 CFR 314.510, Subpart H/21 CFR 601.41, Subpart E (i.e., accelerated approval) or full approval. If accelerated approval, design of the confirmatory trial(s) that will be ongoing at the time of accelerated approval and a timetable of when confirmatory trial(s) will be completed and final clinical study report(s) submitted.
7. Regulatory history, including the following:
 - Orphan Drug designation, Fast Track designation
 - Foreign Regulatory history: Where/when approved and for what indications, whether there are pending applications with foreign regulators, Risk management plans in foreign countries.
 - Key Outcomes from FDA Interactions
 - EOP2 Meeting
 - Special Protocol Assessment Correspondence: any agreements/disagreements on primary endpoints and key secondary endpoints, statistical analysis plan
 - Pre-NDA/BLA meeting
 - Other pertinent meetings/communications with FDA marking agreements/disagreements between you and the Agency

Summary Content of NDA/BLA/Efficacy Supplement Sections:

8. Clinical: Key findings from registration trials – Demographics of subjects and baseline characteristics, outcomes from primary and secondary endpoints, safety findings (most frequently reported adverse events, serious adverse events). Safety findings should also be presented from trials in other phases. NOTE: For demographics, you should address whether your study(s) represent ethnic minorities and whether study population is reflective of the U.S. population in which the drug/biologic is intended to be used.

You should also present results of the following, as appropriate:

- Clinical study sites (foreign or domestic)
- Biomarker development for population selection (if applicable)
- Assay validation (if applicable)

120-day Safety update: Plans for 120-day Safety update, including how many additional patients will be included in safety update and from which studies.

9. Statistics: Study design, description of planned analyses, efficacy analyses, safety analyses, subpopulation analyses of safety and efficacy (age, sex, race, concurrent therapy, number of prior treatments, region/country), length of follow-up, handling of missing data
10. CMC: Manufacturing site locations and dates when available for inspection, brief summary of manufacturing process, comparability of drug substance and drug product after major manufacturing changes, characterization, controls, stability, status of drug master files, discuss any novel excipients, state if application is Quality by Design (ICH Q8, Q9, Q10)
 - For BLAs: Immunogenicity results, validated assay method, and manufacturing schedule for DS and DP.
11. Nonclinical: Brief summary of toxicology studies and findings, genetic toxicology, QT studies, effect on fertility or reproduction, carcinogenicity studies (if needed), qualification of drug impurities
12. Clinical Pharmacology: Exposure response relationship supporting dose selection, pharmacogenomics-related issues, Description/listing of PK studies, PK characteristics (metabolic pathway, metabolites, $t_{1/2}$, ADME, PK in special populations, drug-drug interactions).
13. If a Risk Evaluation and Mitigation Strategy (REMS) is included, you should briefly identify the risks to be addressed, list the goals of the REMS, and outline the REMS components (e.g. Medication Guide, Communication Plans and/or Elements to Assure Safe Use (ETASU).
14. Risk/benefit profile for drug/biologic
15. Summary
16. Q & A

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/s/

AMY C BAIRD
06/20/2011



IND 077456

MEETING MINUTES

Incyte Corporation
Attention: Yung-Ao Hsieh, Ph.D.
Senior Director, Regulatory Affairs CMC
Route 141 & Henry Clay Road, Building 400
Wilmington, DE 19880

Dear Dr. Hsieh:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for INCB018424.

We also refer to the meeting between representatives of your firm and the FDA on November 30, 2010. The purpose of the meeting was to discuss the CMC information for the INCB018424 phosphate immediate release tablets of 5,10,15,20, 25 mg strengths.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Tu-Van Lambert, Product Quality Regulatory Project Manager at (301) 796-4246.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: pre-NDA (CMC)

Meeting Date and Time: Tuesday, November 30, 2010
Meeting Location: White Oak Building 22, Conference Room: 1415

Application Number: IND 077456
Product Name: INCB018424
Indication: treatment of patients with Primary Myelofibrosis (PMF) and Post Polycythemia Vera/Essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)

Sponsor/Applicant Name: Incyte Corporation

Meeting Chair: Sarah Pope Miksinski, Ph.D.
Meeting Recorder: Tu-Van Lambert, M.S.

