U.S. Food and Drug Administration Approval: Ruxolitinib for the Treatment of Patients with Intermediate and High-Risk Myelofibrosis

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Abstract

On November 16, 2011, the U.S. Food and Drug Administration (FDA) granted full approval to ruxolitinib, (Jakafi; Incyte Corp.), an inhibitor of the Janus kinases 1 and 2, for the treatment of patients with intermediate- or high-risk myelofibrosis, including primary myelofibrosis, postpolycythemia vera myelofibrosis, and postessential thrombocythemia myelofibrosis. This approval was based on the results of 2 large randomized phase III trials that enrolled patients with intermediate-2 or high-risk myelofibrosis and compared ruxolitinib with placebo (study 1) or best available therapy (study 2). The primary efficacy endpoint was the proportion of patients who experienced a reduction in spleen volume of ≥35% at 24 weeks (study 1) or 48 weeks (study 2). The key secondary endpoint in study 1 was the proportion of patients who experienced a ≥50% improvement from baseline in myelofibrosis total symptom score at 24 weeks. The results of these studies showed that a greater proportion of patients treated with ruxolitinib experienced a ≥35% reduction in spleen volume as compared with those treated with placebo (42% vs. 1%, \textit{P} < 0.0001) or best available therapy (29% vs. 0%, \textit{P} < 0.0001). A greater proportion of patients in study 1 experienced a ≥50% reduction in the myelofibrosis total symptom score during treatment with ruxolitinib than with placebo (46% vs. 5%, \textit{P} < 0.0001). Ruxolitinib treatment was associated with an increased incidence of grades III and IV anemia, thrombocytopenia, and neutropenia. This is the first drug approved for myelofibrosis.\textit{Clin Cancer Res}; 18(12); 3212–7. ©2012 AACR.

Introduction

Myelofibrosis is a disease characterized by marrow fibrosis, extramedullary hematopoiesis, splenomegaly, leukoerythroblastic blood picture, elevated levels of peripheral blood CD34\textsuperscript{+} cells, and myelofibrosis-related symptoms, such as abdominal discomfort, pain under the left ribs, night sweats, pruritus, bone or muscle pain, and early satiety (1). Myelofibrosis, including primary myelofibrosis, postpolycythemia vera myelofibrosis, and postessential thrombocythemia myelofibrosis, is a chronic disease affecting primarily older patients (2, 3). The median overall survival is 11.3 years for low-risk, 7.9 years for intermediate-1 risk, 4.0 years for intermediate-2 risk, and 2.3 years for high-risk myelofibrosis (4).

The pathogenesis of myelofibrosis is not well understood, but appears to involve the activation of the Janus-activated kinases (JAK)/STAT pathway. Recently, several mutations in this pathway have been described, including V617F-activating mutation of JAK2 found in at least 45% of patients with myelofibrosis (5, 6).

Ruxolitinib (Jakafi, Incyte Corp.), a small-molecule inhibitor of JAK1 and 2, inhibits the binding of ATP to JAKs irrespective of the V617F mutation presence. Described later is a summary of the U.S. Food and Drug Administration (FDA) review of the ruxolitinib new drug application.

Chemistry

Ruxolitinib phosphate, a molecular formula of C\textsubscript{17}H\textsubscript{21}N\textsubscript{6}O\textsubscript{4}P, molecular weight of 404.36 g/mole, and chemical name of \textit{R}-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate, is an ATP mimic. Ruxolitinib phosphate is supplied in 5-, 10-, 15-, 20-, and 25-mg tablets.

Nonclinical pharmacology and toxicology

The inhibitory activity of ruxolitinib was shown \textit{in vitro} and in animal models containing aberrant JAK/STAT signaling. Drug-related toxicities observed in animal studies were lymphoid depletion and reduced size of the thymus.
and spleen. Ruxolitinib did not have teratogenic, genotoxic, or carcinogenic effects. In embryo-fetal development studies, reduced fetal weight and/or increased postimplantation loss were noted in animals only at doses resulting in maternal mortalities. A category C pregnancy classification was assigned to this drug. Ruxolitinib did not impair male or female fertility but resulted in increased postimplantation loss of embryos.

