NOVARTIS

Jakavi®

DESCRIPTION AND COMPOSITION

Pharmaceutical forms

5 mg and 10 mg tablets, round and white

15 mg tablets, oval and white

20 mg tablets, capsule-shaped and white.

Active substance

Ruxolitinib phosphate

Ruxolitinib 5 mg per tablet

Ruxolitinib 10 mg per tablet

Ruxolitinib 15 mg per tablet

Ruxolitinib 20 mg per tablet.

Active Moiety

Ruxolitinib.

Excipients

Cellulose, microcrystalline

Magnesium stearate

Silica, colloidal anhydrous

Sodium starch glycolate (Type A)

Hydroxypropylcellulose

Povidone

Each 5 mg tablet contains 71.45 mg of lactose monohydrate

Each 10 mg tablet contains 142.90 mg of lactose monohydrate

Each 15 mg tablet contains 214.35 mg of lactose monohydrate

Each 20 mg tablet contains 285.80 mg of lactose monohydrate.

INDICATIONS

Myelofibrosis

Jakavi is indicated for the treatment of patients with International Working Group (IWG) Consensus Criteria intermediate-2 or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

Polycythemia vera

Jakavi is indicated for the treatment of patients with polycythemia vera who are resistant to or intolerant of hydroxyurea.

DOSAGE AND ADMINISTRATION

Monitoring instructions

Blood cell counts: a blood cell count must be performed before initiating therapy with Jakavi.

Complete blood counts should be monitored every 2 to 4 weeks until doses are stabilized, and then as clinically indicated (see section WARNINGS AND PRECAUTIONS).

Starting Dose

The recommended starting dose of Jakavi in Myelofibrosis is 15 mg given orally twice daily for patients with a platelet count between 100,000 and 200,000/mm^3 and 20 mg twice daily for patients with a platelet count of >200,000/mm^3. There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm^3 and 100,000/mm^3. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously.

Table: Proposed Jakavi Starting Doses

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

The recommended starting dose of Jakavi in Polycythemia vera is 10 mg given orally twice daily.

Dose modifications

Table: Maximum Restarting Doses for Jakavi After Safety Interruption*

Current Platelet Count	Maximum Dose When Restarting Jakavi Treatment *
Greater than or equal to 125 X 10^9/L	20 mg twice daily
100 to less than 125 X 10^9/L	15 mg twice daily
75 to less than 100 X 10^9/L	10 mg twice daily for at least 2 weeks; if stable, may increase to 15 mg twice daily
50 to less than 75 X 10^9/L	5 mg twice daily for at least 2 weeks; if stable, may increase to 10 mg twice daily
Less than 50 X 10^9/L	Continue hold

*Maximum doses are displayed. When restarting, begin with a dose at least 5 mg twice daily below the dose at interruption.

Table: Dosing Recommendations for Thrombocytopenia

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

Doses may be titrated based on safety and efficacy. Treatment should be interrupted for platelet counts less than 50,000/mm^3 or absolute neutrophil counts less than 500/mm^3.

In polycythemia vera, treatment should also be interrupted when hemoglobin is below 8 g/dL.

After recovery of blood counts above these levels, dosing may be restarted at 5 mg twice daily and gradually increased based on careful monitoring of blood cell counts.

Dose reductions should be considered if the platelet counts decrease below 100,000/ mm^3 with the goal of avoiding dose interruptions for thrombocytopenia.

In polycythemia vera, dose reduction should also be considered if hemoglobin decreases below 12 g/dL and is recommended if hemoglobin decreases below 10 g/dL.

If efficacy is considered insufficient and blood counts are adequate, doses may be increased by a maximum of 5 mg twice daily, up to the maximum dose of 25 mg twice daily.

The starting dose should not be increased within the first four weeks of treatment and thereafter no more frequently than at 2-week intervals.

Table: Polycythemia Vera: Dose Reductions

Hemoglobin and/or Platelet Count	**Dosing Recommendations**
Hemoglobin greater than or equal to 12 g/dL AND platelet count greater than or equal to 100 X 10^9/L	• No change required.
Hemoglobin 10 to less than 12 g/dL AND platelet count 75 to less than 100 X 10^9/L	• Dose reductions should be considered with the goal of avoiding dose interruptions for anemia and thrombocytopenia.

Hemoglobin 8 to less than 10 g/dL OR platelet count 50 to less than 75 X 10^9/L	• Reduce dose by 5 mg twice daily. • For patients on 5 mg twice daily, decrease the dose to 5 mg once daily.
Hemoglobin less than 8 g/dL OR platelet count less than 50 X 10^9/L	• Interrupt dosing.

Table: Polycythemia Vera: Restarting Doses for Jakafi after Safety Interruption for Hematologic Parameter(s)

Hemoglobin, Platelet Count, or ANC	Maximum Restarting Dose
Hemoglobin less than 8 g/dL OR platelet count less than 50 X 10^9/L OR ANC less than 1 X 10^9/L	Continue hold
Hemoglobin 8 to less than 10 g/dL OR platelet count 50 to less than 75 X 10^9/L OR ANC 1 to less than 1.5 X 10^9/L	5 mg twice daily[a] or no more than 5 mg twice daily less than the dose which resulted in dose interruption
Hemoglobin 10 to less than 12 g/dL OR platelet count 75 to less than 100 X 10^9/L OR ANC 1.5 to less than 2 X 10^9/L	10 mg twice daily[a] or no more than 5 mg twice daily less than the dose which resulted in dose interruption
Hemoglobin greater than or equal to 12 g/dL OR platelet count greater than or equal to 100 X 10^9/L OR ANC greater than or equal to 2 X 10^9/L	15 mg twice daily[a] or no more than 5 mg twice daily less than the dose which resulted in dose interruption

[a] Continue treatment for at least 2 weeks; if stable, may increase dose by 5 mg twice daily.

Administration instruction

The maximum dose of Jakavi is 25 mg twice daily.

If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose.

Treatment may be continued as long as the benefit: risk remains positive.

It is recommended that, for patients who had no clinical improvement, or no reduction in spleen volume, the treatment should be discontinued after 6 months. And for patients who have demonstrated some degree of clinical improvement, ruxolitinib therapy be discontinued if they sustain an increase in their spleen length of 40% compared with baseline size (roughly equivalent to a 25% increase in spleen volume) and no longer have tangible improvement in disease-related symptoms.

Dose adjustment with concomitant strong CYP3A4 Inhibitors or fluconazole:

When Jakavi is administered with strong CYP3A4 inhibitors or dual moderate inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole), the total daily dose of Jakavi should be reduced by approximately 50% either by decreasing the twice daily dose or by decreasing the frequency of dosing to the corresponding once daily dose when twice daily dosing is not practical. Avoid the concomitant use of Jakavi with fluconazole doses of greater than 200 mg daily (see section INTERACTION).

More frequent monitoring of hematology parameters and clinical signs and symptoms of Jakavi related adverse reactions is recommended upon initiation of a strong CYP3A4 inhibitor or dual moderate inhibitors of CYP2C9 and CYP3A4 enzymes.

