## Jakavi®

Protein kinase inhibitor.

# DESCRIPTION AND COMPOSITION

## Pharmaceutical form

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

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.

Certain dosage strengths may not be available in all countries.

## 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*

Jakavi is indicated for the treatment of disease-related splenomegaly and/or symptoms in adult patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

*Polycythemia vera*

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

*Acute Graft-versus-host disease*

Jakavi is indicated for the treatment of patients with acute Graft versus Host Disease (aGvHD) aged 6 years and older who have inadequate response to corticosteroids.

*Chronic Graft-versus-host disease*

Jakavi is indicated for the treatment of patients with chronic Graft versus Host Disease (cGvHD) aged 6 years and older who have inadequate response to corticosteroids.

## DOSAGE REGIMEN 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 (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 |
| 75,000 to less than 100,000/mm$^3$ | 10 mg orally twice daily |
| 50,000 to less than 75,000/mm$^3$ | 5 mg orally twice daily |

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

The recommended starting dose of Jakavi in acute graft-versus-host disease (GvHD) is based on age (see Table 2):

**Table 2 Starting doses in acute graft-versus-host disease**

| Age group | Starting dose |
|---|---|
| 12 years old and above | 5 to 10 mg orally twice daily |
| 6 years to less than 12 years old | 5 mg orally twice daily |

The recommended starting dose of Jakavi in chronic graft-versus-host disease (GvHD) is based on age (see Table 3):

**Table 3 Starting doses in chronic graft-versus-host disease**

| Age group | Starting dose |
|---|---|
| 12 years old and above | 10 mg orally twice daily |
| 6 years to less than 12 years old | 5 mg orally twice daily |

In aGvHD and cGvHD, Jakavi can be added to the continued use of corticosteroids and/or calcineurin inhibitors (CNIs).

## Dose modifications

Doses may be titrated based on efficacy and safety.

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.

*Myelofibrosis and Polycythemia vera*

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 should be considered if the platelet counts decrease during treatment as outlined in Table 4, with the goal of avoiding dose interruptions for thrombocytopenia.

**Table 4 Dosing recommendation for thrombocytopenia**

| | Dose at time of platelet decline | | | | |
|---|---|---|---|---|---|
| | 25 mg twice daily | 20 mg twice daily | 15 mg twice daily | 10 mg twice daily | 5 mg twice daily |
| **Platelet count** | **New Dose** | | | | |

| | Dose at time of platelet decline | | | | |
|---|---|---|---|---|---|
| 100,000 to <125,000/mm$^3$ | 20 mg twice daily | 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 | 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 | 5 mg twice daily | No change |
| Less than 50,000/mm$^3$ | Hold | 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.

*Dose modifications for acute and chronic GvHD*

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; 5 mg, twice daily to 5 mg, once daily). In patients who are unable to tolerate Jakavi at the reduced dose level, treatment should be interrupted. Detailed dosing recommendations are provided in Table 5.

**Table 5 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 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 Jakavi until platelet count ≥20,000/mm$^3$, then resume at one lower dose level. |
| Absolute neutrophil count (ANC) ≥500/mm$^3$ to <750/mm$^3$ | Reduce Jakavi by one dose level. Resume at initial dose level if ANC >1,000/mm$^3$. |
| Absolute neutrophil count <500/mm$^3$ | Hold 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 not caused by GvHD (no liver GvHD) | >3.0 to 5.0 x ULN: Continue Jakavi at one lower dose level until ≤3.0 x ULN. |
| | >5.0 to 10.0 x ULN: Hold 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 Jakavi until total bilirubin ≤3.0 x ULN, then resume at one lower dose level. |

| Laboratory parameter | Dosing recommendation |
|---|---|
| Total bilirubin elevation caused by GvHD (liver GvHD) | >3.0 x ULN: Continue Jakavi at one lower dose level until total bilirubin ≤3.0 x ULN. |
| Other Adverse Reactions: Grade 3 | Continue Jakavi at 1 dose level lower until recovery. |
| Other Adverse Reactions: Grade 4 | Discontinue Jakavi. |

*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 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 Jakavi, re-escalation of treatment should be considered.

## Dose adjustment with concomitant strong CYP3A4 inhibitors or dual moderate CYP2C9/CYP3A4 inhibitors

When 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 unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily. The concomitant use of 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 Jakavi related adverse drug reactions (ADRs) is recommended while on 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 count for MF, PV and GvHD patients should be reduced by approximately 50% to be administered twice daily. Patients diagnosed with severe renal impairment while receiving Jakavi should be carefully monitored and may need to have their doses reduced to avoid ADRs.