FDA ATTENDEES

Sarah Pope Miksinski, Ph.D. – Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), Office of New Drug Quality Assessment (ONDQA)
Janice T. Brown, M.S. – CMC Lead, DNDQA I, ONDQA
Joyce Z. Crich, Ph.D. – Product Quality Reviewer, Branch II, DNDQA I, ONDQA
Edvardas Kaminskas, M.D. – Deputy Division Director, Division of Hematology Products (DHP), Office of Oncology Drug Products (OODP)
Albert Deisseroth, M.D. – Medical Officer, DHP/OODP
Tu-Van Le Lambert, M.S. – Product Quality Regulatory Project Manager, DNDQA I, ONDQA

SPONSOR ATTENDEES

Ronald C. Falcone, Ph.D. - Vice President, Regulatory Affairs, Incyte Corporation
Yung-Ao Hsieh, Ph.D. - Senior Director, Regulatory Affairs, CMC, Incyte Corporation
Carl Longfellow - Senior Director, Project Management, CMC, Incyte Corporation
Bhavnish Parikh, Ph.D. - Executive Director, Pharmaceutical Development, Incyte Corporation
Jay Shukla, Ph.D. - Vice President, CMC, Incyte Corporation
Chris Koval – Executive Director, QA GMP/GLP, Incyte Corporation
Joe Zhou, Ph.D. - Executive Director, Process Chemistry, Incyte Corporation
Rich Levy, MD – Executive Vice President, Chief Drug Development and Medical Officer, Incyte Corporation

Meeting Minutes
Type B
November 30, 2010

Office of New Drug Quality Assessment

Rose-Marie Dannenfels - Director, Technical R&D, Novartis Pharmaceuticals
Corporation

Donna Kapples, M.S. - Associate Director, Regulatory CMC, Novartis Pharmaceuticals
Corporation

1.0 BACKGROUND

INCB018424 phosphate, a synthetic inhibitor of the JAKs kinases, is developed for the treatment of patients with myelofibrosis, including primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF), and post-essential thrombocythemia-myelofibrosis (PET-MF). The Sponsor plans to submit a New Drug Application (NDA) during the second quarter of 2011. To prepare for this submission, the Sponsor requested in this meeting to discuss the CMC information for the INCB018424 phosphate immediate release tablets of 5,10,15,20, 25 mg strengths to obtain guidance on content of the Quality section of the eCTD for submission.

2. DISCUSSION

Preliminary responses from the Agency were sent on November 12, 2010. Based on these preliminary responses, the Sponsor requested further discussion of Questions 1, 2, 4, 5 and 9. These questions are included in the discussion below. Questions provided by the Sponsor are ***Bold Italics***, FDA Responses provided in preliminary comments are in Regular, discussion items during the meeting are in *Italics*.

2.1. DRUG SUBSTANCE

Designation of Starting Materials for Drug Substance Synthetic [REDACTED]

Question 1:

Incyte has discussed the company's position on designated starting materials for drug substance synthesis with the Division in EOP 2 CMC meeting (dated December 3, 2008) and Type C CMC meeting (dated July 7, 2009). Your Preliminary Response (dated July 8, 2009) has advised that the Division will consider the acceptability of [REDACTED] as potential starting materials. Incyte is proposing [REDACTED] as the designated starting materials for synthetic [REDACTED]. The justification for the designated starting materials and their controls are provided in Drug Substance, Section 2.3.1, Control of Materials (Attachment 1). Does the Division accept these three compounds as the designated starting materials for [REDACTED]

Agency Response:

Your proposed starting materials [REDACTED] appear to be reasonable. In the NDA, also include the following to support the use of these compounds as starting materials:

1. A detailed description of the impurity profile.
2. Brief description of synthetic strategies and methods of manufacture.
3. Detailed discussion on carry-forward impurities.
4. Controls and analytical methods to separate and measure appropriate impurities.
5. Supplier information for the starting materials.

6. Information on impurity fate studies. Detailed discussion on purging studies to demonstrate the ability of the manufacturing process to remove and control the impurities from the starting materials to the desired levels.
7. Change of control strategies for any potential revisions to the manufacture of proposed starting materials including the vendor's reporting of any changes in starting material specification or control.

Discussion: None

Recycle of [REDACTED] for the Manufacture of the Drug Substance [REDACTED]

Question 2:

[REDACTED]
[REDACTED] *Based on the recommendations from the Division (CMC EOP2 FDA Meeting Minutes, dated January 2, 2009), supporting data provided in Drug Substance, Section 2.2.2, Description of Synthetic [REDACTED] (Attachment 1) include:*

1. *In-process specifications and batch analytical data for [REDACTED]*
2. *Detailed description of [REDACTED]*
3. *Certificate of Analysis of drug substance Lot 08-340-002 manufactured using [REDACTED]*
4. *Comparison of batch analysis data of drug substance Lot 09-340-003 [REDACTED] and Lot 08-340-002 [REDACTED]*
5. *Stability data of Lot 08-340-002 at 25°C/60% RH (12 months) and at 40°C/75% RH (6 months)*
6. *Certificate of Analysis of drug product Lot A48107 (5 mg strength) manufactured from drug substance Lot 08-340-002*
7. *Comparison of batch analysis data of drug product Lot A45578 (manufactured from drug substance Lot 08-340-001R, [REDACTED] and Lot A48107 (manufactured from drug substance Lot 08-340-002)*

Additionally, the process validation report for [REDACTED] (including full validation of the [REDACTED]^{(b) (4)}) and executed batch record of a representative batch manufactured using [REDACTED] will be provided in the NDA.

