NOVARTIS

Ruxolitinib
(as phosphate)

Jakavi®
5 mg, 10 mg, 15 mg, and 20 mg Tablets

Antineoplastic – Protein kinase inhibitor

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

5 mg tablets: round curved white to almost white tablets with 'NVR' debossed on one side and 'L5' debossed on the other side
10 mg tablets: round curved white to almost white tablets with 'NVR' debossed on one side and 'L10' debossed on the other side
15 mg tablets: ovaloid curved white to almost white tablets with 'NVR' debossed on one side and 'L15' debossed on the other side
20 mg tablets: elongated curved white to almost white tablets with 'NVR' debossed on one side and 'L20' debossed on the other side

Active substance(s)
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

Lactose monohydrate

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 (MF)

Ruxolitinib (Jakavi®) is indicated for the treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

Polycythemia vera (PV)

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

Graft-versus-host disease (GvHD)

Ruxolitinib (Jakavi®) is indicated for the treatment of patients with graft-versus-host disease aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies.

DOSAGE REGIMEN AND ADMINISTRATION

Monitoring instructions

Blood cell counts: a blood cell count must be performed before initiating therapy with ruxolitinib (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 ruxolitinib (Jakavi®) in myelofibrosis (MF) is based on platelet counts (see Table 1):

Table 1 Starting Doses in Myelofibrosis

Platelet count	Starting dose
Greater than 200,000/mm^3	20 mg orally twice daily
100,000 to 200,000/mm^3	15 mg orally twice daily
50,000 to less than 100,000/mm^3	10 mg orally twice daily

The recommended starting dose of ruxolitinib (Jakavi®) in Polycythemia vera (PV) and graft-versus-host disease (GvHD) is 10 mg given orally twice daily.

Dose modifications

Doses may be titrated based on efficacy and safety.

Myelofibrosis (MF) and **Polycythemia vera (PV)**

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.

Treatment should be interrupted for platelet counts less than 50,000/mm^3 or absolute neutrophil counts less than 500/mm^3.

In PV, 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 in myelofibrosis should be considered if the platelet counts decrease during treatment as outlined in Table 2, with the goal of avoiding dose interruptions for thrombocytopenia.

Table 2 Dosing Recommendations for Thrombocytopenia in Myelofibrosis

	Dose at Time of Platelet Decline			
	20 mg twice daily	15 mg twice daily	10 mg twice daily	5 mg twice daily
Platelet Count	New Dose			
100,000 to <125,000/mm^3	15 mg twice daily	No change	No change	No change
75,000 to <100,000/mm^3	10 mg twice daily	10 mg twice daily	No change	No change
50,000 to <75,000/mm^3	5 mg twice daily	5 mg twice daily	5 mg twice daily	No change
Less than 50,000/mm^3	Hold	Hold	Hold	Hold

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

Graft-versus-host disease

Dose reductions and temporary interruptions of treatment may be needed in GvHD patients with thrombocytopenia, neutropenia, or elevated total bilirubin after standard supportive therapy including growth-factors, anti-infective therapies and transfusions. One dose level reduction step is recommended (10 mg twice daily to 5 mg twice daily or 5 mg twice daily to 5 mg once daily). In patients who are unable to tolerate ruxolitinib (Jakavi®) at a dose of 5 mg once daily, treatment should be interrupted. Detailed dosing recommendations are provided in Table 3.

Table 1 Dosing recommendations for patients with thrombocytopenia, neutropenia, or elevated total bilirubin in patients with graft-versus-host disease

Laboratory Parameter	Dosing Recommendation
Platelet count <20,000/mm^3	Reduce ruxolitinib (Jakavi®) by one dose level. If platelet count ≥20.000/mm^3 within seven days, dose may be increased to initial dose level, otherwise maintain reduced dose.
Platelet count <15,000/mm^3	Hold ruxolitinib (Jakavi®) until platelet count ≥20,000/mm^3, then resume at one lower dose level.

Laboratory Parameter	Dosing Recommendation
Absolute neutrophil count (ANC) ≥500/mm^3 to <750/mm^3	Reduce ruxolitinib (Jakavi®) by one dose level. Resume at initial dose level if ANC >1,000/mm^3.
Absolute neutrophil count <500/mm^3	Hold ruxolitinib (Jakavi®) until ANC >500/mm^3, then resume at one lower dose level. If ANC >1,000/mm^3, dosing may resume at initial dose level.
Total bilirubin elevation, no liver GvHD	3.0 to 5.0 x ULN: Continue ruxolitinib (Jakavi®) at one lower dose level until ≤3.0 x ULN.
	>5.0 to 10.0 x ULN: Hold ruxolitinib (Jakavi®) up to 14 days until total bilirubin ≤3.0 x ULN. If total bilirubin ≤3.0 x ULN dosing may resume at current dose. If not ≤3.0 x ULN after 14 days, resume at one lower dose level.
	>10.0 x ULN: Hold ruxolitinib (Jakavi®) until total bilirubin ≤3.0 x ULN, then resume at one lower dose level.
Total bilirubin elevation, liver GvHD	>3.0 x ULN: Continue ruxolitinib (Jakavi®)at one lower dose level until total bilirubin ≤3.0 x ULN.

Administration instruction

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

Treatment of MF and PV may be continued as long as the benefit:risk ratio remains positive.

In GvHD, tapering of ruxolitinib (Jakavi®) may be considered in patients with a response and after having discontinued corticosteroids. A 50% dose reduction of Jakavi every two months is recommended. If signs or symptoms of GvHD reoccur during or after the taper of ruxolitinib (Jakavi®), re-escalation of treatment should be considered.

Dose adjustment with concomitant strong CYP3A4 Inhibitors or fluconazole:

When ruxolitinib (Jakavi®) is administered with strong CYP3A4 inhibitors in MF and PV patients or dual moderate inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) in MF, PV or GvHD patients, the total daily dose of ruxolitinib (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. The concomitant use of ruxolitinib (Jakavi®) with fluconazole doses greater than 200 mg daily should be avoided (see section INTERACTION).

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

Special populations

Renal impairment

In patients with severe renal impairment (creatinine clearance (Clcr) less than 30 mL/min) the recommended starting dose based on platelet counts for MF patients should be reduced by approximately 50%. The recommended starting dose for PV and GvHD patients with severe renal impairment is 5 mg twice daily. Patients diagnosed with severe renal impairment while receiving ruxolitinib (Jakavi®) should be carefully monitored and may need to have their doses reduced to avoid ADRs.

There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on dialysis.

Available data in this population suggest that MF patients on dialysis, should be started on an initial single dose of 15 mg or 20 mg based on platelet counts with subsequent single doses only after each dialysis session, and with careful monitoring of safety and efficacy.

The recommended starting dose for PV and GvHD patients with ESRD on hemodialysis is a single dose of 10 mg, to be administered post-dialysis and only on the day of hemodialysis and with careful monitoring of safety and efficacy (see section CLINICAL PHARMACOLOGY).

Hepatic impairment

In MF patients with any hepatic impairment the recommended starting dose based on platelet counts should be reduced by approximately 50%. The recommended starting dose is 5 mg twice daily for PV patients. Patients diagnosed with hepatic impairment while receiving ruxolitinib (Jakavi®) should be carefully monitored and may need to have their dose reduced to avoid ADRs.