Special populations

Renal impairment

No specific dose adjustment is needed in patients with mild or moderate renal impairment.
In patients with severe renal impairment (creatinine clearance less than 30 ml/min) the recommended starting dose based on platelet count for MF patients should be reduced by approximately 50% to be administered twice daily. The recommended starting dose for PV patients with severe renal impairment is 5 mg twice daily. Patients should be carefully monitored with regard to safety and efficacy during Jakavi treatment.
There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on haemodialysis. Pharmacokinetic/pharmacodynamic simulations based on available data in this population suggest that the starting dose for patients with ESRD on haemodialysis is a single dose of 15-20 mg or two doses of 10 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis. A single dose of 15 mg is recommended for patients with platelet count between 100,000/mm^3 and 200,000/mm^3. A single dose of 20 mg or two doses of 10 mg given 12 hours apart is recommended for patients with platelet count of >200,000/mm^3. Subsequent doses (single administration or two doses of 10 mg given 12 hours apart) should be administered only on haemodialysis days following each dialysis session. These dose recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration. The recommended starting dose for PV patients with ESRD on hemodialysis is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis and with careful monitoring of safety and efficacy (see section Pharmacokinetics section).

Hepatic Impairment

In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice daily. Subsequent doses should be adjusted based on careful monitoring of safety and efficacy. Patients diagnosed with hepatic impairment while receiving Jakavi should have complete blood counts, including a white blood cell count differential, monitored at least every one to two weeks for the first 6 weeks after initiation of therapy with Jakavi and as clinically indicated thereafter once their liver function and blood counts have been stabilised. Jakavi dose can be titrated to reduce the risk of cytopenia.

Pediatrics

Safety and efficacy of Jakavi in pediatric patients have not been established.

Geriatrics

No additional dose adjustments are recommended for elderly patients.

Method of administration

Jakavi is dosed orally and can be administered with or without food.

CONTRAINDICATIONS

Hypersensitivity to the active substance or any of the excipients.

WARNINGS AND PRECAUTIONS

Decrease in blood cell count

Treatment with Jakavi can cause hematological adverse reactions, including thrombocytopenia, anemia and neutropenia. A complete blood count must be performed before initiating therapy with Jakavi (for monitoring frequency see section DOSAGE AND ADMINISTRATION).

It has been observed that patients with low platelet counts (<200,000/mm^3) 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 Jakavi. However, platelet transfusions may be required as clinically indicated (see sections DOSAGE AND ADMINISTRATION, and ADVERSE DRUG REACTIONS).

Patients developing anemia may require blood transfusions. Dose modifications or interruption for patients developing anemia may also be considered.

Patients with a haemoglobin level below 10.0 g/dl at the beginning of the treatment have a higher risk of developing a haemoglobin level below 8.0 g/dl during treatment compared to patients with a higher baseline haemoglobin level (79.3% versus 30.1%). More frequent monitoring of haematology parameters and of clinical signs and symptoms of Jakavi-related adverse drug reactions is recommended for patients with baseline haemoglobin below 10.0 g/dl.

Neutropenia (Absolute Neutrophil Count (ANC) <500/mm^3) was generally reversible and was managed by temporarily withholding Jakavi (see sections DOSAGE AND ADMINISTRATION, and ADVERSE DRUG REACTIONS).

Complete blood counts should be monitored as clinically indicated and dose adjusted as required (see sections DOSAGE AND ADMINISTRATION, and ADVERSE DRUG REACTIONS).

Infections

Serious bacterial, mycobacterial, fungal, viral and other opportunistic infections have occurred in patients treated with Jakavi. Patients should be assessed for the risk of developing serious infections. Physicians should carefully observe patients receiving Jakavi for signs and symptoms of infections and initiate appropriate treatment promptly. Jakavi therapy should not be started until active serious infections have resolved. Tuberculosis has been reported in patients receiving Jakavi for myelofibrosis. Before starting treatment, patients should be evaluated for active and inactive (“latent”) tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakavi. The effect of Jakavi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

Herpes Zoster

Physicians should educate patients about early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported with Jakavi treatment. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.

Non-Melanoma Skin Cancer

Non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and Merkel cell carcinoma have been reported in patients treated with Jakavi. Most of these patients had histories of extended treatment with hydroxyurea and prior NMSC or pre-malignant skin lesions. A causal relationship to ruxolitinib has not been established. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Lipid Abnormalities/ Elevations

Treatment with Jakavi has been associated with increases in lipid parameters including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Lipid monitoring and treatment of dyslipidemia according to clinical guidelines is recommended.

Special populations

Renal impairment

In patients with severe renal impairment (creatinine clearance less than 30 ml/min) the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice daily. Patients should be carefully monitored with regard to safety and efficacy during Jakavi treatment.

There are limited data to determine the best dosing options for MF patients with end-stage renal disease (ESRD) on haemodialysis. Pharmacokinetic/pharmacodynamic simulations based on available data in this population suggest that the starting dose for MF patients with ESRD on haemodialysis is a single dose of 15-20 mg or 10 mg given 12 hours apart. A single dose of 15 mg is recommended for patients with platelet count between 100,000/mm^3 and 200,000/mm^3. A single dose of 20 mg or 10 mg given 12 hours apart is recommended for patients with platelet count of >200,000/mm^3. Subsequent doses single administration or 10 mg given 12 hours apart should be administered on haemodialysis days. These dose

recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration.

The recommended starting dose for PV patients with ESRD on hemodialysis is a single dose of 10 mg or 5 mg given 12 hours apart, to be administered on the day of haemodialysis. These dose recommendations are based on simulations and any dose modification in ESRD should be followed by careful monitoring of safety and efficacy in individual patients. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous haemofiltration.

Hepatic impairment

The starting dose of Jakavi should be reduced in patients with hepatic impairment. Further dose modifications should be based on the safety and efficacy of the drug (see sections DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Special populations).

Interactions

If Jakavi is to be co-administered with strong CYP3A4 inhibitors or dual inhibitors of CYP3A4 and CYP2C9 enzymes (e.g. fluconazole), the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily (for monitoring frequency see sections DOSAGE AND ADMINISTRATION and INTERACTIONS).

Withdrawal effects

After discontinuation of treatment, myelofibrosis related symptoms are expected to return. Serious events happening after sudden discontinuation of Jakavi, especially in cases with acute illness, have been reported. It is uncertain whether those events are related to the interruption. Gradual reduction of Jakavi dosage is recommended when discontinuation of treatment is required, although the efficacy has not yet been established.

ADVERSE DRUG REACTIONS

Summary of the safety profile

Safety assessment was based on a total of 982 patients (with myelofibrosis or polycythemia vera) receiving Jakavi in Phase 2 and 3 studies.

Myelofibrosis:

In the randomized period of the two pivotal studies COMFORT-I and COMFORT-II, patients had a median duration of exposure to Jakavi of 10.8 months (range 0.3 to 23.5 months). The majority of patients (68.4%) were treated for at least 9 months. Of the 301 patients, 111 (36.9%) had a baseline platelet count between 100,000/mm^3 and 200,000/mm^3, and 190 (63.1%) had a baseline platelet count >200,000/mm^3.

In these clinical studies, discontinuation due to adverse events, regardless of causality was observed in 11.3% of patients.

The most frequently reported adverse drug reactions were thrombocytopenia and anemia.

Hematological adverse reactions (any CTCAE grade; Common Terminology Criteria for Adverse Events) included anemia (82.4%), thrombocytopenia (69.8%) and neutropenia (16.6 %).