Does the Division agree that there are adequate data, and no additional studies are needed, to establish the equivalency between the drug substance batches manufactured using either [REDACTED]?

Agency Response:

No. In addition to the information listed above, also include the following in your NDA:

Drug Substance

1. Comparative batch analysis for two additional drug substance lots (three lots total) manufactured using [REDACTED]

2. Six months comparative accelerated and available long-term stability data for two additional lots of drug substance manufactured using [REDACTED]

Drug Product

3. Comparative batch analysis including multi-point dissolution profiles (e.g., 15, 30, 45, 60 and 120 minutes or until the asymptote is reached) of drug product using the drug substance manufactured by [REDACTED]
4. Three months comparative accelerated stability for the highest and lowest tablet strength using drug substance manufactured by process [REDACTED]

Other

5. Specify the number of recycle operations can be performed on the same batch of intermediate ([REDACTED]).
6. Include purity and impurity limits in the proposed specification for [REDACTED]

Discussion:

- *The agency requested a detailed description of the recycling operation that includes how many times the [REDACTED] pool would be recycled, specifications for the pool, and characterization analysis.*
- *The Sponsor explained that the [REDACTED]*
- *As previously agreed during the End-of-Phase 2 CMC meeting, the Sponsor stated that [REDACTED] would be submitted at the time of NDA filing. When they intend to submit the NDA in May 2011, the Sponsor should have three month accelerated stability data for two additional lots available. In this submission scenario the Sponsor would commit to submitting amendments at the Agency's guidance. If they have to submit six-month accelerated stability data at the time of NDA filing, they would not be able to file the NDA until August 2011.*
- *The Agency requested that the Sponsor submit a submission proposal with alternate scenarios based on the availability of their stability data. The Sponsor agreed to do so.*

Drug Substance Specification

Question 3:

The proposed specification for INCB018424 phosphate drug substance with supporting data and justifications are provided in Drug Substance, Section 4, Control of Drug Substance (Attachment 1). Does the Division agree that the proposed specification is adequate to ensure the identity, strength, quality and purity of the INCB018424 phosphate drug substance?

Agency Response:

Your proposed specifications for INCB018424 appear to be reasonable provided that any unspecified impurities are below the threshold limits listed in Q3A -Impurities In New Drug Substances. The final determination on the adequacy of the proposed drug substance specification is a review issue and will be determined during the evaluation of your NDA. We note that you have not proposed an in-process control or drug substance specification for particle size distribution. Provide adequate justification for this proposal (see ICH Q6A Decision tree #3) in your NDA.

Discussion: None

2.2. DRUG PRODUCT

Drug Product Specifications for Tablets of 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg Strengths Question 4:

The proposed specification for INCB018424 phosphate drug product tablets of 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg strengths with supporting data and justifications are provided in Drug Product, Section 5, Control of Drug Product (Attachment 2). Does the Division agree that the proposed specification is adequate to ensure the identity, strength, quality and purity of the INCB018424 phosphate drug product tablets?

Agency Response:

In general, your proposed specifications appear reasonable; however, a final determination will be made after reviewing the data in the NDA submission. Your justification for omitting the stereospecific identity test will be a review issue.

Additional Comments:

- **Dissolution Method:** Please provide in your NDA submission the dissolution method report including the complete dissolution profile data collected during the development and validation of the proposed dissolution method. A detailed description of the optimal in vitro dissolution methodology and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) that were used to identify this method as the most optimal, should be provided in the report. The dissolution profile should be complete and cover at least (b) (4) of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable. The dissolution/release data (individual, mean, SD, profiles) should be reported as the cumulative percentage of drug eluted with time (the percentage is based on the product's label claim). The testing conditions used for each test should be clearly specified.

The method's validation information showing that the chosen method is able to detect manufacturing changes (under meaningful testing) that may have an effect on the dissolution of the drug should also be included in the report. Validation studies are important for identifying critical formulation and manufacturing variables during development, establishing relevant controls for the testing of the final product. Include

the testing conducted to demonstrate the discriminating capability of the selected test as well as the validation data for the method (i.e., method robustness, etc.) and assay (precision, accuracy, linearity, stability, etc.). The selected method should be discriminatory and sensitive enough to reject lots that would have less than acceptable clinical performance.