In GvHD patients with any hepatic impairment including liver GvHD, no starting dose modification is recommended. (see section CLINICAL PHARMACOLOGY).

In patients with GvHD liver involvement and an increase of total bilirubin to >3 x ULN, blood counts should be monitored more frequently for toxicity and a dose reduction by one dose level may be considered.

Pediatrics

The safety and efficacy of ruxolitinib (Jakavi®) in pediatric patients with MF and PV have not been established.

In pediatric patients (12 years of age and older) with GvHD, the safety and efficacy of ruxolitinib (Jakavi®) are supported by evidence from the randomized phase 3 studies REACH2 and REACH3. The ruxolitinib (Jakavi®) dose in pediatric patients with GvHD aged 12 years and older is the same as in adults. The safety and efficacy of ruxolitinib (Jakavi®) have not been established in patients less than 12 years of age.

Geriatrics

No additional dose adjustments are recommended for elderly patients.

Method of administration

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

It has been observed that MF 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 ruxolitinib (Jakavi®). However, platelet transfusions may be required as clinically indicated (see sections DOSAGE REGIMEN AND ADMINISTRATION, and ADVERSE DRUG REACTIONS).

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

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

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

Infections

Serious bacterial, mycobacterial, fungal, viral and other opportunistic infections have occurred in patients treated with ruxolitinib (Jakavi®). Patients should be assessed for the risk of developing serious infections. Physicians should carefully observe patients receiving ruxolitinib (Jakavi®) for signs and symptoms of infections and appropriate treatment should be initiated promptly. Ruxolitinib (Jakavi®) therapy should not be started until active serious infections have resolved.

Tuberculosis has been reported in patients receiving ruxolitinib (Jakavi®). Before starting treatment, patients should be evaluated for active and inactive (‘latent’) tuberculosis, as per local recommendations.

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), have been reported in patients with chronic HBV infections taking ruxolitinib (Jakavi®). The effect of ruxolitinib (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 ruxolitinib treatment. Physicians should be alert for neuropsychiatric symptoms suggestive of PML. 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 ruxolitinib (Jakavi®). Most of the MF and PVpatients 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 ruxolitinib (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

The starting dose of ruxolitinib (Jakavi®) should be reduced in patients with severe renal impairment. For patients with ESRD on dialysis the starting dose should be based on platelet counts for MF-patients, while the recommended starting dose is a single dose of 10 mg for PV and GvHDpatients. Subsequent doses for MF, PV and GvHD-patients should be administered only on hemodialysis days following each dialysis session. Further dose modifications should be based on the safety and efficacy of the drug (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Special populations).

Hepatic impairment

The starting dose of ruxolitinib (Jakavi®) should be reduced in MF and PV patients with hepatic impairment. Further dose modifications should be based on the safety and efficacy of the drug. In GvHD patients with hepatic impairment no modification in starting dose is needed (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Special populations).

Interactions

If ruxolitinib (Jakavi®) is to be co-administered with strong CYP3A4 inhibitors in MF and PV patients or dual moderate inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) in MF, PV, and GvHD patients, the dose should be reduced by approximately 50% (for monitoring frequency see sections DOSAGE REGIMEN AND ADMINISTRATION and INTERACTIONS).

Withdrawal effects

After discontinuation of ruxolitinib (Jakavi®) treatment, MF-related symptoms are expected to return. There have been cases of patients discontinuing ruxolitinib (Jakavi®) who experienced severe adverse events (AEs), particularly in the presence of acute intercurrent illness. It has not been established whether abrupt discontinuation of ruxolitinib (Jakavi®) contributed to these events. Unless abrupt discontinuation is required, gradual tapering of the dose of ruxolitinib (Jakavi®) may be considered.

ADVERSE DRUG REACTIONS

Summary of the safety profile

Myelofibrosis

The safety of ruxolitinib (Jakavi®) in MF patients was evaluated using long term follow-up data from the two Phase 3 studies COMFORT-I and COMFORT-II including data from patients initially randomized to ruxolitinib (Jakavi®) (n=301) and patients who received ruxolitinib (Jakavi®) after crossing over from control treatments (n=156). The median exposure upon which the ADR frequency categories for MF patients are based was 30.5 months (range 0.3 to 68.1 months).

The most frequently reported ADRs were anemia (83.8%) and thrombocytopenia (80.5%).

Hematological ADRs (any CTCAE grade; Common Terminology Criteria for Adverse Events) included anemia (83.8%), thrombocytopenia (80.5%) and neutropenia (20.8 %).

Anemia, thrombocytopenia and neutropenia are dose related effects.

The most frequent non-hematological ADRs were bruising (33.3%), dizziness (21.9%) and urinary tract infections (21.4%).

The most frequent non-hematological laboratory abnormalities identified as ADRs were increased ALT (40.7%), increased AST (31.5%) and hypertriglyceridemia (25.2%). However, no CTCAE grade 3 or 4 hypertriglyceridemia and increased AST or grade 4 increased ALT were observed.

Discontinuation due to AEs, regardless of causality, was observed in 30.0% of patients treated with ruxolitinib.

Polycythemia vera

The safety of ruxolitinib (Jakavi®) in PV patients was evaluated using long-term follow-up data from the two phase 3 studies RESPONSE and RESPONSE 2 including data from patients initially randomized to ruxolitinib (Jakavi®) (n=184) and patients who received ruxolitinib (Jakavi®) after crossing over from control treatments (n=156). The median exposure upon which the ADR frequency categories for PV patients are based was 41.7 months (range 0.03 to 59.7 months)

The most frequently reported ADRs were anemia (61.8%) and increased ALT (45.3%).

Hematological ADRs (any CTCAE grade) included anemia (61.8%), thrombocytopenia (25.0%), and neutropenia (5.3%) . Anemia or thrombocytopenia Grade 3 and 4 were reported in respectively 2.9% and 2.6% of the patients, respectively.

The most frequent non-hematological ADRs were weight gain (20.3%), dizziness (19.4%) and headache (17.9%).

The most frequent non-hematological laboratory abnormalities (any CTCAE grade) identified as ADRs were increased ALT (45.3%), increased AST(42.6%)and hypercholesterolemia (34.7%). The majority were Grade 1 to 2 with one CTCAE grade 4 ‘increased AST’.

Discontinuation due to AEs, regardless of causality, was observed in 19.4% of patients treated with ruxolitinib (Jakavi®).

Acute GvHD

The safety of ruxolitinib (Jakavi®) in acute GvHD patients was evaluated in the phase 3 study REACH2, including data from patients initially randomized to Jakavi (n=152) and patients who received ruxolitinib (Jakavi®) after crossing over from control treatment (n=49). The median exposure upon which the ADR frequency categories were based was 8.9 weeks (range 0.3 to 66.1 weeks).

The most frequently reported overall ADRs were thrombocytopenia (85.2%), anemia (75.0%) and neutropenia (65.1%).

Hematological laboratory abnormalities identified as ADRs included thrombocytopenia (85.2%), anemia (75.0%) and neutropenia (65.1%). Grade 3 anemia was reported in 47.7% of patients (Grade 4 not applicable per CTCAE v4.03). Grade 3 and 4 thrombocytopenia were reported in 31.3% and 47.7% of patients, respectively.

The most frequent non-hematological ADRs were cytomegalovirus (CMV) infection (32.3%), sepsis (25.4%) and UTI (17.9%).