Anemia, thrombocytopenia and neutropenia are dose related effects.

The three most frequent non-hematological adverse reactions were bruising (21.6%), dizziness (15.3%) and headache (14.0%).

The three most frequent non-hematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (19.9%) and hypercholesterolemia (16.9%).

Long term safety data from two pivotal phase 3 studies assessing 457 patients with myelofibrosis treated with ruxolitinib, including data from patients initially randomized to ruxolitinib (n=301; exposure 0.3 to 68.1 months, median exposure 33.4 months) and patients who received ruxolitinib after crossing over from control treatments (n=156; exposure: 0.5 to 59.8 months, median exposure 25.0 months): The cumulative frequency of adverse events increased proportionally to the increase in the follow-up time.

With these updated data, therapy discontinuation due to adverse events was observed in 27.4% of patients treated with ruxolitinib.

Polycythemia vera:

The safety of Jakavi was assessed in 184 patients with polycythemia vera in two open-label, randomized, controlled studies, the phase 3 RESPONSE study and the phase 3b RESPONSE2 study. The adverse drug reaction listed below reflect the randomized study period (up to Week 32 for RESPONSE and upto week 28 for RESPONSE 2) with equivalent exposure to ruxolitinib and Best Available Therapy. The median duration of exposure to Jakavi during the randomized study period was 7.85months (range 0.03 to 7.85 months).

Discontinuation for adverse events, regardless of causality, was observed in 2.2% of patients.

Hematological adverse reactions (any CTCAE grade) included anemia (40.8%) and thrombocytopenia (16.8%). Anaemia or thrombocytopenia Grade 3 and 4 were reported in respectively 1.1% or 3.3%.

The three most frequent non-haematological adverse reactions were dizziness (9.2%), constipation (8.7%), and hypertension (6.5%). The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) identified as adverse reactions were raised aspartate aminotransferase (26.1%), raised alanine aminotransferase (22.3%) and hypercholesterolaemia (20.7%). These were all Grade 1 to 2 with the exception of one Grade 3 raised alanine aminotransferase event.

Long term safety was evaluated using data from 367 patients with polycythemia vera treated with ruxolitinib in two phase 3 studies including data from patients initially randomized to ruxolitinib (n=184; exposure 0.03 to 43.5 months, median exposure 18.9 months) and patients who received ruxolitinib after crossing over from control treatments (n=149; exposure: 0.2 to 33.5 months, median exposure 12.0 months): With longer exposure, the cumulative frequency of AEs increased but no new safety findings emerged. When adjusted for exposure, the AE rates were generally comparable with those observed during the initial periods of the randomized studies.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

In the clinical studies program the severity of adverse drug reactions was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) defining grade 1=mild, grade 2= moderate, Grade 3=severe and grade 4=life-threatening or disabling.

Table 1 Percentage of patients with adverse drug reactions in clinical studies

Adverse drug reactions and CTCAE grade[3]	Frequency category for MF patients	Frequency category for PV patients
Infections and infestations		
Urinary Tract infections[1,]	Very common	Common
Pneumonia[1]	Common	-
Herpes zoster[1]	Common	Common
Sepsis	Common	-
Tuberculosis[*]	Uncommon	-
Blood and lymphatic system disorders		
Anaemia[2]		
CTCAE [1] grade 4 (<6.5g/dL)	Very common	Uncommon
CTCAE grade 3 (<8.0 – 6.5g/dL)	Very common	Uncommon
Any CTCAE grade	Very common	Very common
Thrombocytopenia[2]		
CTCAE grade 4 (<25,000/mm^3)	Common	Uncommon
CTCAE grade 3 (50,000 – 25,000/mm^3)	Common	Common
Any CTCAE grade	Very common	Very common
Neutropenia[2]		
CTCAE grade 4 (<500/mm^3)	Common	-
CTCAE grade 3 (<1000 – 500/mm^3)	Common	-
Any CTCAE grade	Very common	-
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)	Very common	Very common
Intracranial bleeding	Common	Uncommon
Gastrointestinal bleeding	Common	Common
Bruising	Very common	Very common
Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria)	Very common	Common
Metabolism and nutrition disorders		
Weight gain[1]	Very common	Common

Adverse drug reactions and CTCAE grade[3]	Frequency category for MF patients	Frequency category for PV patients
Hypercholesterolaemia [2] CTCAE grade 1 and 2	Very common	Very common
Hypertriglyceridaemia[2] CTCAE grade 1	-	Very common
Nervous system disorders		
Dizziness[1]	Very common	Very common
Headache[1]	Very common	-
Gastrointestinal disorders		
Flatulence[1]	Common	-
Constipation[1]	-	Common
Hepatobiliary disorders		
Raised alanine aminotransferase[2]		
CTCAE grade 3 (> 5x – 20 x ULN)	Common	Uncommon
Any CTCAE grade	Very common	Very common
Raised aspartate aminotransferase[2]		
Any CTCAE grade	Very common	Very common
Vascular disorders		
Hypertension[1]	-	Common

[1] Frequency is based on adverse event data.
[2] Frequency is based on laboratory values.
[3] Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0;
Grade 1=mild, Grade 2= moderate, Grade 3=severe, Grade 4=life-threatening or disabling.
ULN = upper limit of normal
[4] Frequency is based on all patients exposed to ruxolitinib in clinical trials (N=4755)

Upon discontinuation MF patients may experience a return of myelofibrosis symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In MF clinical studies the total symptom score for myelofibrosis symptoms gradually returned to baseline values within 7 days after dose discontinuation.

Increase in systolic blood pressure

In a phase 3 pivotal study, patients who had returned for examination at least one time during the trial were observed. The percentage of patients with an increase in blood pressure of 20 mmHg or more, was 31.5% and 19.5%, respectively, in Jakavi group and control group. In COMFORT-I study, the average systolic blood pressure of patients treated with Jakavi and patients treated with placebo, increased 0-2 and 2-5 mmHg, respectively. In COMFORT-II study, there was almost no difference between both groups.

Description of selected adverse drug reactions

Anemia

In phase 3 MF clinical studies, median time to onset of first CTCAE grade 2 or higher anemia was 1.5 months. One patient (0.3%) discontinued treatment because of anemia.

In patients receiving Jakavi mean decreases in hemoglobin reached a nadir of approximately 10g/L below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 5 g/L below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy.

In the randomized, placebo controlled study (COMFORT-I), 60.6% of Jakavi treated patients and 37.7% of patients receiving placebo received red blood cell transfusions during randomized treatment. In the COMFORT-II study, the rate of packed red blood cell transfusions was 53.4% in the Jakavi arm and 41.4% in the best available therapy arm (BAT).

Over the randomized period in the RESPONSE and RESPONSE 2 studies, anaemia was less frequent in PV patients (40.8%) versus 82.4% in MF patients. The CTCAE Grade 3 and 4 events was 2.7% in PV patients, while in the MF patients, the frequency was 42.5%.

Thrombocytopenia

In the Phase 3 MF 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 50,000/mm^3 was 14 days. During the randomized period platelet transfusions were administered to 4.7% of patients receiving Jakavi and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakavi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm^3 to 200,000/mm^3 before starting Jakavi had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm^3 (64.2% versus 38.5%).

