COMFORT-I Trial:
Anemia Data

In intermediate- or high-risk MF

New-onset anemia and efficacy with Jakafi® (ruxolitinib)

Indications and Usage

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

Risk for thrombocytopenia, anemia, and neutropenia

- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery

Please see related and other Important Safety Information on the last page.
Please click here to see Full Prescribing Information for Jakafi.

Jakafi®
ruxolitinib (tablets)
5mg • 10mg • 15mg • 20mg • 25mg

COMFORT-I*

Jakafi® (ruxolitinib) significantly reduced spleen volume and improved symptoms of myelofibrosis. Results were consistent in patients with new-onset anemia[1]

Significantly more patients receiving Jakafi experienced improvement in MF-related splenomegaly and symptoms compared with placebo[1,2]

COMFORT-I Primary Endpoint

42% **of patients receiving Jakafi achieved ≥35% reduction in spleen volume at week 24 vs 0.7% of patients receiving placebo ($P < 0.0001$)[1,2]**

COMFORT-I Secondary Endpoint

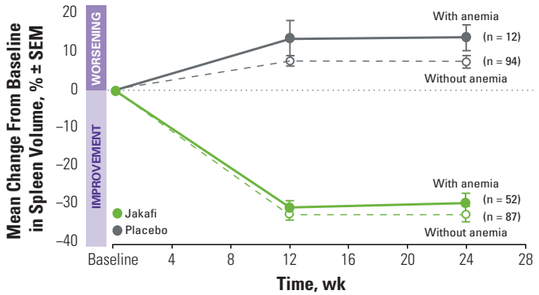
46% **of patients receiving Jakafi achieved ≥50% improvement in TSS at week 24 vs 5% of patients receiving placebo ($P < 0.0001$)[1,2]**

There are no contraindications for the use of Jakafi, including in patients with anemia[2]

- In COMFORT-I, 46% of patients receiving Jakafi had anemia† at baseline; among these patients, mean Hb was 9.2 g/dL (range 6.6 g/dL to 13.7 g/dL)[3]

COMFORT-I additional analysis: New-onset anemia did not impact efficacy for patients on Jakafi[1]

Effect of New-Onset Grade 3/4 Anemia on Spleen Volume Over Time[1,3]



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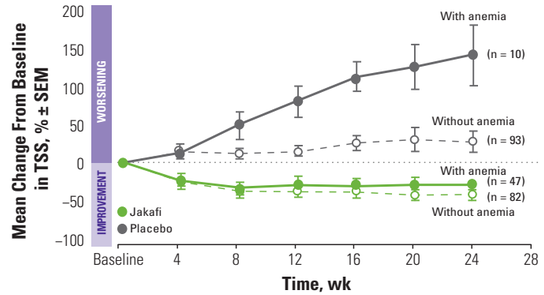
Effect of New-Onset Grade 3/4 Anemia on TSS Over Time[1,3]



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COMFORT-I rates of anemia[1,2]

Jakafi (n = 155)		**Placebo** (n = 151)	
All Grades, %	Grades 3 and 4, %	All Grades, %	Grades 3 and 4, %
96	45	87	19

Presented values are worst Grade values regardless of baseline.

<1% of patients receiving Jakafi in the COMFORT-I study discontinued due to anemia.[1]

Hb, hemoglobin; SEM, standard error of the mean; TSS, Total Symptom Score.

*COMFORT-I (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-I) was a randomized, double-blind, placebo-controlled, phase 3 study with 309 patients with intermediate-2–risk or high-risk MF. The primary endpoint was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline to week 24 as measured by CT or MRI. A secondary endpoint was the proportion of patients with a ≥50% reduction in TSS from baseline to week 24 as measured by the daily patient diary, the modified Myelofibrosis Symptom Assessment Form. TSS encompasses core symptoms of MF: abdominal discomfort, early satiety, pain under left ribs, pruritus, night sweats, and bone/muscle pain. Symptom scores ranged from 0 to 10, with 0 representing symptoms "absent" and 10 representing symptoms "worst imaginable." These scores were added to create the daily total score, which has a maximum of 60. At baseline, mean TSS was 18.0 in the group receiving Jakafi and 16.5 in the group receiving placebo.[1,2]