The most frequent non-hematological laboratory abnormalities identified as ADRs were increased ALT (54.9%), increased AST (52.3%) and hypercholesterolemia (49.2%). The majority were of grade 1 and 2.

Discontinuation due to AEs, regardless of causality, was observed in 29.4% of patients treated with ruxolitinib (Jakavi®).

Chronic GvHD

The safety of ruxolitinib (Jakavi®) in chronic GvHD patients was evaluated in the phase 3 study REACH3, including data from patients initially randomized to ruxolitinib (Jakavi®) (n=165) and patients who received ruxolitinib (Jakavi®) after crossing over from best available treatment (BAT) [n=61]. The median exposure upon which the ADR frequency categories were based was 41.4 weeks (range 0.7 to 127.3 weeks).

The most frequently reported overall ADRs were anemia (68.6%), hypercholesterolemia (52.3%) and increased AST (52.2%).

Hematological laboratory abnormalities identified as ADRs included anemia (68.6%), thrombocytopenia (34.4%) and neutropenia (36.2%). Grade 3 anemia was reported in 14.8% of patients (Grade 4 not applicable per CTCAE v4.03). Grade 3 and 4 neutropenia were reported in 9.5% and 6.7% of patients, respectively.

The most frequent non-hematological ADRs were hypertension (15.0%), headache (10.2%) and UTI (9.3%).

The most frequent non-hematological laboratory abnormalities identified as ADRs were hypercholesterolemia (52.3%), increased AST (52.2%) and increased ALT (43.1%). The majority were Grade 1 and 2.

Discontinuation due to AEs, regardless of causality, was observed in 18.1% of patients treated with ruxolitinib (Jakavi®).

Tabulated summary of adverse drug reactions from clinical trials

ADRs from clinical trials in MF and PV are listed in Table 4. ADRs from clinical trials in acute and chronic GvHD are listed in Table 5. All ADRs are listed by MedDRA system organ class (SOC). Within each SOC, the ADRs are ranked by frequency, with the most frequent adverse drug reactions first. In addition, the corresponding frequency category for each ADR 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 ADRs was assessed based on the CTCAE defining Grade 1=mild, Grade 2= moderate, Grade 3=severe and Grade 4=life-threatening or disabling, Grade 5=death.

Table 4 ADRs reported in the phase 3 studies in MF and PV

ADRs and CTCAE grade[3]	Frequency category for MF patients	Frequency category for PV patients
	Long-term follow-up data Week 256: COMFORT-I Week 256: COMFORT-II	Long-term follow-up data Week 256: RESPONSE Week 156: RESPONSE-2
Infections and infestations		
Urinary tract infections	Very common	Very common
Herpes zoster	Very common	Very common
Pneumonia	Very common	Common -
Tuberculosis[*]	Uncommon	-
Blood and lymphatic system disorders		
Anemia[1]		
CTCAE [1] Grade 4 (<6.5g/dL)	Very common	Uncommon
CTCAE Grade 3 (<8.0 to 6.5g/dL)	Very common	Common
Any CTCAE Grade	Very common	Very common
Thrombocytopenia[1]		
CTCAE Grade 4 (<25,000/mm^3)	Common	Uncommon
CTCAE Grade 3 (50,000 to 25,000/mm^3)	Very common	Common
Any CTCAE Grade	Very common	Very common
Neutropenia[1]		
CTCAE Grade 4 (<500/mm^3)	Common	Uncommon
CTCAE Grade 3 (<1000 to 500/mm^3)	Common	Uncommon
Any CTCAE Grade	Very common	Common
Pancytopenia[2]	Common	Common
Metabolism and nutrition disorders		
Hypercholesterolemia [1] Any CTCAE Grade	Very common	Very common
Hypertriglyceridemia[1]		

CTCAE Grade 1	Very common	Very common
Weight gain	Very common	Very common
Nervous system disorders		
Dizziness	Very common	Very common
Headache	Very common	Very common
Gastrointestinal disorders		
Constipation	Very common	Very common
Flatulence	Common	Common
Skin and subcutaneous tissue disorders		
Bruising	Very common	Very common
Hepatobiliary disorders		
Increased ALT[1]		
CTCAE Grade 3 (> 5x to 20 x ULN)	Common	Common
Any CTCAE Grade	Very common	Very common
Increased AST[1]		
Any CTCAE Grade	Very common	Very common
Vascular disorders		
Hypertension	Very common	Very common

[1] *Frequency is based on new or worsened laboratory abnormalities compared to baseline*

[2] Pancytopenia is defined as hemoglobin level < 100 g/L, platelet count <100 x 109 /L, and neutrophils count <1.5 x 109 /L (or low WBC count of grade 2 if neutrophils count is missing), simultaneously in the same laboratory assessment.

[3]CTCAE Version 3.0

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

Table 5 ADRs reported in the phase 3 studies in GvHD

	Acute GvHD (REACH2) (N=201)			**Chronic GvHD (REACH3) (N=226)**		
ADR	Frequency category	All grades (%)	CTCAE[3] Grade 3 / 4 (%)	Frequency category	All grades (%)	CTCAE[3] Grade 3 / 4 (%)
Infections and infestations						
CMV infections	Very common	32.3	10.9 / 0.5	-	-	- / -
Sepsis	Very common	25.4	4.0 / 17.9[4]	-	-	- / -
Urinary tract infections	Very common	17.9	6.0 / 0.5	Common	9.3	1.3 / 0
BK virus infections	-	-	- / -	Common	4.9	0.4 / 0
Blood and lymphatic system disorders						
Thrombocytopenia[1]	Very common	85.2	31.3 / 47.7	Very common	34.4	5.9 / 10.7
Anaemia[1]	Very common	75.0	47.7 / NA	Very common	68.6	14.8 / NA

	Acute GvHD (REACH2) (N=201)			Chronic GvHD (REACH3) (N=226)		
ADR	Frequency category	All grades (%)	CTCAE[3] Grade 3 / 4 (%)	Frequency category	All grades (%)	CTCAE[3] Grade 3 / 4 (%)
Neutropenia[1]	Very common	65.1	17.9 / 20.6	Very common	36.2	9.5 / 6.7
Pancytopenia[1,2]	Very common	32.8	NA	-	-	- / -
Metabolism and nutrition disorders						
Hypercholesterolaemia[1]	Very common	49.2	3.3 / 5.9	Very common	52.3	5.5 / 0.5
Weight gain	-	-	-	Common	3.5	0 / 0
Nervous system disorders						
Headache	Common	8.5	0.5 / 0	Very common	10.2	1.3 / 0
Vascular disorders						
Hypertension	Very common	13.4	5.5 / 0	Very common	15.0	5.3 / 0
Gastrointestinal disorders						
Increased lipase[1]	-	-	-	Very common	35.9	9.5 / 0.4
Increased amylase[1]	-	-	-	Very common	32.4	4.2 / 2.7
Nausea	Very common	16.4	0.5 / 0	-	-	- / -
Constipation	-	-	-	Common	6.6	0 / 0
Hepatobiliary disorders						
Increased ALT[1]	Very common	54.9	17.6 / 1.5	Very common	43.1	4.7 / 0.9
Increased AST[1]	Very common	52.3	7.8 / 0	Very common	52.2	3.1 / 0.9
Musculoskeletal and connective tissue disorders						
Increased blood CPK[1]	-	-	-	Very common	31.1	1.0 / 1.4
Renal and urinary disorders						
Increased blood creatinine[1]	-	-	-	Very common	38.4	1.3 / 0

[1] *Frequency is based on new or worsened laboratory abnormalities compared to baseline.*

[2] *Pancytopenia is defined as hemoglobin level <100 g/L, platelet count <100 x 10^9/L, and neutrophils count <1.5 x 10^9/L (or low WBC of grade 2 if neutrophil count is missing), simultaneously in the same laboratory assessment. No CTCAE grades defined.*

[3] *CTCAE Version 4.03.*

[4] *Grade 4 sepsis includes 16 (8%) Grade 4 events and 20 (10%) Grade 5 events.*

ADRs from spontaneous reports and literature cases (frequency not known)

Tuberculosis as an ADR has been observed post-marketing with ruxolitinib (Jakavi®) in PV patients via spontaneous case reports and in the literature. Because cases were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate the frequency, which is therefore characterized as ‘not known’.