Over the randomized period in theRESPONSE and RESPONSE 2, the rate of patients experiencing thrombocytopenia was lower in PV (16.8%) compared to MF (69.8%) patients. The frequency of severe (i.e. of CTCAE Grade 3 and 4) thrombocytopenia was lower in PV (2.7%) than in MF (11.6%) patients.

Neutropenia

In the phase 3 clinical studies in MF, in patients who developed Grade 3 or 4 neutropenia, the median time of onset was 12 weeks. During the randomized period of the studies dose holding or reductions due to neutropenia were reported in 1% of patients and 0.3% of patients discontinued treatment because of neutropenia.

Over the randomized period in the RESPONSE and RESPONSE-2, studies in PV, neutropenia was observed in 3 patients (1.6%) of which one patient developed CTCAE Grade 4 neutropenia.

Urinary tract infections

In phase 3 MF clinical studies Grade 3 or 4 urinary tract infection was reported for 1.0% of patients. Urosepsis was reported in 1.0% of patients and kidney infection in 1 patient.

Over the randomized period in theRESPONSE and RESPONSE-2 studies in PV,, one (0.5%) Grade 3-4 urinary tract infection was observed.

Herpes zoster

The rate of herpes zoster was similar in PV (4.3%) patients and MF patients (4.0%). There was one report of Grade 3 and 4 post herpetic neuralgia amongst the PV patients.

Additional Data from the Placebo-controlled Study

25.2% of patients treated with Jakavi 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 Jakavi with 1.3% Grade 3 and no Grade 4 ALT elevations.

17.4% of patients treated with Jakavi 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 Jakavi with no Grade 3 or 4 AST elevations.

16.8% of patients treated with Jakavi 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 Jakavi with no Grade 3 or 4 cholesterol elevations.

Bleeding

In the phase 3 pivotal studies bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 32.6% of patients exposed to Jakavi and 23.2% of patients exposed to the reference treatments (placebo or best available therapy). The frequency of grade 3-4 events was similar for patients treated with Jakavi or reference treatments (4.7% versus 3.1%). Most of the patients with bleeding events during the treatment reported bruising (65.3%). Bruising events were more frequently reported in patients taking Jakavi compared with the reference treatments (21.3% versus 11.6%). Intracranial bleeding was reported in 1% of patients exposed to Jakavi and 0.9% exposed to reference treatments. Gastrointestinal bleeding was reported in 5.0% of patients exposed to Jakavi compared to 3.1% exposed to reference treatments. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage and haematuria) were reported in 13.3% of patients treated with Jakavi and 10.3% treated with reference treatments.

Infections

In the phase 3 pivotal studies grade 3 or 4 urinary tract infection was reported in 1.0% of patients, herpes zoster in 4.3% and tuberculosis in 1.0%.

INTERACTIONS

Agents that may alter plasma concentration of ruxolitinib

Strong CYP3A4 inhibitors: In healthy subjects receiving ketoconazole, a strong CYP3A4 inhibitor, at 200 mg twice daily for four days, the AUC of Jakavi increased by 91% and the half-life was prolonged from 3.7 to 6.0 hours.

When administering Jakavi with strong CYP3A4 inhibitors the total daily dose of Jakavi should be reduced by approximately 50%.

Patients should be closely monitored for cytopenias and dose titrated based on safety and efficacy (see section DOSAGE AND ADMINISTRATION).

Mild or moderate CYP3A4 inhibitors: In healthy subjects receiving erythromycin, a moderate CYP3A4 inhibitor, at 500 mg twice daily for four days, there was a 27% increase in the AUC of Jakavi.

No dose adjustment is recommended when Jakavi is co administered with mild or moderate CYP3A4 inhibitors (e.g. erythromycin). Patients should be closely monitored for cytopenias when initiating therapy with a moderate CYP3A4 inhibitor.

Dual moderate CYP2C9 and CYP3A4 inhibitors (e.g Fluconazole): Based on in silico modeling, AUC increase of ruxolitinib of 2.9-fold and 4.3-fold when co-administered with 200 mg or 400 mg fluconazole, respectively, is predicted. A 50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes. Avoid the concomitant use of Jakavi with fluconazole doses of greater than 200 mg daily.

CYP3A4 inducers: Upon initiation of a CYP3A4 inducer, no dose adjustment is recommended. Gradual dose increases of Jakavi may be considered if the effectiveness of therapy is diminished during treatment with a CYP3A4 inducer.

In healthy subjects receiving rifampin, a potent CYP3A4 inducer, at 600 mg once daily for ten days, the AUC of Jakavi following a single dose decreased by 71% and the half-life decreased from 3.3 to 1.7 hours. The relative amount of active metabolites increased in relation to parent compound.

P-glycoprotein and other transporters: No dose adjustment is recommended when Jakavi is co-administered with substances that interact with P-gp and other transporters.

Other drug interactions studied

CYP3A4 substrates:

A study in healthy subjects indicated that Jakavi had no clinically significant pharmacokinetic interaction with midazolam (CYP3A4 substrate).

Oral contraceptives:

A study in healthy subjects indicated that Jakavi does not affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel. Therefore it is not anticipated that contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY

Women of child-bearing potential

Women of child-bearing potential must take appropriate precautions to avoid becoming pregnant during treatment.

In case pregnancy occurs, risk/benefit evaluations must be carried out on an individual basis with careful counseling regarding potential risk to the fetus using the most recent data available.

Pregnancy

There are no adequate and well-controlled studies of Jakavi in pregnant women.

Embryo-fetal development studies with ruxolitinib in rats and rabbits did not indicate teratogenicity. Ruxolitinib was embryotoxic and fetotoxic in rats (increases in post-implantation loss and reduced fetal weights) (see section NON-CLINICAL SAFETY DATA).

The potential risk for humans is unknown. The use of Jakavi during pregnancy is not recommended.

Breast-feeding

Women taking Jakavi should not breast-feed.

In lactating rats, ruxolitinib and/or its metabolites were excreted into the milk with a concentration that was 13-fold higher than the maternal plasma concentration. It is not known whether Jakavi is excreted in human milk.

Fertility

There are no human data on the effect of ruxolitinib on fertility. In animal studies, no effects were observed on fertility or reproductive performance of male or female rats. In a pre- and postnatal study in rats, fertility in the first generation offspring was also not affected (see section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

There is no known antidote for overdoses with Jakavi. 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 Jakavi.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 (IC_{50} values of 3.3 nM and 2.8 nM for JAK1 and JAK2 enzymes, respectively). These 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.

Myelofibrosis (MF) and Polycythemia vera (PV) are myeloproliferative neoplasms (MPN) known to be associated with dysregulated JAK1 and JAK2 signaling. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK-STAT pathway, gain-of function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signaling regardless of JAK2V617F mutation status. Activating mutations in JAK2 (V617F or exon 12) are found in >95% of PV patients.

Ruxolitinib inhibits JAK-STAT signaling and cell proliferation of cytokine-dependent cellular models of hematological malignancies, as well as of Ba/F3 cells rendered cytokine-independent by expressing the JAK2V617F mutated protein, with IC_{50}'s ranging from 80-320 nM. In a mouse model of JAK2V617F-positive MPN, oral administration of ruxolitinib prevented splenomegaly, preferentially decreased JAK2V617F mutant cells in the spleen, decreased circulating inflammatory cytokines (e.g., TNF-α, IL-6) and resulted in significantly prolonged survival in the mice at doses that did not cause myelosuppressive effects.