- **Dissolution Acceptance Criterion:** The provided dissolution data indicate a very fast dissolution for your product. Therefore, the proposed acceptance criterion of $Q = \blacksquare$ at 30 minutes may not be adequate for your product. Provide in your NDA submission the dissolution profile data from the clinical and stability batches supporting the selection of this criterion (i.e., specification-sampling time point and specification value). In general, for immediate release product the selection of the specification time point should be where $Q = \blacksquare^{(b)(4)}$ dissolution occurs.
- **BA/BE Waiver Request:** When several strengths of the same dosage form are proportionally similar in their active and inactive ingredients, an in vivo waiver can be given for one or more than one lower strengths based on comparability of the dissolution profiles and a successful in vivo study on the highest strength. Similarly, it is also possible to get a waiver for a higher strength that is proportionally similar, if the following 3 conditions are satisfied: **1)** clinical safety and efficacy data exist for this higher dose, **2)** the drug exhibits linear pharmacokinetic characteristics over the therapeutic dose range, and **3)** comparability of the dissolution profiles among the different strengths.

We acknowledge your submission dated July 8, 2010, requesting a BA/BE waiver for INCB018424 phosphate 10 mg, 15 mg, 20 mg and 25 mg higher strengths tablets. The preliminary review of this submission indicates that a biowaiver is appropriate for your product; however, the final recommendation will be made under the NDA. Please include in your NDA submission the biowaiver request for the 10, 15, 20, and 25 mg tablets and the supportive information described above.

Discussion:

The Sponsor asked whether following the ICH A6A decision tree is acceptable. With respect to the dissolution acceptance criteria, the Sponsor also asked whether to $\blacksquare^{(b)(4)}$ the acceptance criterion at 30 minutes to $Q = \blacksquare$ or to pick a time point where a specification of $Q = \blacksquare$ dissolution.

The Agency requested that this inquiry should be formally submitted for review and comment from the ONDQA Biopharmaceutics Team.

Administration using a Nasogastric (NG) Tube

Question 5:

For patients who have difficulty swallowing solids, INCB018424 phosphate tablets can be dispersed in water and administered through a nasogastric (NG) tube. The proposed study protocol to evaluate the in-use stability of the INCB018424 phosphate tablet aqueous

suspensions is provided in Attachment 3. Does the Division agree that the proposed study protocol is adequate to establish the in-use stability to support the preparation, storage and administration of the drug product suspension through a NG tube?

Agency Response:

Your proposal appears reasonable provided that the in-use study replicates the administration procedure that occurs in clinical practice and is conducted as described in the proposed labeling. In your NDA, include analytical test methods for in-use stability study, detailed procedure description of tablet suspension preparation, and data from compatibility studies with NG tubes.

Additional Comment:

Because crushing and dissolving the tablet prior to administration results in a new formulation (disperse solution/suspension) that could change the rate and extent of drug absorption, you will need to conduct a bioequivalence study comparing the disperse solution/suspension product to the intact tablet using the highest 25 mg strength tablets. Please provide your BE study protocol for review and concurrence by the Agency.

Discussion:

The Sponsor affirmed that the formulation of the aqueous suspension for administration through an NG tube is the same as the tablet since the same inert excipients are present. Since the drug product has already been considered as a BCS class 1, the Sponsor would like to submit a biowaiver for the NG tube formulation instead of bioequivalence data. The Agency stated that this request should be formally submitted for review and comment from the ONDQA Biopharmaceutics Team.

10.2.3. Drug Product Stability Study Protocol

Question 6:

The INCB018424 phosphate immediate release tablets of 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg strengths are (b) (4) Tablets of the five strengths are packaged in the same container/closure system, ie, 60 counts in 75 cc HDPE bottles. A bracketing stability study protocol for the drug product is described in Drug Product, Section 8, Stability (Attachment 2). Since the stability of the tablets of the intermediate strengths is represented by the stability of the extreme strengths, the shelf-life under the recommended long-term storage conditions of the tablets of 10 mg, 15 mg, and 20 mg strength is established based on the data obtained from testing of three batches of the 5 mg and 25 mg strength tablets stored under similar conditions. The bracketing stability study protocol was submitted to the Division in a request for a Special Protocol Assessment (IND No. 77,456 SN 0084, dated March 5, 2009). In the Division's correspondence dated March 24, 2009, you have advised us that the proposed stability study protocol does not qualify for special protocol assessment because "it is covered in ICH Q1D, Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products". Does the Agency agree that the proposed bracketing protocol is acceptable?