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 ruxolitinib (Jakavi®) mean decreases in hemoglobin reached a nadir of approximately 15 to 20 g/L below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 10 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, 59.4% of ruxolitinib (Jakavi®) treated patients and 37.1% 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 51.4% in the ruxolitinib (Jakavi®) arm and 38.4% in the best available therapy arm (BAT).

In the phase 3 acute and chronic GvHD studies, anemia CTCAE Grade 3 was reported in 47.7% and 14.8% of patients, respectively.

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 4.5% of patients receiving ruxolitinib (Jakavi®) and to 5.8% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving ruxolitinib (Jakavi®) and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000 to 200,000/mm^3 before starting ruxolitinib (Jakavi®) had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm^3 (64.2% versus 35.4%).

In the phase 3 acute GvHD study, Grade 3 and 4 thrombocytopenia was observed in 31.3% and 47.7% of patients, respectively. In the phase 3 chronic GvHD study Grade 3 and 4 thrombocytopenia was lower (5.9% and 10.7%) than in acute GvHD.

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.

In the phase 3 acute GvHD study, Grade 3 and 4 neutropenia was observed in 17.9% and 20.6% of patients, respectively. In the phase 3 chronic GvHD study, Grade 3 and 4 neutropenia was lower (9.5% and 6.7%) than in acute GvHD.

Infections

In the randomized period of the two phase 3 MF clinical studies, Grade 3 or 4 urinary tract infection was reported in 1.0% of patients. Urosepsis was reported in 1.0% of patients and kidney infection in one patient. The rate of herpes zoster was 4.0%. During long-term follow up, urinary tract infection and herpes zoster of any Grade were observed in 21.4% and 19.7% of patients, respectively.

In the randomized period of the two phase 3 PV clinical studies, one (0.5%) Grade 3 / 4 urinary tract infection was observed. The rate of herpes zoster was 4.3% including one report of Grade 3 and 4 post herpetic neuralgia. During long-term follow up, urinary tract infection and herpes zoster of any Grade were observed in 11.8% and 14.7% of patients, respectively.

In the phase 3 acute GvHD study, Grade 3 and 4 CMV infections were reported in 10.9% and 0.5% of patients, respectively. CMV infection with organ involvement was seen in very few patients; CMV colitis, CMV enteritis and CMV gastrointestinal infection of any Grade were reported in four, two and one patients, respectively.

Sepsis events including septic shock of any Grade were reported in 25.4% of patients.

In the phase 3 chronic GvHD study, Grade 3 urinary tract infections and BK virus infections were reported in 1.3% and 0.4% of patients, respectively.

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 ruxolitinib increased by 91% and the half-life was prolonged from 3.7 to 6.0 hours.

When administering ruxolitinib (Jakavi®) with strong CYP3A4 inhibitors the total daily dose of ruxolitinib (Jakavi®) should be reduced by approximately 50%, except in GvHD patients. The effect of strong CYP3A4 inhibitors in patients with GvHD was not found to have a significant impact on any parameter in the Population PK model.

Patients should be closely monitored for cytopenias and dose titrated based on safety and efficacy (see section DOSAGE REGIMEN 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 ruxolitinib.

No dose adjustment is recommended when ruxolitinib (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): in healthy subjects receiving fluconazole, a dual CYP2C9 and CYP3A4 inhibitor, as a single 400 mg dose followed by 200 mg once daily for seven days, there was a 232% increase in the AUC of ruxolitinib. A 50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes. The concomitant use of ruxolitinib (Jakavi®) with fluconazole doses of greater than 200 mg daily should be avoided.

CYP3A4 inducers: upon initiation of a CYP3A4 inducer, no dose adjustment is recommended. Gradual dose increases of ruxolitinib (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 ruxolitinib 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 ruxolitinib (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 ruxolitinib (Jakavi®) had no clinically significant pharmacokinetic interaction with midazolam (CYP3A4 substrate).

Oral contraceptives

A study in healthy subjects indicated that ruxolitinib (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.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There are no adequate and well-controlled studies in pregnant women. Reproductive studies in rats and rabbits have demonstrated ruxolitinib-induced embryotoxicity and fetotoxicity. Following prenatal exposure, increases in post-implantation loss in rabbits and reduced fetal weights in rats and rabbits were observed. In rats and rabbits these effects occurred at exposures approximately 2-fold and 0.07 fold, respectively, relative to clinical exposure at the maximum human recommended dose of 25 mg b.i.d based on AUC.

The use of ruxolitinib (Jakavi®) during pregnancy is not recommended. The patient should be advised of the risk to a fetus if ruxolitinib (Jakavi®) is used during pregnancy or if the patient becomes pregnant while taking this medicinal product.

Data

Animal data

Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There was no evidence of teratogenicity. However, decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 0.07 times the clinical exposure at the maximum recommended dose.

In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryo-fetal survival, growth and development parameters at the highest dose evaluated (0.3 times the clinical exposure at the maximum recommended dose of 25 mg twice daily).

Lactation

Risk summary

It is not known if ruxolitinib is transferred to human milk. There are no data on the effects of ruxolitinib on the breast-fed child or the effects of ruxolitinib on milk production. Ruxolitinib and/or its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse drug reactions in nursing infants from ruxolitinib (Jakavi®), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is recommended that women should not breast-feed during treatment with ruxolitinib (Jakavi®).

Data

Animal data

In lactating rats administered a single dose of 30 mg/kg, exposure to ruxolitinib was 13-fold higher in milk than in maternal plasma.

Females and males of reproductive potential

Contraception

Females of reproductive potential should be advised that animal studies have been performed showing ruxolitinib to be harmful to the developing fetus. Sexually active females of reproductive potential should use effective contraception (methods that result in <1% pregnancy rates) during treatment with ruxolitinib (Jakavi®).

Infertility

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.

OVERDOSAGE

There is no known antidote for overdoses with ruxolitinib (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 ruxolitinib.

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 signal transducers and activators of transcription(STATs) 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.

MF and 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-alpha, IL-6) and resulted in significantly prolonged survival in the mice at doses that did not cause myelosuppressive effects.

JAK-STAT signaling pathways play a role in regulating the development, proliferation, and activation of several immune cell types important for GvHD pathogenesis. In a mouse model of acute GvHD, oral administration of ruxolitinib was associated with decreased expression of inflammatory cytokines in colon homogenates and reduced immune-cell infiltration in the colon.