Available data in patients with end-stage renal disease (ESRD) suggest that MF patients on hemodialysis 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 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. 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 (see section CLINICAL PHARMACOLOGY).

There are limited data to determine the best dosing options for GvHD patients with ESRD on hemodialysis. There are no data for GvHD patients with ESRD.

### Hepatic Impairment

In MF and PV patients with any hepatic impairment the recommended starting dose based on platelet counts 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.

### GvHD: Dose modifications for patients with hepatic impairment

| **Hepatic Impairment Status** | **Recommended starting dose** |
|---|---|
| Mild, moderate, or severe based on Child-Pugh, including liver GvHD | No dose modification |
| Mild, moderate, or severe based on Child-Pugh without liver involvement | 5 mg BID |
| GvHD with liver involvement and an increase of total bilirubin to >3 x ULN | Monitor blood counts more frequently for toxicity and a dose reduction by one dose level may be considered |

*[See section Pharmacokinetics (PK)]*

### Pediatrics

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

In pediatric patients (6 years of age and older) with GvHD, the safety and efficacy of Jakavi have been established based on clinical studies (see section CLINICAL STUDIES).

### 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 may cause hematological ADRs, including thrombocytopenia, anemia, and neutropenia. A complete blood count must be performed before initiating therapy with 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 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 be considered.

Neutropenia (Absolute Neutrophil Count (ANC) <500/$mm^3$) was generally reversible and was managed by temporarily withholding 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 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 appropriate treatment should be initiated promptly. Jakavi therapy should not be started until active serious infections have resolved.

Tuberculosis has been reported in patients receiving 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 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 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 Jakavi. Most of these MF and PV patients had histories of extended treatment with hydroxyurea and prior NMSC or pre-malignant skin lesions. A causal relationship to Jakavi 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

The starting dose of 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 patients. Subsequent doses for MF and PV patients should be administered only on hemodialysis days following each dialysis session. In GvHD patients with severe renal impairment, the starting dose of Jakavi should be reduced by approximately 50%. Further dose modifications should be based on the safety and efficacy of the drug (see section DOSAGE REGIMEN AND ADMINISTRATION and section CLINICAL PHARMACOLOGY, Special populations).

#### Hepatic impairment

The starting dose of 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 patients with mild, moderate or severe hepatic impairment not related to GvHD, the starting dose of ruxolitinib should be reduced by 50% (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Special populations).

### Interactions

If 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 unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily (for monitoring frequency see sections DOSAGE REGIMEN AND ADMINISTRATION and INTERACTIONS).

The concurrent use of cytoreductive therapies or haematopoietic growth factors with Jakavi has not been studied. The safety and efficacy of these co-administrations are not known (see

section INTERACTIONS)

### Withdrawal effects

Following interruption or discontinuation of Jakavi, symptoms of myelofibrosis may return over a period of approximately one week. There have been cases of patients discontinuing Jakavi who sustained more severe events, particularly in the presence of acute intercurrent illness. It has not been established whether abrupt discontinuation of Jakavi contributed to these events. Unless abrupt discontinuation is required, gradual tapering of the dose of Jakavi may be considered, although the utility of the tapering is unproven.

## ADVERSE DRUG REACTIONS

### Summary of the safety profile

***Myelofibrosis:***

The safety of 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 randomised to Jakavi (n=301) and patients who received 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 anaemia (83.8%) and thrombocytopenia (80.5%).

Haematological ADRs (any Common Terminology Criteria for Adverse Events [CTCAE] grade) included anaemia (83.8%), thrombocytopenia (80.5%) and neutropenia (20.8%). Anaemia, thrombocytopenia, and neutropenia are dose-related effects.

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

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

***Polycythemia vera***

The safety of 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 randomised to Jakavi (n=184) and patients who received 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 anaemia (61.8%) and increased ALT (45.3%)

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

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

The most frequent non-haematological laboratory abnormalities (any CTCAE grade) identified as ADRs were increased ALT (45.3%), increased AST (42.6%), and hypercholesterolaemia (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 Jakavi.

***Acute graft-versus-host-disease***

The safety of Jakavi in acute GvHD patients was evaluated in the phase 3 study REACH2 and in the phase 2 study REACH4.