Agency Response:

Your approach appears reasonable. In your NDA submission, provide a detailed scientific justification for your current proposed bracketing protocol with comparative calculations for the factors could impact stability (e.g. surface areas/tablet weight or surface areas/tablet volume of each strength, and the head space in each bottle, etc.), to demonstrate that the stability of any intermediate levels is represented by the stability of these two extremes tested. If such justification can not be established, you need to modify the proposed bracketing protocol (such as including additional tablet strength(s) as needed) with justification, to ensure that the stability of each of the five strengths of drug product is represented by the stability of the proposed strengths for testing.

Discussion: None.

Question 7:

Incyte intends to request a Priority Review for this NDA, as the drug is being developed for an unmet medical need to treat myelofibrosis. If a Priority Review is granted for this application, the stability update (long term data at the 18-month time point) will be submitted during the review cycle (at least 30 days before the PDUFA due date). Does the Division agree that the proposed timeline for the submission of stability update is acceptable?

Agency Response:

No. Per the *Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products* (GRMPs), all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. Any information submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow. International Conference on Harmonization (ICH) Q1A (R2) states “long term testing should cover a minimum of 12 months’ duration on at least three primary batches at the time of submission”. While ICH Q1E: Evaluation of Stability Data, allows for the use of extrapolation to extend the shelf life beyond the available real-time long term data, it does not negate the recommended 12 months of long term data cited in ICH Q1A(R2).

Discussion: None

2.3. REGULATORY

Drug Product Sections 3.2.P and 2.3.P

Question 8:

INCB018424 phosphate immediate release tablets will be marketed in 5 mg, 10 mg, 15 mg, 20 mg and 25 mg strengths. For lifecycling purposes, Incyte plans to file separate documents for each of the strengths. For example, under 3.2.P.1 there will be five documents. Does the Division agree with the proposed format?

Agency Response:

Yes, however, it is preferable to include information on each strength in a single document. Data for all strengths in a tabular format will facilitate the review of your application.

Discussion: None

Submission of Supporting Documentation

Question 9:

Analytical methods, their validation reports, Certificates of Analysis (CoAs), process validation protocols and/or reports and literature references will be provided. The narrative text will contain hyperlinks to these respective documents. Study reports (e.g., analytical method development reports and process development reports) in electronic form will be submitted for review upon request. Does the Division agree with the proposed plan?

Agency Response:

No. Development report(s) should be included in the Pharmaceutical Development section.

Discussion:

The Sponsor stated that these summary development reports can be many pages long and asked whether these should be submitted in the summary section of the NDA or submitted within the quality section of the Application. The Agency recommended that the summary reports be submitted in section 3.2.S.2.6 Manufacturing Process Development.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion were identified.

4.0 ACTION ITEMS

The Sponsor will submit an amendment to the IND to include a submission proposal for drug substance and drug product synthesized by both the [REDACTED]. Information to be submitted should include the availability of data requested and what will be submitted by NDA filing and in possible NDA amendments. Biopharmaceutical questions and supportive data should also be submitted in this IND amendment. The Agency committed to review this proposal as expeditiously as feasible before NDA filing.

5.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts were provided for this meeting.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH P MIKSINSKI
12/20/2010

MEETING MINUTES

MEETING/TELECON DATE: November 3, 2010 **TIME:** 3 pm – 4 pm
LOCATION: FDA, White Oak Building 22, Conference Room 1313

IND: 077456

Meeting Request Submission Date: July 15, 2010

FDA Response Date: August 1, 2010

Briefing Document Submission Date: October 1, 2010

DRUG: INCB018424 Phosphate

SPONSOR/APPLICANT: Incyte Corporation

TYPE of MEETING: Pre-NDA meeting to discuss the content and format of the planned NDA submission for treatment of myelofibrosis.

FDA PARTICIPANTS:

Ann T. Farrell, M.D., Acting Director, DHP

Edvardas Kaminskas, M.D., Acting Deputy Director, DHP

Albert Deisseroth, M.D., Medical Officer, DHP

Ashkan Emadi, M.D., Medical Officer, DHP

R. Angelo De Claro, M.D., Medical Officer, DHP

Robert Kane, M.D., Acting Deputy Director, Safety, DHP

S. Leigh Verbois, Ph.D., Supervisory Pharmacologist

Julie Bullock, Pharm.D., Team Leader, Office of Clinical Pharmacology, DCP5

Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer, DCP5

Hong (Laura) Lu, Ph.D., Biostatistics Reviewer

Alberta Davis-Warren, B.S., Regulatory Health Project Manager

INDUSTRY PARTICIPANTS:

Ron C. Falcone, Ph.D., Vice President, Regulatory Affairs

Richard Levy, M.D., Exec. Vice Pres., Chief Drug Development and Medical Officer

Adam Boyd, Ph.D., Program Statistician, Novartis Pharma AG

Susan Erickson-Viitanen, Ph.D., Exec. Director, Clinical Research Scientist

Donna Gillian-Brown, M.S., Sr. Director, Medical Writing

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Roger Waltzman, M.D., M.B.A., Sr. Director, Oncology Global Development,
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William V. Williams, M.D., Vice President, Exploratory Development
Neil Wummer, Exec. Director, Regulatory Affairs
Swamy Yeleswaram, PhD, Vice President, Drug Metabolism and Biopharmaceutics