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 MF 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 patients with MF were decreased following treatment with ruxolitinib. Patients with MF did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with PV 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 PK 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 MF patients with an inter-subject variability of 29.4% and 75 L in PV 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 and CYP2C9 are the major enzymes responsible for metabolism of ruxolitinib. 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 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.

Elimination

Following a single oral dose of [^{14}C] 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 PK were observed with regard to gender and race. In a population PK evaluation in MF 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 MF patients. Clearance was 12.7 L/h in PV 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 ruxolitinib (Jakavi®) in pediatric patients have not been established.

Renal impairment

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. However, plasma AUC values of ruxolitinib metabolites tended to increase with increasing severity of renal impairment, and most markedly in the subjects with ESRD 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). For patients with ESRD a modification of the dosing schedule is recommended (see section DOSAGE REGIMEN AND ADMINISTRATION).

Hepatic impairment

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 dose reduction is recommended for MF and PV patients with hepatic impairment (see section DOSAGE REGIMEN AND ADMINISTRATION).

Mild, moderate or severe hepatic impairment in patients with GvHD was not found to have a significant impact on any parameter in the Population PK model.

CLINICAL STUDIES

Myelofibrosis

Two randomized Phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with MF (PMF, PPV-MF or PET-MF). 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 ruxolitinib (Jakavi®) was based on platelet count. Patients with a platelet count between 100,000 and 200,000/mm^3 were started on ruxolitinib (Jakavi®) 15 mg twice daily and patients with a platelet count >200,000/mm^3 were started on ruxolitinib (Jakavi®) 20 mg twice daily. Of the 301 patients, 111 (36.9%) had a baseline platelet count between 100,000 and 200,000/mm^3, and 190 (63.1%) had a baseline platelet count >200,000/mm^3 [Table 1]. Patients with platelet counts ≤100,000/mm^3 were not eligible in COMFORT studies. Maximum safe starting dose (MSSD) for patients with baseline platelet counts ≥50,000 and <100,000/mm^3 was confirmed as 10 mg twice daily in EXPAND, a Phase Ib, open label, dose-finding study in patients with PMF, PPV-MF or PET-MF. In COMFORT studies, doses were 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 ruxolitinib (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 a ≥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 ruxolitinib (Jakavi®) versus BAT. BAT was selected by the investigator on a patient-by-patient basis. In the BAT 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 PMF, 31% had PPV-MF and 18% had PET-MF. Twenty-one percent (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 (76%) 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 ruxolitinib (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 ruxolitinib (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 patients had PMF, 31% had PPV-MF, and 16% had PET-MF. Nineteen percent (19%) of the 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 ruxolitinib (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 the patients in the ruxolitinib (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 6. A significantly larger proportion of patients in the ruxolitinib (Jakavi®) arm achieved a ≥35% reduction in spleen volume from baseline in both studies compared to placebo in COMFORT-I and BAT in COMFORT-II.

Table 6 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	
	Ruxolitinib (Jakavi®) (N=155)	Placebo (N=153)	Ruxolitinib (Jakavi®) (N=144)	BAT (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 ruxolitinib (Jakavi®) arm achieved a ≥35% reduction in spleen volume from baseline compared with 0.7% in the placebo arm at Week 24. A similar proportion of patients in the ruxolitinib (Jakavi®) arm achieved a ≥50% reduction in palpable spleen length.

In COMFORT-II, 28.5% of patients in the ruxolitinib (Jakavi®) arm achieved a ≥35% reduction in spleen volume from baseline compared with none (0%) in the BAT arm 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 ruxolitinib (Jakavi®) group 46 patients (31.9%) achieved a ≥35% reduction in spleen volume from baseline compared to no (0%) patients in the BAT arm (p-value <0.0001).

A significantly higher proportion of patients in the ruxolitinib (Jakavi®) arm achieved a ≥ 35% reduction from baseline in spleen volume regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (PMF, PPV-MF, PET-MF).

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 ruxolitinib (Jakavi®) arm 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 arm 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

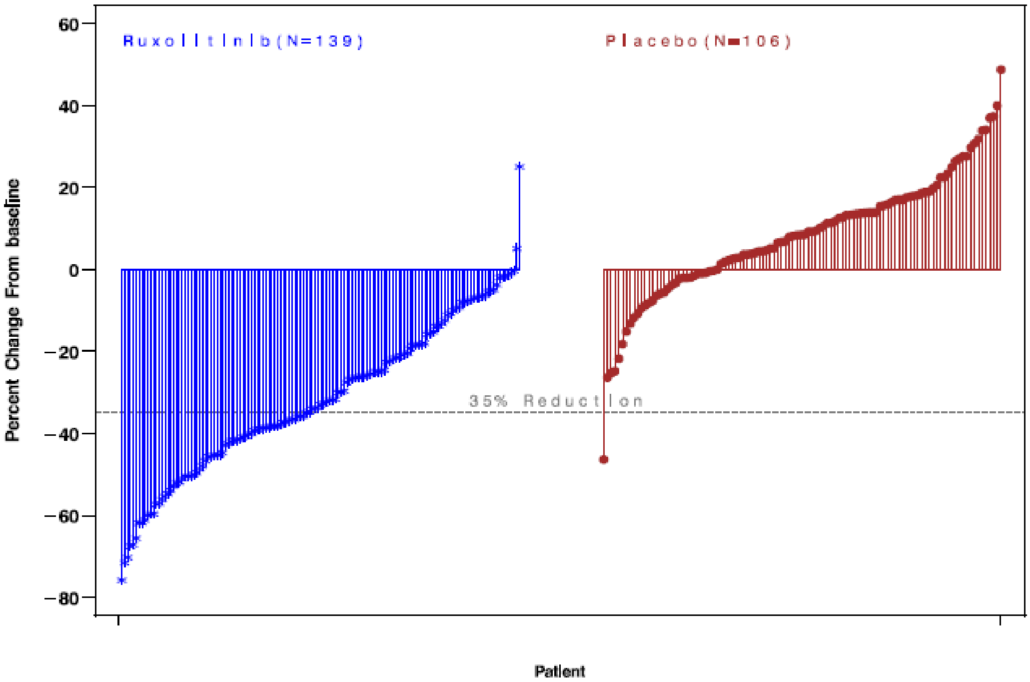
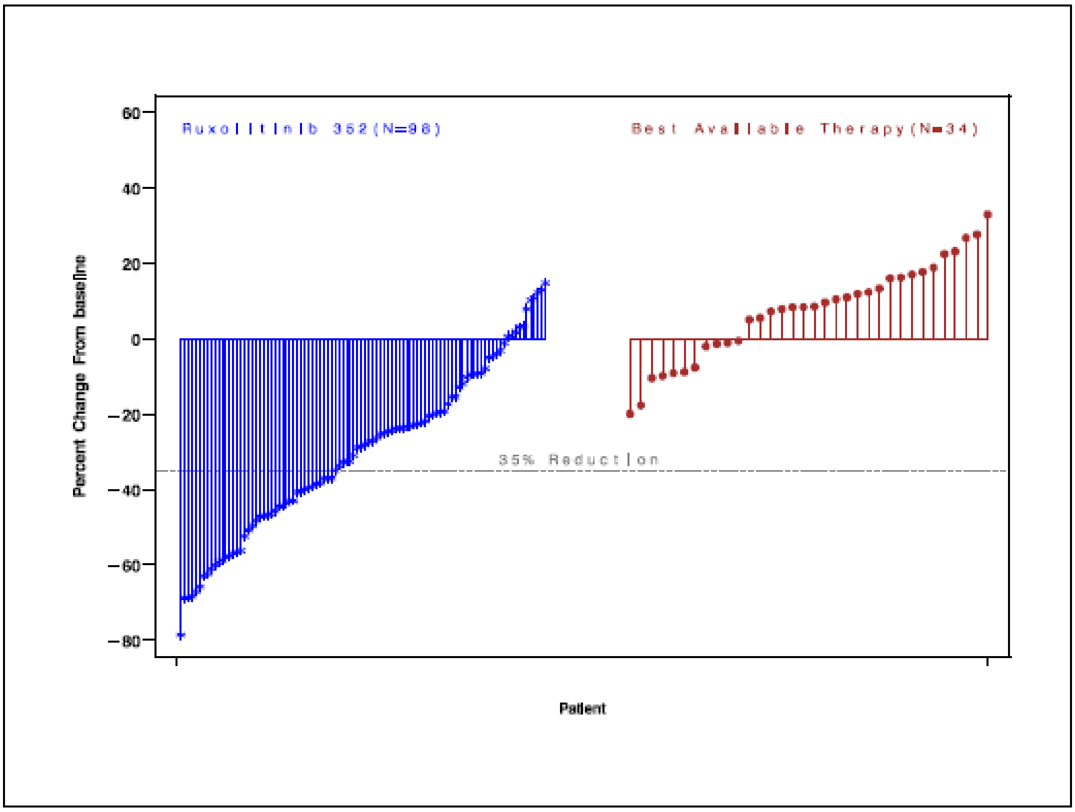