Pharmacodynamics (PD)

Ruxolitinib inhibits cytokine induced STAT3 phosphorylation in whole blood from healthy subjects and MF and PV patients. Ruxolitinib resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 8 hours in both healthy subjects and myelofibrosis patients, indicating no accumulation of either parent or active metabolites.

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNFalpha, IL-6, and CRP in subjects with MF were decreased following treatment with ruxolitinib. Patients with myelofibrosis did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with polycythemia vera also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with ruxolitinib.

In a thorough QT study in healthy subjects, there was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up to a supratherapeutic dose of 200 mg indicating that ruxolitinib has no effect on cardiac repolarization.

Pharmacokinetics (PK)

Absorption

Ruxolitinib is a Class 1 molecule under the Biopharmaceutical Classification System, with high permeability, high solubility and rapid dissolution characteristics. In clinical studies, ruxolitinib is rapidly absorbed after oral administration with maximal plasma concentration (C_{max}) achieved approximately 1 hour post-dose. Based on a mass balance study in humans, oral absorption of ruxolitinib was 95% or greater. Mean ruxolitinib C_{max} and total exposure (AUC) increased proportionally over a single dose range of 5 to 200 mg. There was no clinically relevant change in the pharmacokinetics of ruxolitinib upon administration with a high-fat meal. The mean C_{max} was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) upon dosing with a high-fat meal.

Distribution

The mean volume of distribution at steady-state is 72 L in myelofibrosis patients with an inter-subject variability of 29.4% and 75 L in polycythemia vera patients with an associated inter-subject variability of 22.6%. At clinically relevant concentrations of ruxolitinib, binding to plasma proteins *in vitro* is approximately 97%, mostly to albumin. A whole body autoradiography study in rats has shown that ruxolitinib does not penetrate the blood-brain barrier.

Biotransformation/metabolism

In vitro studies indicate that CYP3A4 is the major enzyme responsible for metabolism of ruxolitinib (>50%), and CYP2C9 is the minor one. Parent compound 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 metabolites have one half to one fifth of the parent JAK-related pharmacological activity. The sum total of all active metabolites contribute to 18% of the overall pharmacodynamics of ruxolitinib. At clinically relevant concentrations, ruxolitinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4. Based on *in vitro* studies, ruxolitinib might inhibit CYP3A4, P-gP & BCRP in gastrointestinal tract.

Elimination

Following a single oral dose of [^{14}C]-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.

Linearity/non-linearity

Dose proportionality was demonstrated in the single and multiple dose studies.

Special populations

Effects of age, gender, or race

Based on studies in healthy subjects, no relevant 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. Clearance was 17.7 L/h in women and 22.1 L/h in men, with 39% inter-subject variability in myelofibrosis patients. Clearance was 12.7 L/h in polycythemia vera patients, with a 42% inter-subject variability, and no relationship was apparent between oral clearance and gender, patient age or race in this patient population.

Pediatric

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

Renal insufficiency

Following a single ruxolitinib dose of 25 mg, the pharmacokinetics were similar in subjects with various degrees of renal impairment and in those with normal renal function, according to Modification of Diet in Renal Disease (MDRD) and urinary creatinine in urea. However, plasma AUC values of ruxolitinib metabolites tended to increase with increasing severity of renal impairment, and most markedly in the subjects with end stage renal disease requiring hemodialysis. Ruxolitinib is not removed by dialysis. A dose modification is recommended for patients with severe renal impairment (Clcr less than 30 mL/min). Dosing only after haemodialysis sessions can reduce exposure of active metabolites, and would also decrease the effect of ruxolitinib.(see section DOSAGE AND ADMINISTRATION).

Hepatic insufficiency

Following a single ruxolitinib dose of 25 mg in patients with varying degrees of hepatic impairment, the pharmacokinetics and pharmacodynamics of ruxolitinib were assessed. The mean AUC for ruxolitinib was increased in patients with mild, moderate and severe hepatic impairment by 87%, 28% and 65%, respectively, compared to patients with normal hepatic function and indicating no clear relationship to the degree of hepatic impairment based on Child-Pugh scores. 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). A 50% of dose reduction is recommended for patients with hepatic impairment (see section DOSAGE AND ADMINISTRATION).

CLINICAL STUDIES

Myelofibrosis

Two randomized Phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with Myelofibrosis (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 prognostic factors that comprise the IWG criteria consist of age >65 years, presence of constitutional symptoms (weight loss, fever, night sweats) anemia (hemoglobin <10 g/dL), leukocytosis (history of WBC >25 X 10^9/L) and circulating blasts ≥1%. The starting dose of Jakavi was based on platelet count. Patients with a platelet count between 100,000 and 200,000/mm^3 were started on Jakavi 15 mg twice daily and patients with a platelet count >200,000/mm^3 were started on Jakavi 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 100,000 to ≤125,000/mm^3, of 10 mg twice daily for patients with platelet counts between 75,000 to ≤100,000/mm^3, and of 5 mg twice daily for patients with platelet counts between 50,000 to ≤75,000/mm^3.

COMFORT-I was a double-blind, randomized, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. Patients were dosed with Jakavi or matching placebo. The primary efficacy endpoint was proportion of subjects achieving ≥35% reduction from baseline in spleen volume at Week 24 as measured by MRI or CT.

Secondary endpoints included duration of maintenance of a ≥35% reduction from baseline in spleen volume, proportion of patients who had ≥50% reduction in total symptom score from baseline to Week 24 as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary, change in total symptom score from baseline to Week 24 as measured by the modified MFSAF v2.0 diary and overall survival.

COMFORT-II was an open-label, randomized study in 219 patients. Patients were randomized 2:1 to Jakavi versus best available therapy. Best available therapy was selected by the investigator on a patient-by-patient basis. In the best available therapy arm, 47% of patients received hydroxyurea and 16% of patients received glucocorticoids. The primary efficacy endpoint was proportion of patients achieving ≥35% reduction from baseline in spleen volume at Week 48 as measured by MRI or CT.

A secondary endpoint in COMFORT-II was the proportion of patients achieving a ≥35% reduction of spleen volume measured by MRI or CT from baseline to Week 24. Duration of maintenance of a ≥35% reduction from baseline in responding patients was also a secondary endpoint.

In COMFORT-I, patient baseline demographics and disease characteristics were comparable between the treatment arms. The median age was 68 years with 61% of patients older than 65 years and 54% male. Fifty percent (50%) of patients had primary myelofibrosis, 31% had post-polycythemia myelofibrosis and 18% had post-essential thrombocythemia myelofibrosis. Twenty-one (21%) of patients had red blood transfusions within 8 weeks of enrollment in the study. The median platelet count was 251,000/mm^3. Seventy-six percent of patients had the mutation encoding the V617F substitution present in the JAK protein. Patients had a median palpable spleen length of 16 cm. At baseline 37.4% of the patients in the Jakavi arm had grade 1 anemia, 31.6% grade 2 and 4.5% grade 3, while in the placebo arm 35.8% had grade 1, 35.1% grade 2, 4.6% grade 3, and 0.7% grade 4 . Grade 1 thrombocytopenia was found in 12.9 % of patients in the Jakavi arm and 13.2% in the placebo arm.