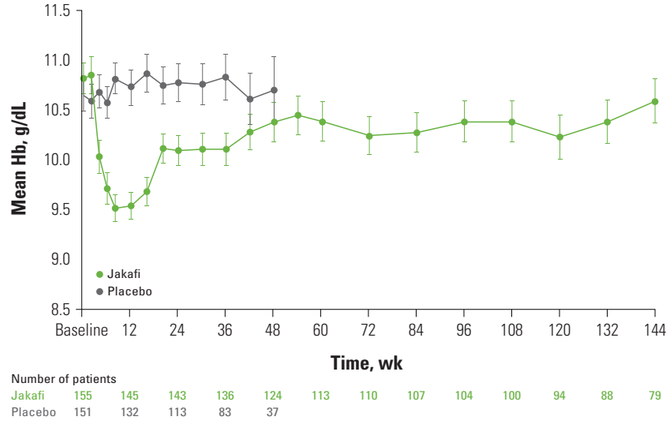
† Anemia at baseline was defined as red blood cell transfusion within the first 12 weeks prior to the initial dose of Jakafi, or baseline Hb < 10 g/dL.[3]

COMFORT-I

Hemoglobin levels and RBC transfusions over time

Hemoglobin partially recovered to a new steady state after initial decrease and remained stable over time[4]

Mean Hb Levels Over Time[4]



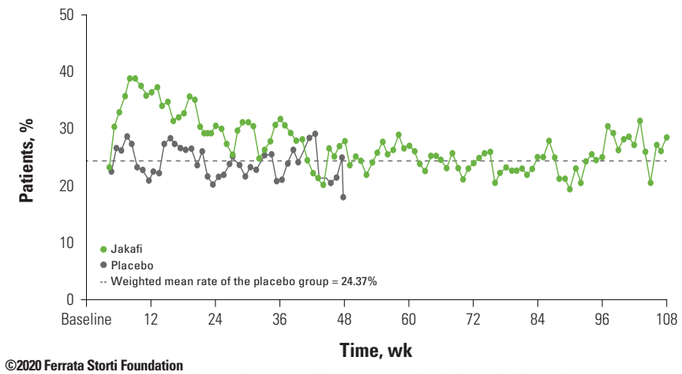
Number of patients

Jakafi	155	145	143	136	124	113	110	107	104	100	94	88	79
Placebo	151	132	113	83	37								

- Mean decreases in hemoglobin levels reached a nadir of approximately 1.5 g/dL to 2 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 g/dL below baseline[4]

Proportion of patients requiring RBC transfusions[5]*

Proportion of Patients Requiring RBC Transfusions During the Previous 4 Weeks[5]



- Through week 24, 60% of patients treated with Jakafi and 38% of patients receiving placebo required RBC transfusions[2]
- 123 of 155 patients in the group receiving Jakafi were transfusion independent at baseline, compared with 119 of 151 patients in the group receiving placebo. Of the 123 transfusion-independent patients in the group receiving Jakafi, 27% became transfusion dependent† during the 8 weeks before data cutoff, compared with 14.4% of patients in the group receiving placebo[3]

Identification and management of new-onset anemia[2]

- Perform a pre-treatment CBC, and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Dose modifications and/or transfusions may be required for patients who develop anemia

CBC, complete blood count; RBC, red blood cell.

* One or more units of red blood cells.[5]

† New-onset transfusion dependency: The use of 2 or more units of red blood cell product(s) during the final 8 weeks before database lock in a patient who was not transfusion dependent at baseline.[1]

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Important Safety Information

- Treatment with Jakafi® (ruxolitinib) can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. Use active surveillance and prophylactic antibiotics according to clinical guidelines
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines
- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers (NMSC) including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- Another JAK-inhibitor has increased the risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, and stroke (compared to those treated with tumor TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur
- Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients with myelofibrosis (MF) and polycythemia vera (PV) treated with Jakafi in clinical trials, the rates of thromboembolic events were similar in Jakafi and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately
- Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers
- In myelofibrosis and polycythemia vera, the most common nonhematologic adverse reactions (incidence ≥15%) were bruising, dizziness, headache, and diarrhea. In acute graft-versus-host disease, the most common nonhematologic adverse reactions (incidence >50%) were infections (pathogen not specified) and edema. In chronic graft-versus-host disease, the most common nonhematologic adverse reactions (incidence ≥20%) were infections (pathogen not specified) and viral infections
- Avoid concomitant use with fluconazole doses greater than 200 mg. Dose modifications may be required when administering Jakafi with fluconazole doses of 200 mg or less, or with strong CYP3A4 inhibitors, or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for 2 weeks after the final dose

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References: 1. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med.* 2012;366(9):799-807. **2.** Jakafi [package insert]. Wilmington, DE: Incyte Corporation. **3.** Data on file. Incyte Corporation. Wilmington, DE. **4.** Verstovsek S, Mesa RA, Gotlib J, et al. Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I. *Haematologica.* 2015;100(4):479-488. **5.** Verstovsek S, Mesa RA, Gotlib J, et al. Efficacy, safety and survival with ruxolitinib in patients with myelofibrosis: results of a median 2-year follow-up of COMFORT-I. *Haematologica.* 2013;98(12):1865-1871.

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