REACH2 included data from 201 patients ≥12 years of age, including patients initially randomized to Jakavi (n=152) and patients who received 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). In the pool of pediatric patients in REACH2 and REACH4, the median exposure was 16.7 weeks (range 1.1 to 48.9 weeks).

The most frequent ADRs (>50%) in adult and adolescent patients in REACH2 were thrombocytopenia, anaemia, neutropenia, increased alanine aminotransferase (ALT), and increased aspartate aminotransferase (AST). The most frequent ADRs (>50%) in the pool of pediatric patients in REACH2 and REACH4 were anaemia, neutropenia, increased ALT, hypercholesterolaemia and thrombocytopenia.

The most frequent haematological laboratory abnormalities identified as ADRs in adult and adolescent patients in REACH2 and in the pool of pediatric patients in REACH2 and REACH4 were thrombocytopenia (85.2% and 55.1%), anaemia (75.0% and 70.8%) and neutropenia (65.1% and 70.0%). Grade 3 anaemia was reported in 47.7% of adult and adolescent patients in REACH2 and in 45.8% of pooled pediatric patients in REACH2 and REACH4. Grade 3 and grade 4 thrombocytopenia were reported in 31.3% and 47.7% of adult and adolescent patients in REACH2 and in 14.6% and 22.4% of pooled pediatric patients in REACH2 and REACH4. Grade 3 and 4 neutropenia were reported in 17.9% and 20.6% of adult and adolescent patients in REACH2 and in 32.0% and 22.0% of pooled pediatric patients in REACH2 and REACH4, respectively.

The most frequent (>15%) non-haematological ADRs in adult and adolescent patients in REACH2 and in the pool of pediatric patients in REACH2 and REACH4 were cytomegalovirus (CMV) infection (32.3% and 31.4%), sepsis (25.4% and 9.8%), urinary tract infections (UTI) (17.9% and 9.8%), hypertension (13.4% and 17.6%) and nausea (16.4% and 3.9%), respectively.

The three non-haematological laboratory abnormalities identified as ADRs in adult and adolescent patients in REACH2 and in the pool of pediatric patients in REACH2 and REACH4 were increased ALT (54.9% and 63.3%), increased AST (52.3% and 50.0%) and hypercholesterolaemia (49.2% and 61.2%), respectively. The majority were of grade 1 and 2, however grade 3 increased ALT was reported in 17.6% of adult and adolescent patients in REACH2 and in 27.3% of pooled of pediatric patients in REACH2 and REACH4.

Discontinuation due to AEs, regardless of causality, was observed in 29.4% of adult and adolescent patients treated with Jakavi in REACH2 and in 21.6% of pooled pediatric patients in REACH 2 and REACH4.

***Chronic graft-versus-host disease***

The safety of Jakavi in chronic GvHD patients was evaluated in the phase 3 study REACH3 and in the phase 2 study REACH5.

REACH3 included data from 226 patients ≥12 years of age, including patients initially randomized to Jakavi (n=165) and patients who received 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). In the pool of pediatric patients in REACH3 and REACH5, the median exposure was 57.1 weeks (range 2.1 to 155.4 weeks).

The most frequent ADRs (>50%) in adult and adolescent patients in REACH3 were anaemia, hypercholesterolaemia and increased AST. The most frequent ADRs (>50%) in the pool of pediatric patients in REACH3 and REACH5 were neutropenia, hypercholesterolaemia, and increased ALT.

The most frequent haematological laboratory abnormalities identified as ADRs in adult and adolescent patients in REACH3 and in the pool of pediatric patients in REACH3 and REACH5 were anaemia (68.6% and 49.1%), neutropenia (36.2% and 59.3%) and thrombocytopenia (34.4% and 35.2%), respectively. Grade 3 anaemia was reported in 14.8% of adult and adolescent patients in REACH3 and in 17.0% of pooled pediatric patients in REACH3 and REACH5. Grade 3 and 4 thrombocytopenia were reported in 5.9% and 10.7% of adult and adolescent patients in REACH3 and in 7.7% and 11.1% of pooled pediatric patients in REACH3 and REACH5, Grade 3 and grade 4 neutropenia were reported in 9.5% and 6.7% of adult and adolescent patients in REACH3 and in 17.3% and 11.1% of pooled pediatric patients in REACH3 and REACH5, respectively.