In COMFORT-II, patient baseline demographics and disease characteristics were comparable between the treatment arms. The median age was 66 years with 52% of patients older than 65 years and 57% male. Fifty-three percent (53%) of the subjects had primary myelofibrosis, 31% had post-polycythemia vera myelofibrosis, and 16% had post-essential thrombocythemia myelofibrosis. 19% of patients were considered transfusion dependent at baseline. Patients had a median palpable spleen length of 15 cm.

At baseline 34.2% of the patients in the Jakavi arm had grade 1 anemia , 28.8% grade 2, and 7.5% grade 3, while in the BAT arm 37% had grade 1, 27.4% grade 2, 13.7% grade 3, and 1.4% grade 4 . Thrombocytopenia of grade 1 was found in 8.2% of patients in the Jakavi arm, and 9.6% in the BAT arm. Efficacy analyses of the primary endpoint in COMFORT-I and COMFORT-II are presented in Table 2 below. A significantly larger proportion of patients in the Jakavi group achieved a ≥35% reduction in spleen volume from baseline in both studies compared to placebo in COMFORT-I and best available therapy in COMFORT-II.

Table 2 Percent of Patients with ≥35% Reduction from Baseline in Spleen Volume at Week 24 in COMFORT-I and at Week 48 in COMFORT-II (ITT)

	COMFORT-I		COMFORT-II	
	Jakavi (N=155)	Placebo (N=153)	Jakavi (N=144)	Best Available Therapy (N=72)
Time Points	Week 24		Week 48	
Number (%) of Subjects with Spleen Volume Reduced by ≥35%	65 (41.9)	1 (0.7)	41 (28.5)	0
95% Confidence Intervals	34.1, 50.1	0, 3.6	21.3, 36.6	0.0, 5.0
P-value	< 0.0001		< 0.0001	

In COMFORT-I, 41.9% of patients in the Jakavi group achieved a ≥35% reduction in spleen volume from baseline compared with 0.7% in the placebo group at Week 24. A similar proportion of patients in the Jakavi group achieved a ≥50% reduction in palpable spleen length.

In COMFORT-II, 28.5% of patients in the Jakavi group achieved a ≥35% reduction in spleen volume from baseline compared with none (0%) in the best available therapy group at Week 48. A secondary endpoint was the proportion of patients achieving a ≥35% reduction of spleen volume at Week 24. A significantly larger proportion of patients in the Jakavi group 46 (31.9%) achieved a ≥35% reduction in spleen volume from baseline compared to no (0%) patients in the best available therapy group (p-value <0.0001).

A significantly higher proportion of patients in the Jakavi group achieved ≥ 35% reduction from baseline in spleen volume regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (primary myelofibrosis, post-polycythemia vera myelofibrosis, post-essential thrombocythemia myelofibrosis).

Figure 1 shows a waterfall plot of the percent change from baseline in spleen volume at Week 24 in COMFORT-I. Among the 139 patients in the Jakavi group who had both baseline and Week 24 spleen volume evaluations, all but two patients had some level of reduction in spleen volume at Week 24, with a median reduction of 33%. Among the 106 patients in the placebo group who had both baseline and Week 24 spleen volume evaluations, there was a median increase of 8.5%.

Figure 1 Waterfall Plot of Percent Change From Baseline in Spleen Volume at Week 24 (Observed Cases) COMFORT- I

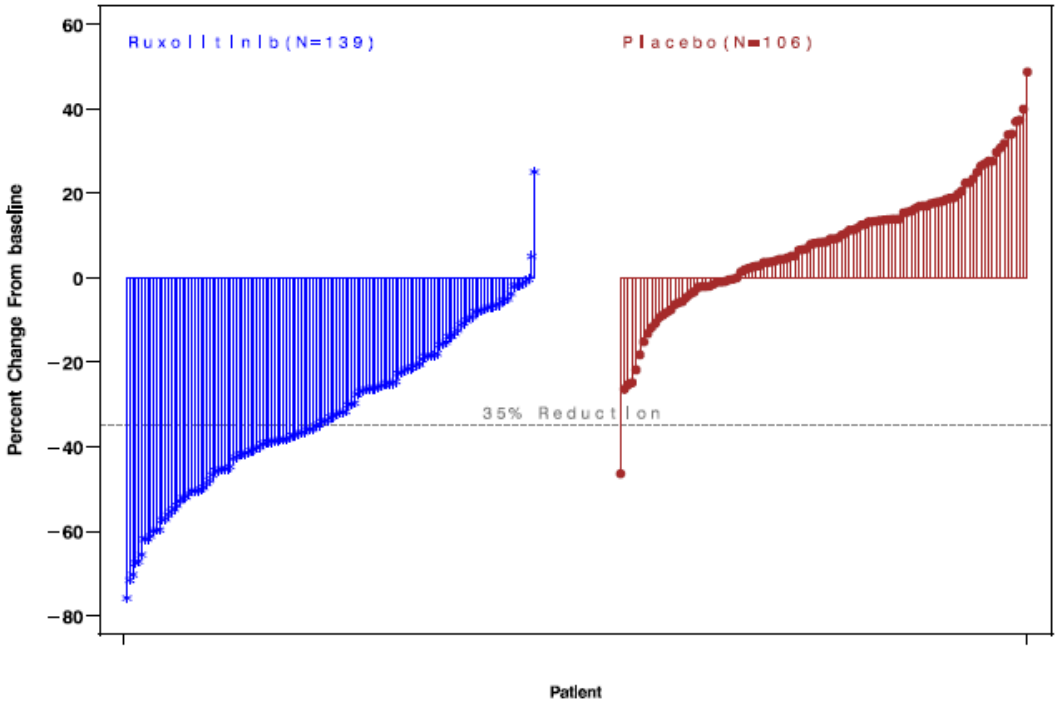
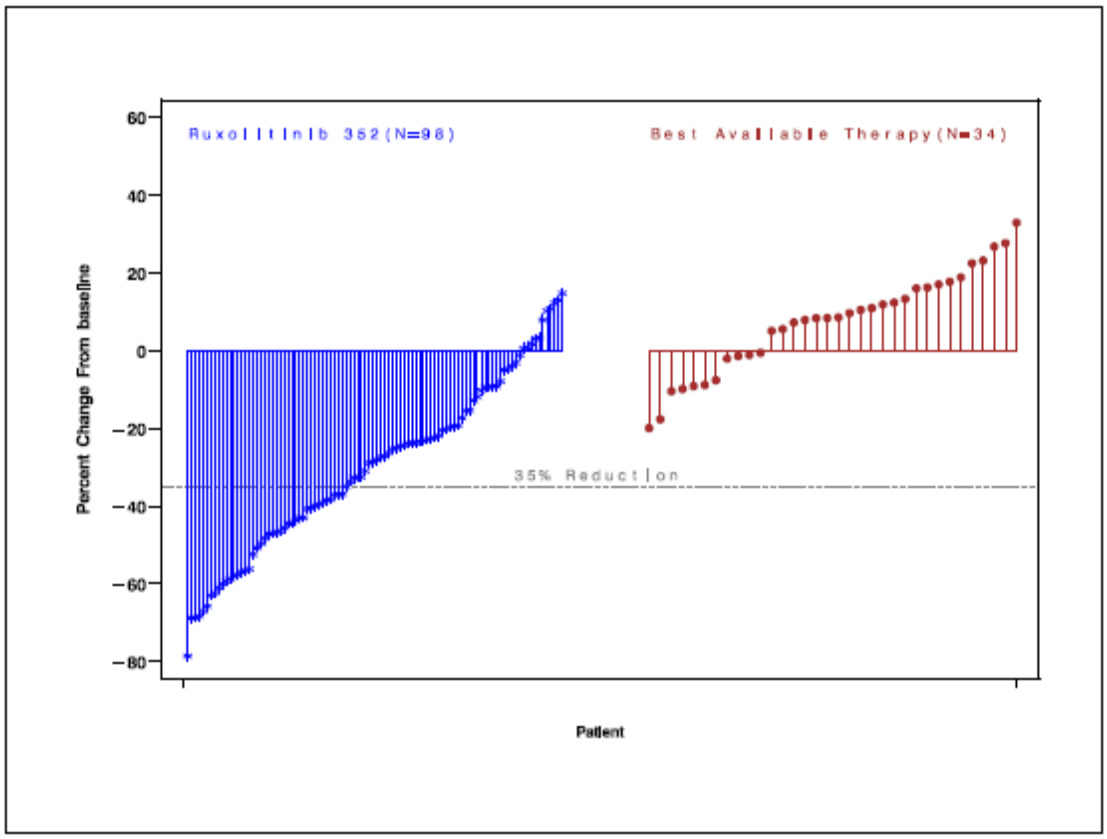