BACKGROUND: Sponsor is using INCB018424 phosphate to investigate the treatment of myeloproliferative neoplasms, hematologic malignancies and solid tumors. On July 15, 2010 Incyte Corporation submitted a meeting request to discuss the content and format of the planned electronic common technical document NDA. The proposed indication for this NDA submission is myelofibrosis. The Sponsor submitted a subsequent background package on October 1, 2010. To facilitate the meeting FDA sent preliminary responses by email on October 28, 2010.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Question 1:

Does the Division agree with the content and format of the planned eCTD NDA for INCB018424 as described in Attachment A: Planned Contents INCB018424 eCTD NDA?

FDA Response:

We agree with the following caveats:

- **It is unclear from the Sponsor's planned eCTD nomenclature if the biopharmaceutics (2.7.1) and clinical pharmacology (2.7.2) sections will be a mere summary of studies or a comprehensive review across studies. These reports should contain both a summary of individual studies as well as a comprehensive review across studies and populations identifying clinically relevant trends and parameters regarding the PK, PD, exposure/response/ safety, and an evaluation of the effects of covariates such as age, weight, gender, race, etc. on the PK (pharmacokinetics) of INCB018424.**
- **In the appropriate clinical pharmacology and biopharmaceutics sections of the eCTD provide a table listing of patients with renal or hepatic impairment who have received INCB018424 organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation, AST/ALT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.**

Meeting Discussion: The Sponsor will provide a comprehensive review across studies as requested above. In the table listing of patients with hepatic impairment, the Sponsor will use the NCI organ dysfunction working group criteria for hepatic impairment with the main parameter of stratification of total bilirubin.

Question 2:

Does the Division agree with Incyte's proposal, as detailed in the applicant position, to fulfill the requirements of 21 CFR 314.50(d)(5)(v) and (vi) calling for an Integrated Summary of

Effectiveness (ISE) and Integrated Summary of Safety (ISS) through the written Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) provided in CTD Module 2 with appropriate appendices located in Module 5?

FDA Response: No.

Meeting Discussion: The Sponsor and the Agency discussed the guidance for industry on integrated summaries of effectiveness and safety. A consensus was reached that would provide for detailed not comprehensive summaries of the efficacy and safety in module 2 and in module 5 complete reports for every clinical trial important for the analysis of the NDA, as well as an exhaustive and complete analyses of all the trials relevant to the discussion of efficacy and safety for INCB18424.

Question 3:

Does the Division agree with Incyte's plan to provide raw data and analysis datasets, with corresponding define files, for the studies as described below?

- Incyte plans to provide raw and analysis datasets, formatted as traditional datasets in accordance with the FDA's Draft Guidance document titled, "*Providing Regulatory Submissions in Electronic Format – General Considerations*" October 2003, for the clinical pharmacology studies INCB 18424-131, -132, -133, -134, -135, -136, -137, -138, -139, -142; Study -231 in patients with rheumatoid arthritis; Study -254 in patients with prostate cancer; and Study -255 in patients with relapsed or refractory multiple myeloma.

FDA response: Agree. However, please see our response to Question 10 for additional clarification.

- Data from Study INCB 18424-138, the Thorough QT study, will also be converted and provided as Clinical Data Interchange Standards Consortium (CDISC) compliant Study Data Tabulation Model (SDTM) raw data and analysis datasets as per the request of FDA. Data from Studies -254 and -255 will also be converted and provided as CDISC compliant SDTM for pooling with safety data from other Phase 2 and 3 studies.
- Incyte plans to provide only CDISC compliant SDTM raw data and analysis datasets for studies INCB 18424-251, -256, -351 and -352, as well as CDISC compliant integrated databases and analysis datasets for the SCS and SCE.

FDA Response: Yes

Question 4:

Does the Division agree with Incyte's plan to provide the statistical programs (SAS code) for the primary analyses, and select secondary analyses listed in the Applicant position, from Studies INCB 18424-138, -351 and -352, as both ASCII files and as Adobe pdf documents? Incyte does

not plan to provide the programs for the Summary of Clinical Safety (SCS) and Summary of Clinical Efficacy (SCE).

FDA Response: Yes

Question 5:

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 from subjects who experienced a serious adverse event while enrolled in Studies INCB 18424-251, -256, -351 and -352?

FDA Response: Yes.