The most frequent (>10%) non-haematological ADRs in adult and adolescent patients in REACH3 and in the pool of pediatric patients in REACH3 and REACH5 were hypertension (15.0% and 14.5%) and headache (10.2% and 18.2%), respectively.

The most frequent (>50%) non-haematological laboratory abnormalities identified as ADRs in adult and adolescent patients in REACH3 and in the pool of pediatric patients in REACH3 and REACH5 were hypercholesterolaemia (52.3% and 54.9%), increased AST (52.2% and 45.5%) and increased ALT (43.1% and 50.9%). The majority were grade 1 and grade 2, however grade 3 laboratory abnormalities increased ALT and increased AST were reported in 4.7% and 3.1% of adult and adolescent patients in REACH3 and in 14.9% and 11.5% of pooled pediatric patients in REACH3 and REACH5.

Discontinuation due to AEs, regardless of causality, was observed in 18.1% of adult and adolescent patients treated with Jakavi in REACH3 and in 14.5% of pooled pediatric patients in REACH3 and REACH5.

## Tabulated summary of adverse drug reactions from clinical studies

ADRs from clinical studies in MF and PV are listed in Table 6. ADRs from clinical trials in acute and chronic GvHD are listed in Table 7 and Table 8. All ADRs are listed by MedDRA system organ class (SOC). Within each SOC, the ADRs are ranked by frequency, with the most frequent 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 study 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 6 ADRs reported in the Phase 3 Studies COMFORT-I, COMFORT-II, RESPONSE, and RESPONSE 2**

| **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** | | |
| Anaemia[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 – 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 – 500/mm$^3$) | Common | Uncommon |
| Any CTCAE grade | Very common | Common |
| Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding | Very common | Very common |
| Gastrointestinal bleeding | Very Common | Common |
| Intracranial bleeding | Common | Uncommon |
| Other bleeding (including epistaxis, post-procedural haemorrhage and haematuria) | Very common | Very common |
| Pancytopenia[2] | Common | Common |
| **Metabolism and nutrition disorders** | | |
| Hypercholesterolaemia [1] Any CTCAE grade | Very common | Very common |
| Hypertriglyceridaemia [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 – 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 $10^9$ /L, and neutrophils count < 1.5 x $10^9$ /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 value within 7 days after dose discontinuation (see section WARNINGS AND PRECAUTIONS).

**Table 7 ADRs reported in clinical studies in acute graft-versus-host disease**

| | **Adult and adolescent patients (REACH2) (N=201)** | | | **Pediatric patients (REACH2 and REACH4) (N=51)** | | |
|---|---|---|---|---|---|---|
| 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 | Very common | 31.4 | 5.9 / 0 |
| Sepsis[4] | Very common | 25.4 | 4.0 / 17.9 | Common | 9.8 | 2.0 / 5.9 |
| Urinary tract infections | Very common | 17.9 | 6.0 / 0.5 | Common | 9.8 | 2.0 / 0 |
| **Blood and lymphatic system disorders** | | | | | | |

| | Adult and adolescent patients (REACH2) (N=201) | | | Pediatric patients (REACH2 and REACH4) (N=51) | | |
|---|---|---|---|---|---|---|
| ADR | Frequency category | All grades (%) | CTCAE[3] grade 3 / 4 (%) | Frequency category | All grades (%) | CTCAE[3] grade 3 / 4 (%) |
| Thrombocytopenia[1] | Very common | 85.2 | 31.3 / 47.7 | Very common | 55.1 | 14.6 / 22.4 |
| Anaemia[1] | Very common | 75.0 | 47.7 / NA | Very common | 70.8 | 45.8 / NA |
| Neutropenia[1] | Very common | 65.1 | 17.9 / 20.6 | Very common | 70.0 | 32.0 / 22.0 |
| Pancytopenia[1,2] | Very common | 32.8 | NA | Very common | 25.5 | NA |
| **Metabolism and nutrition disorders** | | | | | | |
| Hypercholesterolaemia[1] | Very common | 49.2 | 3.3 / 5.9 | Very common | 61.2 | 0 / 0 |
| **Nervous system disorders** | | | | | | |
| Headache | Common | 8.5 | 0.5 / 0 | Common | 5.9 | 0 / 0 |
| **Vascular disorders** | | | | | | |
| Hypertension | Very common | 13.4 | 5.5 / 0 | Very common | 17.6 | 15.7 / 0 |
| **Gastrointestinal disorders** | | | | | | |
| Nausea | Very common | 16.4 | 0.5 / 0 | Common | 3.9 | 0 / 0 |
| **Hepatobiliary disorders** | | | | | | |
| Increased ALT[1] | Very common | 54.9 | 17.6 / 1.5 | Very common | 63.3 | 27.3 / 0 |
| Increased AST[1] | Very common | 52.3 | 7.8 / 0 | Very common | 50.0 | 6.1 / 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.*