Figure 2 shows a waterfall plot of the percent change from baseline in spleen volume at Week 48 in COMFORT-II. Among the 98 patients in the Jakavi group who had both baseline and Week 48 spleen volume evaluations, the median reduction in spleen volume at Week 48 was

28%. Among the 34 patients in the Best Available Therapy group who had both baseline and Week 48 spleen volume evaluations, there was a median increase of 8.5%.

Figure 2 Waterfall Plot of Percent Change from Baseline in Spleen Volume at Week 48 in COMFORT-II



The probability of duration from 1st ≥35% reduction of spleen volume to 25% increase from nadir and loss of response in COMFORT-I and COMFORT-II is shown in Table 3 below.

Table 3 Kaplan-Meier Analysis of Duration from 1st ≥ 35% Reduction of Spleen Volume to 25% Increase from Nadir and Loss of Response in Jakavi Patients (COMFORT- I and - II)

Statistics	Jakavi (COMFORT-I)	Jakavi (COMFORT-II)
Probability of >12 weeks of duration (95% CI)	0.98 (0.89, 1.00)	0.92 (0.82, 0.97)
Probability of >24 weeks of duration (95% CI)	0.89 (0.75, 0.95)	0.87 (0.76, 0.93)
Probability of >36 weeks of duration (95% CI)	0.71 (0.41, 0.88)	0.77 (0.63, 0.87)
Probability of >48 weeks of duration (95% CI)	not applicable	0.52 (0.18, 0.78)

Among the 80 patients that showed a ≥35% reduction at any time point in COMFORT-I and of the 69 patients in COMFORT-II, the probability that a patient would maintain a response on Jakavi for at least 24 weeks was 89% and 87% in COMFORT-I and COMFORT-II respectively and the probability of maintaining a response for at least 48 weeks was 52% in COMFORT -II.

Jakavi improves myelofibrosis-related symptoms and quality of life (QOL) in patients with PMF, PPV-MF and PET-MF. In COMFORT-I symptoms of MF were captured using the modified MFSAF diary v2.0 as an electronic diary, which subjects completed daily. The change from Baseline in the Week 24 total score was a secondary endpoint in this study. Significantly larger proportion of subjects in the Jakavi group achieved a ≥50% improvement from Baseline in the Week 24 total symptom score compared with the placebo group (45.9% and 5.3%, respectively, p <0.0001 using the Chi-Squared test).

An improvement in overall quality of life was measured by the EORTC QLQ-C30 in both COMFORT-I and COMFORT-II. COMFORT-I compared Jakavi to placebo at 24 weeks and COMFORT-II compared Jakavi to best available therapy at 48 weeks. At baseline for both studies, EORTC QLQ-C30 individual subscale scores for the Jakavi and comparator groups were similar. At Week 24 in COMFORT-I, the Jakavi group showed significant improvement in the global health status/quality of life of the EORTC QLQ-C30 compared with the placebo group (mean change of +12.3 and -3.4 for Jakavi and placebo, respectively, p <0.0001). At week 24 and week 48, the Jakavi group in COMFORT-II showed a trend towards greater improvement of global health status/quality of life compared to best available therapy, an exploratory endpoint, consistent with the COMFORT-I findings.

In COMFORT-I, after a median follow–up of 34.3 months, the death rate in patients randomized to the ruxolitinib arm was 27.1% (42 of 155 patients) versus 35.1% (54 of 154) in patients randomized to placebo. There was a 31.3% reduction in the risk of death in the ruxolitinib arm as compared to placebo (HR 0.687; 95%CI 0.459-1.029; p= 0.0668). At final analysis, after a median follow up of 61.7 months, the reduction in risk of death was 30.7% (HR 0.69; 95% Cl: 0.50, 0.96, p=0.025).

In COMFORT-II, after a median follow-up of 34.7 months, the death rate in patients randomized to ruxolitinib was 19.9% (29 of 146 patients) versus 30.1% (22 of 73 patients) in patients randomized to best available therapy (BAT). There was a 52% reduction in risk of death in the ruxolitinib arm compared to BAT arm (HR 0.48; 95% CI 0.28-0.85; p= 0.009). At final analysis, after a median follow up of 55.9 months, the reduction in risk of death was 33% (HR 0.67, 95% CI 0.44-1.02, p=0.062).

Polycythemia vera

A randomized, open-label, active-controlled Phase 3 study (RESPONSE) was conducted in 222 patients with polycythemia vera who were resistant to or intolerant of hydroxyurea. 110 patients were randomized to the ruxolitinib arm and 112 patients to the BAT arm. The starting dose of Jakavi was 10 mg twice daily. Doses were then adjusted in individual patients based on tolerability and efficacy with a maximum dose of 25 mg twice daily. BAT was selected by the investigator on a patient-by-patient basis and included hydroxyurea (59.5%), interferon/pegylated interferon (11.7%), anagrelide (7.2%), pipobroman (1.8) and observation (15.3%).

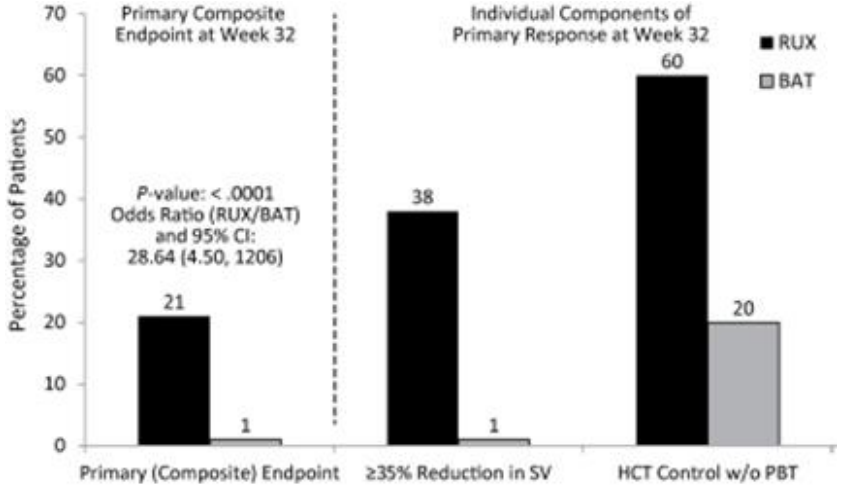
Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. Most patients (> 80%) had received at least two phlebotomies in the last 24 weeks prior to screening.