Clinical pharmacology
Jakafi exhibits at least 95% oral absorption with a T_{\text{max}} of approximately 1 to 2 hours and linear pharmacokinetics over the approved dose range. Ruxolitinib and 8 metabolites comprise >90% of the radioactivity in human subjects to whom ^{14}C-radionuclide–labeled ruxolitinib was administered. All of these metabolites are pharmacodynamically active, contributing 15% to 18% of the overall ruxolitinib pharmacodynamic activity in healthy subjects. The plasma half-life of ruxolitinib is 3.1 hours and 5.8 hours for ruxolitinib with its active metabolites. Ruxolitinib is metabolized by CYP3A4. Only 1% of the parent compound is excreted unchanged. The area under the curve (AUC) and half-life of ruxolitinib’s active metabolites, rather than of ruxolitinib itself, was found to increase with progressing severity of renal impairment. The AUC was increased by approximately 70% in patients with renal disease undergoing hemodialysis. The mean AUC for ruxolitinib was also increased in patients with increasing severity of hepatic impairment (range, 28%–87%). Co-administration of ruxolitinib with ketoconazole, a potent CYP3A4 inhibitor, in healthy volunteers resulted in a 91% increase of plasma AUC of ruxolitinib. Ruxolitinib is not a potent inducer of CYP isozymes and is likely not a substrate for P-glycoprotein. Ruxolitinib dose should be adjusted for thrombocytopenia, hepatic impairment, moderate or severe renal impairment, and with concurrent use of strong CYP3A4 inhibitors.

Clinical data
Study 1. The study protocol underwent a special protocol assessment, and agreement was reached by the sponsor and the FDA on the design of study 1, including endpoints of spleen volume reduction (SVR) and of improvement of patient symptoms, development of a criteria, methodology of evaluation of treatment results, and the statistical analysis plan. Study 1 was a double-blind, prospectively randomized, placebo-controlled phase III trial enrolling 309 patients with intermediate-2 risk or high-risk myelofibrosis who had progressive disease or were not candidates for available therapy, had splenomegaly, and required treatment. Patients were randomized (1:1) to receive either ruxolitinib or placebo. The trial was conducted in the United States, Canada, and Australia. Patients assigned to the placebo arm could receive ruxolitinib when all entered patients had completed 24 weeks of treatment and 50% of the patients entered had completed 36 weeks from the time of randomization, or they experienced an increase of ≥25% in spleen volume by MRI or if they had both of the following criteria: an increase in early satiety accompanied by ≥10% of weight loss and increased intensity of sustained abdominal pain despite increased narcotic doses.

The baseline and demographic characteristics of the patients entered onto study 1 are summarized in Table 1. Patients had a median spleen volume, as measured by MRI or computer-assisted tomography (CT) scan, of 2,595 cm³, with a range between 478 and 8,881 cm³ (the upper limit of normal spleen volume is ~300 cm³). The starting ruxolitinib dose was 20 mg orally twice daily if the pretreatment platelet count was >200,000/μL or 15 mg orally twice daily if the platelet count was 100,000 to 200,000/μL. Patients with platelet counts <100,000/μL were ineligible. During the trial, the dose was adjusted according to platelet count.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Ruxolitinib (N = 155)</th>
<th>Placebo (N = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, female</td>
<td>49.0%</td>
<td>42.0%</td>
</tr>
<tr>
<td>PMF</td>
<td>45.0%</td>
<td>55.0%</td>
</tr>
<tr>
<td>PPV-MF</td>
<td>32.0%</td>
<td>31.0%</td>
</tr>
<tr>
<td>PET-MF</td>
<td>23.0%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Spleen volume (median), cm³</td>
<td>2,598</td>
<td>2,566</td>
</tr>
<tr>
<td>Spleen volume (range), cm³</td>
<td>478–7,462</td>
<td>521–8,881</td>
</tr>
<tr>
<td>Total symptom score (mean)</td>
<td>18.0</td>
<td>16.5</td>
</tr>
<tr>
<td>Mean individual symptom score at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night sweats</td>
<td>3.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Itching</td>
<td>2.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>3.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Pain under left ribs</td>
<td>2.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Early satiety</td>
<td>3.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Bone/muscle pain</td>
<td>3.3</td>
<td>2.8</td>
</tr>
<tr>
<td>IWG high-risk vs. intermediate-2 risk, %</td>
<td>58 vs. 41</td>
<td>64 vs. 35</td>
</tr>
<tr>
<td>Percent positive for V617F</td>
<td>73%</td>
<td>80%</td>
</tr>
<tr>
<td>Platelet count (median)</td>
<td>262,000/μL</td>
<td>238,000/μL</td>
</tr>
<tr>
<td>Hemoglobin (median)</td>
<td>10.5 g/dL</td>
<td>10.5 g/dL</td>
</tr>
<tr>
<td>ANC (median)</td>
<td>11,900/μL</td>
<td>15,200/μL</td>
</tr>
<tr>
<td>Prior hydroxyurea</td>
<td>67%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Abbreviations: ANC, absolute neutrophil count; IWG, International Working Group; MF, myelofibrosis; PET, post essential thrombocytopenia; PMF, primary myelofibrosis; PPV, post polycythemia vera.