Question 6:

Does the Division agree that a table of the very common adverse reactions and clinically relevant laboratory findings from the placebo-controlled INCB 18424-351 study (Study 1) and a table of the very common adverse reactions and clinically relevant laboratory findings from the comparative study to best available therapy INCB 18424-352 study (Study 2) are appropriate to include in the labeling to present the safety profile in the myelofibrosis patient population?

FDA Response: Yes, as long as a full and complete clinical study report for each of the studies listed above is included in the NDA.

Question 7:

Incyte, in partnership with Novartis, is developing a global Risk Management Plan (RMP) for INCB018424 for the treatment of MF. Pending data analyses at the conclusion of the ongoing Phase 3 trials, further review/analyses will be conducted and the safety information will be updated as warranted. These data will be integrated into the global RMP which is planned for inclusion in Module 1.16 of the NDA. Based on a review of the current safety profile, we believe that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary as the known toxicities can be managed with product labeling, patient information instructions and a robust pharmacovigilance plan. This assessment will be revisited when the full, unblinded safety database has been reviewed. Incyte would appreciate the Division's guidance regarding whether a REMS might be required?

FDA Response: It is premature to comment on whether a REMS might be required prior to the completion of a full review of the NDA.

Question 8:

Does the Division agree with Incyte's plan to provide financial disclosure statements only for Study INCB 18424-251 A Phase 1/2 Open-Label Study in patients with PMF and Post-PV/ET MF, and the Phase 3 Studies INCB 18424-351 and -352 in patients with PMF, PPV-MF, or PET-MF?

FDA Response: Financial disclosure statements should be provided for each of the trials which are used to support the NDA and from which labeling information could be taken.

Question 9:

Does the Division agree with Incyte's proposal to include electronic datasets, consistent with the CDISC SEND standards, from only the 6 month Tg.rasH2 mice carcinogenicity study?

FDA Response: Although the agency indicated it was only necessary to submit the mouse study in 2008 at the time of NDA submission, additional guidance has been published describing oncology indications (ICH S9). It is now clear that the patient population in the proposed NDA is limited to a non-oncology patient population, and that ICH S9 is not applicable. Given the proposed patient population, the submission of the rat carcinogenicity study is also necessary at the time of NDA submission. Please see ICH S1A for additional information.

Meeting Discussion: After consideration the Agency indicated that given the refractory nature of patient population the rat carcinogenicity data would not be necessary at the time of filing but would likely be a post marketing requirement.

Question 10:

Does the Division agree with the proposed formats of the pharmacokinetic and pharmacodynamic data?

FDA Response:

We agree with the following caveats:

- **Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.**
- **Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with range as appropriate.**
- **We encourage you use the following submission guidelines (<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm>) when submitting pharmacometric data and models. For any population PK models all datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation**

model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Question 11:

Does the Division agree with Incyte's plan to include information from Studies INCB 18424-251 and -351 in the Population PK report provided in the NDA submission? Does the Division agree with Incyte's proposal to provide an expanded Population PK report, which will also include data from Study -352. [REDACTED]

FDA Response:

We agree to including information from studies INCB 18424-251, -351, and -352 in the population PK analysis. However, we do not agree with the timelines. The final population PK report and exposure-response analyses for efficacy and safety endpoints should be included in the NDA submission. The corresponding data sets and statistical programs should be submitted as described in our response to Question 10.

Meeting Discussion: The Sponsor will provide the population PK analysis report at the time of NDA submission with studies 251 and 351 in the main dataset and study 352 as validation data.

Question 12:

Does the Division agree with Incyte's proposal that all efficacy analyses will be displayed in the SCE side by side without pooling the data together based on the design differences (eg, double blind vs. open label; placebo controlled vs. active comparator) between studies INCB 18424-351 and -352?

FDA Response: Yes, as long as a unique patient identifier number is assigned to each patient so that patients from different trials can be distinguished.

Question 13:

Does the Division agree with the proposed statistical analysis plan for the SCE presentation of duration of maintenance of a $\geq 35\%$ reduction from Baseline in spleen volume in Studies INCB 18424 -351 and -352?

FDA Response Yes.

Question 14:

Does the Division agree with Incyte's proposal not to include a meta-analysis of the survival data from INCB 18424-351 and INCB 18424-352 because of differences in the trial designs and patient populations?

FDA Response: Yes.

Question 15:

Does the Division wish to have the MRI/CT images of the spleen from Studies INCB 18424-251, -351 and -352 provided as a review-aid by (b)(4)? If yes, does the Division prefer to be able to review the images using the Timepoint Patient Browser or the Image Query Tool?