Figure 2 shows a waterfall plot of the percent change from baseline in spleen volume at Week 48 in COMFORT-II. Among the 98 patients in the ruxolitinib (Jakavi®) arm who had both baseline and Week 48 spleen volume evaluations, the median reduction in spleen volume at Week 48 was 28%. Among the 34 patients in the BAT arm 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 7.

Table 7 Kaplan-Meier Analysis of Duration from 1st ≥ 35% Reduction of Spleen Volume to 25% Increase from Nadir and Loss of Response in ruxolitinib (Jakavi®) Patients (COMFORT- I and - II)

Statistics	Ruxolitinib (Jakavi®) (COMFORT-I)	Ruxolitinib (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 to ruxolitinib (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.

Ruxolitinib (Jakavi®) improved MF-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 patients completed daily. The change from baseline in the Week 24 total score was a secondary endpoint in this study. Significantly larger proportion of patients in the ruxolitinib (Jakavi®) arm achieved a ≥50% improvement from baseline in the Week 24 total symptom score compared with the placebo arm (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 European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 in COMFORT-I and COMFORT-II. COMFORT-I compared ruxolitinib (Jakavi®) to placebo at 24 weeks and COMFORT-II compared ruxolitinib (Jakavi®) to BAT at 48 weeks. At baseline for both studies, EORTC QLQ-C30 individual subscale scores for the ruxolitinib (Jakavi®) and comparator arms were similar. At Week 24 in COMFORT-I, the ruxolitinib (Jakavi®) arm showed significant improvement in the global health status/QOL of the EORTC QLQ-C30 compared with the placebo arm (mean change of +12.3 and -3.4 for ruxolitinib (Jakavi®) and placebo, respectively, p <0.0001). At week 24 and week 48, the ruxolitinib (Jakavi®) arm in COMFORT-II showed a trend towards greater improvement of global health status/QOL compared to BAT, 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 maintained at 30.7% (HR: 0.693; 95% Cl: 0.503, 0.956, 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 BAT. There was a 52% reduction in risk of death in the ruxolitinib arm compared to the 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 consistent with COMFORT-I (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 PV who were resistant to or intolerant of hydroxyurea. A total of 110 patients were randomized to the ruxolitinib arm and 112 patients to the BAT arm. The starting dose of ruxolitinib (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%).

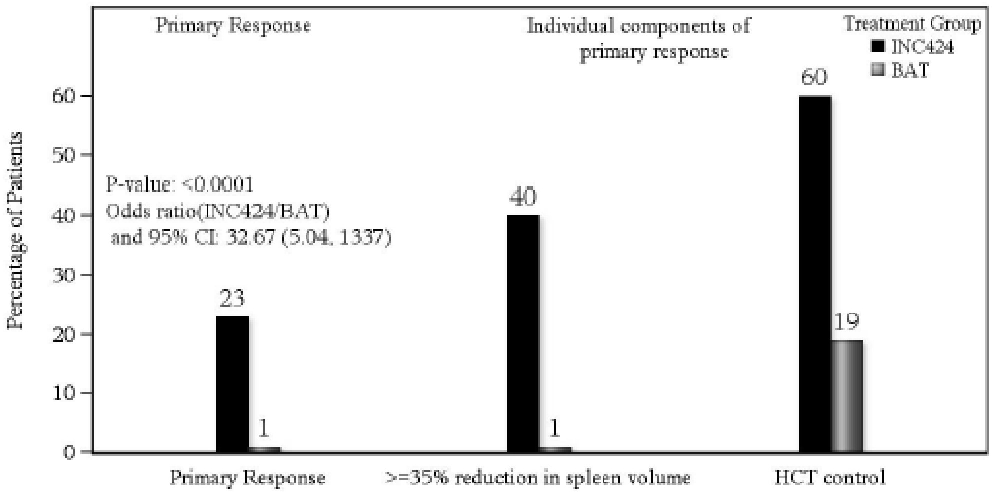
Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. 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 ruxolitinib (Jakavi®) arm achieved the primary composite endpoint and each of its individual components. Significantly more patients on ruxolitinib (Jakavi®) (23%) compared to BAT (0.9%) achieved a primary response (p<0.0001). HCT control was achieved in 60% of patients in the ruxolitinib (Jakavi®) arm compared to 18.75% in the BAT arm and ≥ 35% reduction in spleen volume was achieved in 40% of patients in the ruxolitinib (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 ruxolitinib (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 ruxolitinib (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- Symptoms Assessment Form (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. A total of 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 and week 256 following randomization. Out of 25 patients who had achieved primary response at week 32, 3 patients had progressed by week 80 and 6 patients by week 256. The probability to have maintained a response from week 32 up to week 80 and week 256 was 92% and 74%, respectively (see Table 8).

Table 8 Durability of Primary Response in the RESPONSE Study up to Week 256

	Week 32	Week 80	Week 256
Primary response achieved at week 32*, n/N (%)	25/110 (23%)	n/a	n/a
Patients maintaining primary response	n/a	22/25	19/25
Probability of maintaining primary response	n/a	92%	74%

* *According to the primary response composite endpoint criteria: absence of phlebotomy eligibility (HCT control) and a ≥35% reduction in spleen volume from baseline.*
n/a: not applicable

A second randomized, open label, active-controlled phase IIIb study (RESPONSE-2) was conducted in 149 PV 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 ruxolitinib (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 ruxolitinib (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 ruxolitinib (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 ruxolitinib (Jakavi®) arm and 22.7% in the BAT arm.