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guidelines. These eligibility requirements and dose adjustment guidelines were based on observations in the phase I/II trial showing that the dose-limiting toxicity was grade IV thrombocytopenia and that the incidence of grade III thrombocytopenia was increased with increasing ruxolitinib doses.

The primary efficacy endpoint was the proportion of patients who achieved a ≥35% SVR from baseline to week 24 as measured by MRI or CT scan. The key secondary endpoint was the proportion of patients who experienced a ≥50% improvement (reduction) from baseline in the total symptom score (TSS) in week 24 of treatment. TSS was based on modified Myelofibrosis Symptom Assessment Form version 2 (MFSAF v2.0). A numerical rating scale from 0 to 10 was used; 0 indicated an absence of a symptom and 10 indicated worst symptom severity of patients’ daily experiences with 6 common symptoms: night sweats, itching, abdominal discomfort, pain under left ribs, early satiety, and bone/muscle pain (7).

Daily TSS for a patient was a sum of 6 symptom scores, recorded by patients every 24 hours using a wireless electronic reporting device with a reminder function. Baseline TSS was calculated using an unweighted average of the daily scores for a baseline week. Week 24 TSS was an average of daily scores for the 28 days preceding week 24. As shown in Table 1, the mean baseline TSS was 18.0 on the ruxolitinib arm and 16.5 on the placebo arm. The mean TSS scores for each of the individual symptoms at baseline are also presented in Table 1. These data show that the individual symptom scores in many of the patients entered into study 1 were on the low side. An additional secondary efficacy endpoint was the percentage change in TSS from baseline to week 24.

At 6 months from the time of randomization, 93% of the patients randomized to the ruxolitinib arm continued to receive ruxolitinib, and 83% randomized to the placebo arm continued to receive placebo. Ten percent on the placebo arm had crossed over to treatment with ruxolitinib.

The results for the primary efficacy endpoint, the key secondary endpoint, and other secondary and exploratory endpoints at week 24 are presented in Table 2. The percentages of randomized patients who were evaluable for the primary endpoint was 99% on both arms. The percentages of randomized patients who were evaluable for the key secondary endpoint (the proportion of patients on each arm with ≥50% reduction in the TSS) at
week 24 on the ruxolitinib and placebo arms were 95% and 99%, respectively.

Ninety-nine percent of the patients in the ruxolitinib arm had some degree of SVR and 42% had SVR of ≥35%. In contrast, only 1% of the patients on the placebo arm had SVR of ≥35%; most patients in the placebo arm had increases in spleen volume. The difference between groups in the primary endpoint was highly statistically significant (P < 0.0001, Fisher exact test). Forty-six percent of those in the ruxolitinib arm experienced ≥50% reduction of TSS at week 24 of therapy, whereas only 5% in the placebo arm achieved this endpoint (P < 0.0001, Fisher exact test). As shown by the means of the individual symptom scores, all 6 symptoms in the TSS decreased concurrently. TSS decreased from baseline at week 24 by a mean of 46% in patients on the ruxolitinib arm experienced ≥50% reduction of TSS at week 24 of therapy, whereas only 5% in the placebo arm had some degree of SVR and 42% had SVR of 35%. In contrast, only 1% of the patients on the placebo arm had achieved this endpoint (P < 0.0001, Wilcoxon rank-sum test).