The primary composite endpoint was the proportion of patients achieving both the absence of phlebotomy eligibility (HCT control) and ≥ 35% reduction in spleen volume from baseline at Week 32. Phlebotomy eligibility was defined as a confirmed HCT > 45% that is at least 3 percentage points higher than the HCT obtained at baseline or a confirmed HCT > 48%, whichever is lower. Key secondary endpoints included the proportion of patients who achieved the primary endpoint and who remained free from progression at Week 48, and the proportion of patients achieving complete hematological remission at Week 32.

The study met its primary objective and a higher proportion of patients in the Jakavi group achieved the primary composite endpoint and each of its individual components. Significantly more patients on Jakavi (23%) compared to BAT (0.9%) achieved a primary response (p<0.0001). Hematocrit control was achieved in 60% of patients in the Jakavi arm compared to 18.8% in the BAT arm and ≥ 35% reduction in spleen volume was achieved in 40% of patients in the Jakavi arm compared to 0.9% in the BAT arm (Figure 3).

Both key secondary endpoints were also met: The proportion of patients achieving a complete hematologic remission was 23.6% on Jakavi compared to 8.0% on BAT (p=0.0013), and the proportion of patients achieving a durable primary response at week 48 was 20% on Jakavi and 0.9% on BAT (p<0.0001).

Figure 3: Patients achieving the primary endpoint and components of the primary endpoint at Week 32



Symptom burden was assessed using the MPN-SAF total symptom score (TSS) electronic patient diary consisting of 14 questions. At Week 32, 49% and 64% of patients treated with ruxolitinib achieved a ≥50% reduction in TSS-14 and TSS-5, respectively, compared to only 5% and 11% of patients on BAT.

Treatment benefit perception was measured by the Patient Global Impression of Change (PGIC) questionnaire. 66 % of ruxolitinib-treated patients compared to 19% in BAT reported an improvement as early as 4 weeks after the start of treatment. Improvement in perception of treatment benefit was also higher in ruxolitinib-treated patients at Week 32 (78% versus 33%).

Additional analyses from the RESPONSE study to assess durability of response were conducted at Week 80 in the Jakavi arm. In this arm, 83% (91) of patients were still on treatment at the time of the Week 80 data cut-off. Of the 25 patients who met the primary endpoint at Week 32, 80% maintained their response for at least 48 weeks after the initial response. Of the 38.2% of patients who achieved the spleen response component of the primary endpoint at Week 32, none lost spleen response through the Week 80 data cutoff. For the 60% of patients who had achieved the HCT control component of the primary endpoint at Week 32, the probability of maintaining HCT control for 80 weeks was 89%. Of the 26 patients who achieved complete hematologic remission at Week 32, 69% of patients maintained this response for at least 48 weeks.

A second randomized, open label, active-controlled phase IIIb study (RESPONSE-2) was conducted in 149 polycythemia vera patients who were resistant to or intolerant of hydroxyurea but without palpable splenomegaly. Seventy-four patients were randomized to the ruxolitinib arm and 75 patients to the BAT arm. The starting dose and dose adjustments of Jakavi and investigator-selected BAT were similar to the RESPONSE study. Baseline demographics and disease characteristics were comparable between the two treatment arms and similar to the patient population of the RESPONSE study. The primary endpoint was the proportion of patients achieving HCT control (absence of phlebotomy eligibility) at Week 28. The key secondary endpoint was the proportion of patients achieving complete hematological remission at Week 28.

RESPONSE-2 met its primary objective with a higher proportion of patients in the Jakavi arm (62.2%) compared to the BAT arm (18.7%) achieving the primary endpoint ($p<0.0001$). The key secondary endpoint was also met with significantly more patients achieving a complete hematologic remission in the Jakavi arm (23.0%) compared to the BAT arm (5.3%; $p=0.0019$). At week 28, the proportion of patients achieving a ≥50% reduction in symptom burden as measured by the MPN-SAF total symptom score was 45.3% in the Jakavi arm and 22.7% in the BAT arm.

NON-CLINICAL SAFETY DATA

Ruxolitinib has been evaluated in safety pharmacology, repeat dose toxicity, genotoxicity, reproductive toxicity studies and a carcinogenicity study. Target organs associated with the pharmacological action of ruxolitinib in repeat dose studies include bone marrow, peripheral blood and lymphoid tissues. Infections generally associated with immunosuppression were noted in dogs. Adverse decreases in blood pressure along with increases in heart rate were noted in a dog telemetry study, and an adverse decrease in minute volume was noted in a respiratory study in rats. The margins (based on unbound C_{max}) at the non-adverse level in the dog and rat studies were 15.7-fold and 10.4 fold greater, respectively, than the maximum human recommended 25 mg twice daily dose. No effects were noted in an evaluation of the neuropharmacologic effects of ruxolitinib.

Administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. Ruxolitinib was administered daily by oral gavage at doses from 1.5 to 75 mg/kg/day from days 7 (the human equivalent of a newborn) to 63 post-partum (pp), 15 mg/kg/day from days 14 (the human equivalent of 1 year of age) to 63 pp and 5, 15 and 60 mg/kg/day from days 21 (the human equivalent of 2 to 3 years of age) to 63 pp. Doses ≥30 mg/kg/day (1,200 ng*h/mL based on unbound AUC) resulted in fractures and early termination of the groups when treatment started on day 7 pp. Reduced bone growth was observed at doses ≥5 mg/kg/day (≥150 ng*h/mL based on unbound AUC) when treatment started on day 7 pp and at ≥15 mg/kg/day (≥150 ng*h/mL based on unbound AUC) when treatment started on day 14 pp or day 21 pp. Based on unbound AUC, fractures and reduced bone growth occurred at exposures 13- and 1.5- fold the exposure in adult patients at the maximum recommended dose of 25 mg BID, respectively. The effects were generally more severe when administration was initiated earlier in the postnatal period. Other than the effects on bone development, the toxicity profile in juvenile rats was comparable to that observed in adult rats.

Ruxolitinib was not teratogenic but was associated with increases in post-implantation loss and decreases in fetal weights. No effects were noted on fertility. In a pre- and post-natal development study, there were no adverse findings for fertility indices and maternal and embryofetal survival, growth, and developmental parameters. Ruxolitinib was not mutagenic or clastogenic. Ruxolitinib was not carcinogenic in the Tg.rasH2 transgenic mouse model nor in a 2-year study in rats.

INCOMPATIBILITIES

Not applicable.

STORAGE

There are 2 package type available, PVC/PCTFE BLISTER and HDPE bottle. Jakavi should be stored under 30˚C.

See folding box.

Jakavi should not be used after the date marked “EXP” on the pack.

Jakavi must be kept out of the reach and sight of children.

Manufacturer:

See folding box.

International Package Leaflet

Information issued: IPL-16Apr2018

TWI-310818

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