[3] *CTCAE Version 4.03.*

[4] *Grade 4 sepsis includes 16 (8%) grade 4 events and 20 (10%) grade 5 events in REACH2. There were no grade 5 events in the pediatric pool.*

*NA: Not applicable. No CTCAE grade defined based on laboratory values.*

**Table 8 ADRs reported in clinical studies in chronic graft-versus-host disease**

| | Adult and adolescent patients (REACH3) (N=226) | | | Pediatric patients (REACH3 and REACH5) (N=55) | | |
|---|---|---|---|---|---|---|
| ADR | Frequency category | All grades (%) | CTCAE[2] grade 3 / 4 (%) | Frequency category | All grades (%) | CTCAE[2] grade 3 / 4 (%) |
| **Infections and infestations** | | | | | | |
| Urinary tract infections | Common | 9.3 | 1.3 / 0 | Common | 5.5 | 1.8 / 0 |
| BK virus infections | Common | 4.9 | 0.4 / 0 | Common | 1.8 | 0 / 0 |

| | Adult and adolescent patients (REACH3) (N=226) | | | Pediatric patients (REACH3 and REACH5) (N=55) | | |
|---|---|---|---|---|---|---|
| ADR | Frequency category | All grades (%) | CTCAE[2] grade 3 / 4 (%) | Frequency category | All grades (%) | CTCAE[2] grade 3 / 4 (%) |
| **Blood and lymphatic system disorders** | | | | | | |
| Anaemia[1] | Very common | 68.6 | 14.8 / NA | Very common | 49.1 | 17.0 / NA |
| Neutropenia[1] | Very common | 36.2 | 9.5 / 6.7 | Very common | 59.3 | 17.3 /11.1 |
| Thrombocytopenia[1] | Very common | 34.4 | 5.9 / 10.7 | Very common | 35.2 | 7.7 / 11.1 |
| **Metabolism and nutrition disorders** | | | | | | |
| Hypercholesterolaemia[1] | Very common | 52.3 | 5.5 / 0.5 | Very common | 54.9 | 4.1 / 5.9 |
| Weight gain | Common | 3.5 | 0 / 0 | Common | 5.5 | 3.6 / 0 |
| **Nervous system disorders** | | | | | | |
| Headache | Very common | 10.2 | 1.3 / 0 | Very common | 18.2 | 1.8 / 0 |
| **Vascular disorders** | | | | | | |
| Hypertension | Very common | 15.0 | 5.3 / 0 | Very common | 14.5 | 3.6 / 0 |
| **Gastrointestinal disorders** | | | | | | |
| Increased lipase[1] | Very common | 35.9 | 9.5 / 0.4 | Very common | 20.4 | 3.8 /1.9 |
| Increased amylase[1] | Very common | 32.4 | 4.2 / 2.7 | Very common | 25.9 | 9.4 / 0 |
| Constipation | Common | 6.6 | 0 / 0 | Common | 5.5 | 0 / 0 |
| **Hepatobiliary disorders** | | | | | | |
| Increased AST[1] | Very common | 52.2 | 3.1 / 0.9 | Very common | 45.5 | 11.5 / 0 |
| Increased ALT[1] | Very common | 43.1 | 4.7 / 0.9 | Very common | 50.9 | 14.9 / 3.6 |
| **Musculoskeletal and connective tissue disorders** | | | | | | |
| Increased blood CPK[1] | Very common | 31.1 | 1.0 / 1.4 | Very common | 22.6 | 0 / 0 |
| **Renal and urinary disorders** | | | | | | |
| Increased blood creatinine[1] | Very common | 38.4 | 1.3 / 0 | Common | 7.3 | 0 / 0 |

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

[2] *CTCAE Version 4.03.*

*NA: Not applicable. No CTCAE grade defined based on laboratory values.*

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

The following ADRs are derived from post-marketing experience with Jakavi via spontaneous case reports and literature cases. As these reactions are reported voluntarily from a population of

uncertain size, it is not possible to reliably estimate their frequency, which is therefore characterized as 'not known'.

Infections and infestations: Tuberculosis (PV patients).