The absolute magnitude of the mean changes of each symptom appears to have been relatively small on each arm, although the direction of the change of symptom intensity during therapy was in the opposite directions for each of the individual symptoms (decreased on the ruxolitinib arm and increased on the placebo arm).

The duration of the SVR response could not be estimated at 24 weeks because most patients continued in SVR response. Overall survival could not be estimated at 24 weeks, because only 7% of patients on the ruxolitinib arm and 9% on the placebo arm had died.

Study 2. This trial was an open-label, prospectively randomized trial conducted in Europe, enrolling 219 patients with high-risk or intermediate-2 risk myelofibrosis who were ineligible for an allograft, had splenomegaly, and required treatment due to symptoms. Patients were randomized (2:1) to receive either ruxolitinib or best available therapy (BAT). Two thirds of the patients in the BAT arm were treated with medication, most commonly hydroxyurea (47% of patients). The baseline disease and demographic characteristics are summarized in Table 3.

The primary efficacy endpoint was the proportion of subjects who achieved a ≥35% SVR from baseline to week 48, and the key secondary endpoint was the proportion of patients who achieved a ≥35% SVR from baseline to week 24. The significance of differences in SVR responses was assessed by the Cochran–Mantel–Haenszel test, stratified by prognostic category (intermediate-2 risk or high-risk).

The results for the primary and secondary efficacy endpoints in study 2 are presented in Table 2. Almost all (97%) of the patients in the ruxolitinib arm had some degree of SVR and 29% had SVR of ≥35% after 48 weeks (33% of patients after 24 weeks) of treatment. In contrast, none of patients in the BAT arm had achieved SVR of ≥35% after 48 weeks (or 24 weeks) of therapy (P < 0.0001). Almost one-half of the patients (44%) in the BAT arm experienced an increase in spleen volume.

The follow-up of patients was too short to reliably evaluate response duration, with most of the responders continuing the response at datalock. The follow-up was also too short to evaluate overall survival (only 6 and 4 deaths occurred in the ruxolitinib and BAT arms, respectively) at the time of datalock.

Safety analysis

Safety data were available from a total of 528 patients with myelofibrosis who entered the 2 randomized clinical trials (study 1 and 2). Of these, 301 had been treated with ruxolitinib at initial doses of either 15 or 20 mg orally twice daily and 227 had been treated with either placebo (n = 154) or BAT (n = 73).

Median exposure duration to ruxolitinib was 9.5 months (range, 0.5–17) in the 2 trials. Discontinuations (withdrawal of consent, adverse events, progression of myelofibrosis, progression to acute myelogenous leukemia, and death) were higher among patients in the comparator arm than in the ruxolitinib arm (Table 4), with the exception of withdrawal of consent in study 2. A dose-tapering strategy at ruxolitinib discontinuation was recommended in both trials. Short-term courses of corticosteroids were permitted in this setting. There was no evidence of rebound of symptoms at the time of ruxolitinib discontinuation.

There was no increase in the number of early deaths, serious adverse events, or discontinuations due to adverse events in patients in the ruxolitinib arm compared with the comparator arms. As shown in Table 4, the only adverse events of grade ≥III that increased in the ruxolitinib arm in study 1 were anemia, thrombocytopenia, and neutropenia.

Despite the increase in thrombocytopenia in the ruxolitinib arms of both phase III trials, no increase in clinically
significant bleeding occurred reflecting the extensive use of prespecified ruxolitinib dose adjustments in patients with thrombocytopenia. Median hemoglobin levels reached a nadir of 9.6 g/dL between 8 and 12 weeks of therapy, then slowly returned to the baseline value of 10 g/dL over the ensuing 12 weeks of ruxolitinib therapy.

Discussion

The FDA approved ruxolitinib based on reduction in splenic volume and amelioration of disease-related symptoms observed with ruxolitinib treatment in patients with intermediate-2 risk and high-risk myelofibrosis. The FDA approval included patients with high-risk and intermediate-2 risk as well as intermediate-1 risk myelofibrosis, as these patients may have symptoms that require treatment. Two clinical trials were submitted to support this application.

