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 # **Supplement #**	202192
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:	*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.
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 Orencia, 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. Fiszman, 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

IRT/QT=Interdisciplinary Review Team for QT Studies
CDTL=Cross-Discipline Team Leader

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 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 symtomatology 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 ≥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 ≥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 cm^3, 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 ≥35% at week 24	41.9%	0.7%[#]	P<0.0001*
Key Secondary Endpoint	N=148[&]	N=154	
%↓TSS by ≥50% week 24	45.9%	5.3%	P<0.0001**

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

Interestingly, only about one-half (54%) of the patients who had SVR ≥35% also had TSS reduction of TSS by ≥50%, and likewise only about one-half (51%) of patients who had TSS reduction by ≥50% also had SVR ≥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 ≥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 ≥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 ≥35% at 48 weeks	29%	0%	<0.0001
Key Secondary Endpoint: % SVR ≥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 ≥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 ≥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	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 anlyze 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 anlyze 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.

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

/s/

EDVARDAS KAMINSKAS
11/15/2011