## Description of selected adverse drug reactions

### Anaemia

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 anaemia.

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

In the randomised, placebo-controlled study COMFORT-I 60.6% of Jakavi-treated patients and 37.7% of placebo-treated patients 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 41.1% in the best available therapy arm.

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 frequency of CTCAE grade 3 and 4 events was 1.1% in PV patients, while in the MF patients, the frequency was 42.5%.

In the phase 3 acute (REACH2) and chronic (REACH3) GvHD studies, respectively, anemia (all grades) was reported in 75.0% and 68.6% of adult and adolescent patients; CTCAE Grade 3 was reported in 47.7% and 14.8% of adult and adolescent patients. In the pool of pediatric patients with acute (REACH2 and REACH4) and chronic (REACH3 and REACH5) GvHD, anaemia (all grades) was reported in 70.8% and 49.1% of patients, respectively. CTCAE grade 3 was reported in 45.8% and 17.0% of acute and chronic GvHD patients, respectively.

### Thrombocytopenia

In the phase 3 MF clinical studies, in patients who developed grade 3 or grade 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 grade 4 thrombocytopenia compared to patients with platelet count >200,000/mm$^3$ (64.2% versus 38.5%).

Over the randomized period in the RESPONSE 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 (3.3%) than in MF (11.6%) patients.

In the phase 3 acute GvHD study in adult and adolescent patients (REACH2), grade 3 and grade 4 thrombocytopenia was observed in 31.3% and 47.7% of patients, respectively. In the phase 3 chronic GvHD study in adult and adolescent patients (REACH3), the frequency of grade 3 and grade 4 thrombocytopenia was lower (5.9% and 10.7%) than in acute GvHD. The frequency of grade 3 (14.6%) and grade 4 (22.4%) thrombocytopenia in the pool of pediatric patients with acute GvHD in REACH2 and REACH4 was lower than in adult and adolescent patients in REACH2. In the pool of pediatric patients with chronic GvHD in REACH3 and REACH5, grade 3 and grade 4 thrombocytopenia was lower (7.7% and 11.1%) than in pediatric patients with acute GvHD in REACH2 and REACH4.

### Neutropenia

In the phase 3 clinical studies in MF, in patients who developed grade 3 or grade 4 neutropenia, the median time to onset was 12 weeks. During the randomized period of the studies dose holding or reductions due to neutropenia were reported in 1.0% 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.

During the long term follow-up, 2 patients reported CTCAE grade 4 neutropenia.

In the phase 3 acute GvHD study (REACH2), grade 3 and grade 4 neutropenia was observed in 17.9% and 20.6% of adult and adolescent patients, respectively. In the phase 3 chronic GvHD study REACH3, grade 3 and grade 4 neutropenia was lower (9.5% and 6.7%) than in acute GvHD. In pediatric patients with acute GvHD in REACH2 and REACH4, the frequency of grade 3 and grade 4 neutropenia was 32.0% and 22.0%, respectively. In pediatric patients with chronic GvHD in REACH3 and REACH5 the frequency of grade 3 and grade 4 neutropenia was 17.3% and 11.1%, respectively.

### Bleeding

In the phase 3 MF 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.

In the randomised period of the pivotal study in PV patients, bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 20% of patients treated with Jakavi and 15.3% patients receiving best available therapy. Bruising was reported in similar frequencies in Jakavi and BAT arms (10.9% versus 8.1%). No intracranial bleeding or gastrointestinal haemorrhage events were reported in patients receiving Jakavi. One

patient treated with Jakavi experienced a grade 3 bleeding event (post-procedural bleeding); no grade 4 bleeding was reported. Other bleeding events (including events such as epistaxis, post-procedural haemorrhage, gingival bleeding) were reported in 11.8% of patients treated with Jakavi and 6.3% treated with best available therapy.

### Infections

In the randomised period of the Phase 3 MF pivotal studies, grade 3 or grade 4 UTI was reported in 1.0% of patients, herpes zoster in 4.3% and tuberculosis in 1.0%.

Over the randomized period in the RESPONSE and RESPONSE-2 studies in PV, one (0.5%) grade 3-4 UTI was observed.

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 grade 4 post herpetic neuralgia amongst the PV patients

During the long term follow-up, UTI of any grade was observed in 21.4% and 11.8% of MF and PV patients, respectively. Herpes zoster of any grade was observed in 11.6% and 14.7% of MF and PV patients, respectively.