Graft-versus-host disease

Two randomized phase 3, open-label, multi-center studies investigated ruxolitinib (Jakavi®) in patients 12 years of age and older with acute GvHD (REACH2) and chronic GvHD (REACH3) after allogeneic hematopoietic stem cell transplantation (alloSCT) and insufficient response to corticosteroids and other systemic therapies. The starting dose of ruxolitinib (Jakavi®) was 10 mg twice daily.

Acute graft-versus-host disease

In REACH2, 309 patients with Grade II to IV corticosteroid-refractory, acute GvHD were randomized 1:1 to ruxolitinib (Jakavi®) or BAT. Patients were stratified by severity of acute

GvHD at the time of randomization. Corticosteroid refractoriness was determined when patients had progression after at least 3 days, failed to achieve a response after 7 days or failed corticosteroid taper.

BAT was selected by the investigator on a patient-by-patient basis and included anti-thymocyte globulin (ATG), extracorporeal photopheresis (ECP), mesenchymal stromal cells (MSC), low dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), etanercept, or infliximab.

In addition to ruxolitinib (Jakavi®) or BAT, patients could have received standard allogeneic stem cell transplantation supportive care including anti-infective medications and transfusion support as well as standard acute GvHD prophylaxis and treatment medications initiated before randomization including systemic corticosteroids and calcineurin inhibitors (CNIs) such as cyclosporine or tacrolimus. Topical or inhaled corticosteroid therapies were allowed to be continued per institutional guidelines.

Patients randomized to the BAT arm were allowed to cross over to the ruxolitinib (Jakavi®) arm after the Day 28 visit. Tapering of ruxolitinib (Jakavi®) was allowed after the Day 56 visit for patients with treatment response.

Baseline demographics and disease characteristics were balanced between the two treatment arms. The median age was 54 years (range 12 to 73 years). The study included 2.9% adolescent, 59.2% male and 68.9% white patients. The majority of enrolled patients had malignant underlying disease.

The severity of acute GvHD was Grade II in 34% and 34%, Grade III in 46% and 47%, and Grade IV in 20% and 19% of the ruxolitinib (Jakavi®) and BAT arms, respectively.

The reasons for patients' insufficient response to corticosteroids in the ruxolitinib (Jakavi®) and BAT arm were i) failure in achieving a response after 7 days of corticosteroid treatment (46.8% and 40.6%, respectively), ii) failure of corticosteroid taper (30.5% and 31.6%, respectively) or iii) disease progression after 3 days of treatment (22.7% and 27.7%, respectively).

Among all patients, the most common organs involved in GvHD were skin (54.0%) and lower GI tract (68.3%). More patients in the ruxolitinib (Jakavi®) arm had acute GvHD involving skin (60.4%) and liver (23.4%), compared to the BAT arm (skin: 47.7% and liver: 16.1%).

The most frequently used prior systemic acute GvHD therapies were corticosteroids+CNIs (49.4% in the ruxolitinib (Jakavi®) arm and 49%% in the BAT arm).

The primary endpoint was the overall response rate (ORR) on Day 28, defined as the proportion of patients in each arm with a complete response (CR) or a partial response (PR) without the requirement of additional systemic therapies for an earlier progression, mixed response or non-response based on investigator assessment following the criteria by Harris et al (2016).

The key secondary endpoint was the proportion of patients who achieved an ORR at Day 28 and maintained it at Day 56.

A further secondary endpoint was Failure Free Survival (FFS), a composite time to event endpoint defined as the time from randomization to i) relapse or recurrence of underlying disease, ii) non-relapse mortality, or iii) addition or initiation of another systemic therapy.

REACH2 met its primary objective. ORR at Day 28 of treatment was higher in the Jakavi arm (62.3%) compared to the BAT arm (39.4%). There was a statistically significant difference between the treatment arms (stratified Cochrane-Mantel-Haenszel test p<0.0001, one-sided, OR: 2.64; 95% CI: 1.65, 4.22).

There was also a higher proportion of complete responders in the ruxolitinib (Jakavi®) arm (34.4%) compared to BAT arm (19.4%).

Day-28 ORR was 76% for Grade II GvHD, 56% for Grade III GvHD, and 53% for Grade IV GvHD in the ruxolitinib (Jakavi®) arm, and 51% for Grade II GvHD, 38% for Grade III GvHD, and 23% for Grade IV GvHD in the BAT arm.

Among the non-responders at Day 28 in the ruxolitinib (Jakavi®) and BAT arms, 2.6% and 8.4% had disease progression, respectively.

Overall results are presented in Table 9.

Table 9 Overall response rate at Day 28 in REACH2

	Ruxolitinib (Jakavi®) N = 154		**BAT** N = 155	
	n (%)	**95% CI**	**n (%)**	**95% CI**
Overall Response	96 (62.3)	54.2, 70.0	61 (39.4)	31.6, 47.5
OR (95% CI)	2.64 (1.65,4.22)			
p-value	p <0.0001			
Complete Response	53 (34.4)		30 (19.4)	
Partial Response	43 (27.9)		31 (20.0)	

The study met its key secondary endpoint. Durable ORR at Day 56 was 39.6% (95% CI: 31.8, 47.8) in the ruxolitinib (Jakavi®) arm and 21.9% (95% CI: 15.7, 29.3) in the BAT arm. There was a statistically significant difference between the two treatment arms (OR: 2.38; 95% CI: 1.43, 3.94; p=0.0005). The proportion of patients with a CR was 26.6% in the ruxolitinib (Jakavi®) arm vs. 16.1% in the BAT arm. Overall, 49 patients originally randomized to the BAT arm crossed over to the ruxolitinib (Jakavi®) arm.

For the secondary endpoint FFS there were fewer events in the ruxolitinib (Jakavi®) arm (91; 59.1%) than in the BAT arm (121; 78.1%). Among the randomized patients, the estimated incidence rate of a FFS event at one month was lower in the ruxolitinib (Jakavi®) arm (18.47%; 95% CI: 12.74, 25.04) than in the BAT arm (49.13%; 95% CI: 40.94, 56.80). Additional follow-up data remain in favor of ruxolitinib (Jakavi®). Median FFS with ruxolitinib (Jakavi®) was statistically significantly longer than with BAT (4.86 months vs. 1.02 months; HR: 0.49, 95% CI: 0.37, 0.63; p<0.0001).

Chronic graft-versus-host disease

In REACH3, 329 patients with moderate or severe corticosteroid-refractory, chronic GvHD were randomized 1:1 to ruxolitinib (Jakavi®) or BAT. Patients were stratified by severity of chronic GvHD at the time of randomization. Corticosteroid refractoriness was determined when patients had lack of response or disease progression after 7 days, or had disease persistence for 4 weeks or failed corticosteroid taper twice.

BAT was selected by the investigator on a patient-by-patient basis and included extracorporeal photopheresis (ECP), low dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), infliximab, rituximab, pentostatin, imatinib, or ibrutinib.

In addition to ruxolitinib (Jakavi®) or BAT, patients could have received standard allogeneic stem cell transplantation supportive care including anti-infective medications and transfusion support as well as standard chronic GvHD prophylaxis and treatment medications initiated before randomization including systemic corticosteroids and CNIs (cyclosporine or tacrolimus). Topical or inhaled corticosteroid therapy was allowed to be continued per institutional guidelines.

Patients randomized to the BAT arm were allowed to cross over to the ruxolitinib (Jakavi®) arm after the Cycle 7 Day 1 visit (week 24). Tapering of ruxolitinib (Jakavi®) was allowed after the Cycle 7 Day 1 visit.