FDA Response: No. The Division does not review MRI or CAT scans, but depends on the attributions of the Independent Review Committee (IRC). Please submit the tabulated results of the reviews of the IRC for every patient along with a tabulated summary of the IRC results along with the Charters of the IRC in your upcoming NDA. Please ensure that the identifiers in this report of the IRC are the same as the unique identifying numbers used for each patient throughout the NDA.

Question 16:

Does the Division agree with the proposal to integrate the safety data per the following three separate datasets?

1. Studies with myelofibrosis patients in randomized studies receiving the proposed labeled dose: Studies INCB 18424-351 and -352 (not including data from patients who cross over from placebo or Best Available Therapy to INCB018424).
2. Studies with myelofibrosis patients receiving all doses and regimens: Studies INCB 18424-351 and -352 (including patients who cross over from placebo or Best Available Therapy to INCB018424), and -251.
3. Studies with hematological disorders or other oncology indications including patients receiving all doses and regimens: Studies INCB 18424-351, -352, -251, -256, -254, and -255.

FDA Response: Please submit with the NDA the following separate data sets: the data sets listed in option 1, and the data sets listed in option 2. In addition, submit the data sets listed in option 3. Please integrate the safety data sets described in option 2 above into a single data set. Remember to use identifying numbers for each patient that are uniform for each patient throughout the NDA.

Meeting Discussion: A consensus was reached regarding datasets for safety. Specifically individual datasets would be provided for each study as far as for efficacy and safety, in

addition a pooled data set of safety would be provided for those studies listed under option 2; 351, 352, 251. A flagging system would be used to identify those patients in the integrated safety datasets for whom crossover had occurred.

Question 17:

Does the Division have any specific comments on the draft SCS & RMP Report Analysis Plan as detailed in the Applicant Position and in Attachment J provided with this briefing package?

FDA Response: No.

Question 18:

Does the Division agree with Incyte's plan to submit ECG datasets from all studies, including all individual ECG intervals, interpretations and comments, with the clinical study reports? ECG waveforms will be submitted to the ECG warehouse only from Study INCB 18424-138, the thorough QT study.

FDA Response: Please submit data sets and waveforms only for the TQT study and just reports from the other studies.

Question 19:

Does the Division agree with the safety data that Incyte plans to provide in the NDA for the two investigator-initiated studies?

FDA Response: Yes

Question 20:

Incyte will include the clinical study reports, including the required case report forms, from (b) (4), but does not plan to include the raw or analyses datasets from these studies. Does the Division agree?

FDA Response: Yes

Question 21:

Does the Division agree with Incyte's plan for information to be included in the 4-month safety update?

FDA response: Yes

Question 22:

In the event that INCB018424 would need to be referred to an FDA Oncology Drugs Advisory Committee (ODAC), would the Division consider meeting with Incyte prior to any planned

Advisory Committee meeting to discuss the clinical study results and any other issues in order for a mutual understanding between both parties prior to an ODAC meeting?

FDA response: Yes

Additional comments from Statistics:

1. Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will be appearing in the label.
2. For efficacy and safety analysis datasets, you are encouraged to follow the practice noted in the *Study Data Specifications*, (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>).
3. To facilitate the review process, efficacy information including patient disposition, demographics, and derived primary and secondary endpoints should be included in one analysis dataset for each study unless the data structures are not compatible due to the nature of the endpoints, e.g., one record per patient type of endpoint vs. multiple records per patient type of endpoint.

OTHER FDA COMMENTS:

REGULATORY

1. NDA/sNDA Presentations to CDER's Division of Oncology

The Center for Drug Evaluation and Research's Division of Drug Oncology Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

2. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 “*Guidance for Industry: Financial Disclosure By Clinical Investigators*” (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

3. PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

Meeting Discussion: Sponsor has orphan drug status.

4. PEDIATRIC EXCLUSIVITY

Pediatric studies conducted under the terms of section 505A of the Federal Food, clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

Meeting discussion: The Sponsor mentioned an ongoing pediatric study being conducted by COG. The Agency suggested the Sponsor submit this protocol for review.

5. DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG
Gender	Males	All Females	Females >50
Age:	0-#1 Mo.	>1 Mo.-#2 Year	>2-#12
	12-16	17-64	65
Race:	White Other	Black	Asian

6. QT Evaluation

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.

7. Office of Surveillance and Epidemiology (OSE)

- If the Sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).
- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fnl.htm>

Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fnl.htm>

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>

- **If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.**
- **The Sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.**

8. Please complete the following table for Study X and submit this with your NDA.

Site Address Point of Contact	# Enrolled	Efficacy Measure	# Gr 3-4 AEs	# Major Protocol Violations

Alberta E. Davis-Warren
Project Manager

Concurrence Chair: Edvardas Kaminskas, M.D.
Medical Team Leader

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/s/

EDVARDAS KAMINSKAS
12/01/2010