Because neither overall survival, progression-free survival, nor overall response rate (by International Working Group/Myelofibrosis Research and Treatment criteria) were feasible or would accurately capture ruxolitinib treatment effect, the efficacy was measured by 2 novel endpoints—reduction of spleen volume and improvements in symptoms. A phase I/II study showed that patients treated with ruxolitinib experienced decreases of splenomegaly and improvements in myelofibrosis-related symptoms. A ≥35% reduction in spleen volume as measured by MRI (approximately ≥50% decrease in length as estimated by palpation) has no prior regulatory background as an efficacy endpoint and was proposed by the sponsor and accepted by the FDA as a response measure.

The results of studies 1 and 2 are robust and corroborate the effect of ruxolitinib on SVR, with 42% of patients in study 1 experiencing a ≥35% SVR at week 24 and 29% experiencing a ≥35% SVR at week 48 in study 2. In both studies, only 1% patients in study 1 and none in study 2 treated with either placebo or BAT, respectively, experienced this predefined degree of SVR. The second novel endpoint in study 1 was improvement of myelofibrosis-related symptoms, potentially a direct measure of clinical benefit. The assessment of this endpoint involved a newly developed patient-reported outcome instrument, the modified MFSAF v2.0. The original MFSAF was based on a symptom list derived from a survey of 458 patients (8–9). A wireless electronic reporting device with a reminder function was implemented in this trial that facilitated a high (>95%) retrieval of daily symptom scores minimizing missing data elements. Although the mean change from baseline of each individual symptom was modest in absolute magnitude because the mean baseline scores were low, the percentage changes were statistically significant. Patients treated with ruxolitinib showed on the average a decrease in intensity in this score, whereas those on the placebo arm showed increasing intensity.

The experience with ruxolitinib may provide a model for the future use of patient-reported outcome instruments in marketing applications. Instruments of disease-specific symptoms should be developed early in product development based on qualitative and quantitative research in the intended target population. To avoid problems in the interpretation of phase III trial results, patient-reported outcome instruments should be included as endpoints in preliminary trials before their use in phase III trials (10).

Anemia, thrombocytopenia, and neutropenia were the only adverse events occurring above the grade II level of SVR. Adverse events occurring at ≥35% were:

<table>
<thead>
<tr>
<th>Event</th>
<th>Study 1 (N = 155)</th>
<th>Placebo (N = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade ≥ III</td>
<td>All grades</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69.7%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Anemia</td>
<td>96.1%</td>
<td>45.2%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18.7%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Bruising</td>
<td>23.2%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18.1%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Headache</td>
<td>14.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>9.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

These results show that ruxolitinib is effective and well-tolerated in patients with myelofibrosis.
severity that were increased in patients in the ruxolitinib treatment arms of the 2 randomized trials. Ruxolitinib was approved without a minimal platelet count because the thrombocytopenia was rapidly reversible on dose reduction, and treatment is based on a titration of dose regulated by response and toxicity.

These 2 randomized trials showed responses both in the patients who were negative and those who were positive for the V617F mutation of JAK2. These findings suggest that other JAK1 and JAK2 activating mutations, as yet undiscovered, may exist or other mutations in proteins upstream of JAK1 and JAK2 may play a role in the pathogenesis of myelofibrosis. Alternatively, other factors than the acquired mutations could activate the JAK/STAT pathway causing symptoms and splenomegaly.

The approval of ruxolitinib for myelofibrosis represents the first approved drug for patients with myelofibrosis who require treatment and for whom other therapies are ineffective. The approval was based on 2 different myelofibrosis-related endpoints—a biologic endpoint, reduction in splenic volume, and a patient-reported outcome endpoint, improvement of disease symptoms. These endpoints provide evidence of both a biologic effect of ruxolitinib and a direct patient benefit.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions

Development of methodology: L. Burke
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.B. Deisseroth, E. Kaminskas, H. Lu, M.D. Rothmann, S.S. Brar, J. Wang, C. Garnett, L. Burke, R. Sridhara
Writing, review, and/or revision of the manuscript: A.B. Deisseroth, E. Kaminskas, J. Grillo, W. Chen, H. Saber, M.D. Rothmann, S.S. Brar, J. Wang, C. Garnett, J. Bullock, L. Burke, A. Farrell

Interpretation of data: A. Rahman

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References


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