Baseline demographics and disease characteristics were balanced between the two treatment arms. The median age was 49 years (range 12 to 76 years). The study included 3.6% adolescent, 61.1% male and 75.4% white patients. The majority of enrolled patients had malignant underlying disease.

The severity at diagnosis of corticosteroid-refractory chronic GvHD was balanced between the two treatment arms, with 41% and 45% moderate, and 59% and 55% severe, in the ruxolitinib (Jakavi®) and the BAT arms, respectively.

Patients' insufficient response to corticosteroids in the ruxolitinib (Jakavi®) and BAT arm were characterized by i) a lack of response or disease progression after corticosteroid treatment for at least 7 days at 1mg/kg/day of prednisone equivalents (37.6% and 44.5%, respectively), ii) disease persistence after 4 weeks at 0.5 mg/kg/day (35.2% and 25.6%), or iii) corticosteroid dependency (27.3% and 29.9%, respectively).

Among all patients, 73% and 45% had skin and lung involvement in the ruxolitinib (Jakavi®) arm, compared to 69% and 41% in the BAT arm.

The most frequently used prior systemic chronic GvHD therapies were corticosteroids only (43% in the ruxolitinib (Jakavi®) arm and 49% in the BAT arm) and corticosteroids+CNIs (41% patients in the ruxolitinib (Jakavi®) arm and 42% in the BAT arm).

The primary endpoint was the ORR on Day 1 of Cycle 7, defined as the proportion of patients in each arm with a CR or a PR without the requirement of additional systemic therapies for an earlier progression, mixed response or non-response based on investigator assessment per NIH criteria.

Key secondary endpoints were Failure Free Survival (FFS) and proportion of patients with improvement of the modified Lee symptoms score (mLSS) at Cycle 7 Day 1. FFS, a composite time to event endpoint, incorporated the earliest of the following events: i) relapse or recurrence of underlying disease or death due to underlying disease, ii) non-relapse mortality, or iii) addition or initiation of another systemic therapy for chronic GvHD.

REACH3 met its primary objective. ORR at week 24 was higher in the ruxolitinib (Jakavi®) arm (49.7%) compared to the BAT arm (25.6%). There was a statistically significant difference between the treatment arms (stratified Cochrane-Mantel-Haenszel test $p<0.0001$, one-sided, OR: 2.99; 95% CI: 1.86, 4.80). Results are presented in Table 10.

Among the non-responders at Cycle 7 Day 1 in the ruxolitinib (Jakavi®) and BAT arms, 2.4% and 12.8% had disease progression, respectively.

Table 10 Overall response rate at Cycle 7 Day 1 in REACH3

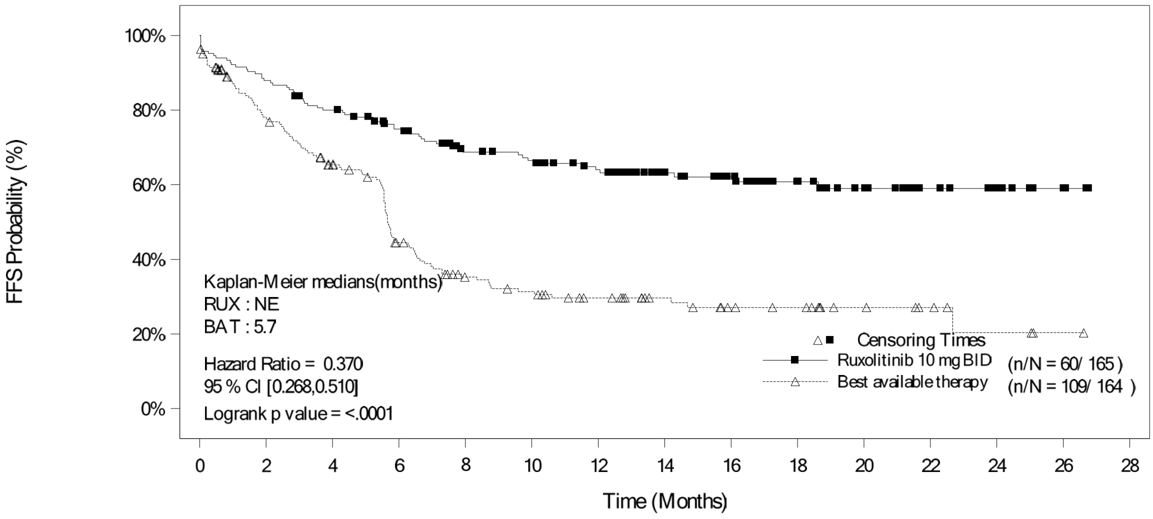
	Ruxolitinib (Jakavi®) N = 165		BAT N = 164	
	n (%)	**95% CI**	**n (%)**	**95% CI**
Overall Response	82 (49.7)	41.8, 57.6	42 (25.6)	19.1, 33.0
OR (95% CI)	2.99 (1.86, 4.80)			
p-value	p < 0.0001			
Complete Response	11 (6.7)		5 (3.0)	
Partial Response	71 (43.0)		37 (22.6)	

Both key secondary endpoints were also met. FFS demonstrated a statistically significant superiority of ruxolitinib (Jakavi®) versus BAT (HR: 0.370; 95% CI: 0.268, 0.510) with a 63% decreased risk (See Figure 4). The 6-months FFS probability (95% CI) was 74.9% (67.5%, 80.9%) and 44.5% (36.5%, 52.1%) for the ruxolitinib (Jakavi®) and BAT arms, respectively. The majority of FFS events were 'addition or initiation of another systemic therapy for cGvHD'. The 6-months probability for this event was 13.5% and 48.5% for the ruxolitinib (Jakavi®) and BAT arms, respectively. The rate of responders as per improvement of ≥7 points of total symptom score (TSS) from baseline of the mLSS showed a statistically significant difference (p=0.0011) between the ruxolitinib (Jakavi®) (24.2%) and BAT arms (9.8%).

Another secondary endpoint was best overall response (BOR) defined as the proportion of patients who achieved ORR (CR+PR) at any time point up to Cycle 7 Day 1. The BOR up to Cycle 7 Day 1 was higher in the ruxolitinib (Jakavi®) arm (76.4%) than in the BAT arm (60.4%).

The estimated probability of maintaining BOR at 12 months was higher in the ruxolitinib (Jakavi®) arm compared to the BAT arm (64.5% [95% CI: 58.9, 76.3] vs 40.3% [95% CI: 30.3, 50.2]).

Figure 4 Kaplan-Meier estimate of Failure Free Survival



No. of patients still at risk

Time(Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Ruxolitinib 10 mg BID	165	145	130	115	92	87	76	58	49	37	27	15	9	4	0
Best available therapy	164	123	100	64	45	39	31	23	17	15	9	6	3	1	0

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 b.i.d., 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.

Reproductive toxicity data are quoted in section Pregnancy, lactation, females and males of reproductive potential. 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.

AVAILABILITY

5mg, 10mg, 15mg, and 20 mg Tablets: Alu/PVC/PCTFE Blister Pack of 14’s (Box of 14’s and Box of 56’s)

STORAGE

Store at temperatures not exceeding 30°C.

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

Drugs should be kept out of the reach and sight of children.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**

The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

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