In the phase 3 acute GvHD study REACH2, grade 3 and grade 4 CMV infections were reported in 10.9% and 0.5% of adult and adolescent 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. CMV infections were reported in 31.4% of pooled pediatric patients with acute GvHD in REACH2 and REACH4 (grade 3, 5.9%).

Sepsis events including septic shock of any grade were reported in 25.4% of adult and adolescent patients in REACH2.

UTI and sepsis were reported with lower frequency in the pool of pediatric patients with acute GvHD in REACH2 and REACH4 (9.8%, each) compared with adult and adolescent patients in REACH2.

In the phase 3 chronic GvHD study REACH3, grade 3 UTI and BK virus infection were reported in 1.3% and 0.4% of patients, respectively.

In the pool of pediatric patients in REACH3 and REACH5 with chronic GvHD, UTI (all grades) were reported in 5.5% (grade 3, 1.8%) of patients and BK virus infection was reported in 1.8% (no grade ≥3) of patients.

### Increased systolic blood pressure

In the phase 3 MF pivotal clinical studies an increase in systolic blood pressure of 20 mmHg or more from baseline was recorded in 31.5% of patients on at least one visit compared with 19.5% of the control-treated patients. In COMFORT-I the mean increase from baseline in systolic BP was 0-2 mmHg on Jakavi versus a decrease of 2-5 mmHg in the placebo arm. In COMFORT-II mean values showed little difference between the ruxolitinib-treated and the control-treated patients.

## INTERACTIONS

Interaction studies have only been performed in adults.

Ruxolitinib is eliminated through metabolism catalysed by CYP3A4 and CYP2C9. Thus, medicinal products inhibiting these enzymes can give rise to increased ruxolitinib exposure.

### Agents that may alter plasma concentration of ruxolitinib

#### Strong CYP3A4 inhibitors (such as, but not limited to, boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole)

In healthy subjects co-administration of Jakavi (10 mg single dose) with a strong CYP3A4 inhibitor, ketoconazole, resulted in ruxolitinib $C_{max}$ and AUC that were higher by 33% and 91%, respectively, than with ruxolitinib alone. The half-life was prolonged from 3.7 to 6.0 hours with concurrent ketoconazole administration.

When administering Jakavi with strong CYP3A4 inhibitors the unit dose of Jakavi should be reduced by approximately 50%, to be administered twice daily, 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 (e.g. twice weekly) for cytopenias, and dose titrated based on safety and efficacy (see section DOSAGE REGIMEN AND ADMINISTRATION).

#### Mild or moderate CYP3A4 inhibitors (such as, but not limited to, ciprofloxacin, erythromycin, amprenavir, atazanavir, diltiazem, cimetidine)

In healthy subjects co-administration of ruxolitinib (10 mg single dose) with erythromycin 500mg twice daily for four days resulted in ruxolitinib $C_{max}$ and AUC that were higher by 8% and 27%, respectively, than with ruxolitinib alone.

No dose adjustment is recommended when ruxolitinib is co-administered with mild or moderate CYP3A4 inhibitors (e.g., erythromycin). However, 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 400mg dose followed by 200mg 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 Jakavi with fluconazole doses of greater than 200 mg daily should be avoided.

#### CYP3A4 inducers (such as, but not limited to, avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St.John's wort (Hypericum perforatum))

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

In healthy subjects given ruxolitinib (50 mg single dose) following the potent CYP3A4 inducer rifampicin (600 mg daily dose for 10 days), ruxolitinib AUC was 70% lower than after administration of Jakavi alone. The exposure of ruxolitinib active metabolites was unchanged. Overall, the ruxolitinib pharmacodynamic activity was similar, suggesting the CYP3A4 induction resulted in minimal effect on the pharmacodynamics. However, this could be related to the high ruxolitinib dose resulting in pharmacodynamic effects near $E_{max}$. It is possible that in the individual patient, an increase of the ruxolitinib dose is needed when initiating treatment with a strong enzyme inducer.

#### Substances transported by P-glycoprotein or other transporters

Ruxolitinib may inhibit P-glycoprotein and breast cancer resistance protein (BCRP) in the intestine. This may result in increased sytemic exposure of substrates of these transporters, such as dabigatran etixilate, ciclosporin, rosuvastatin and potentially digoxin. Therapeutic drug monitoring (TDM) or clinical monitoring of the affected substance is advised.

It is possible that the potential inhibition of P-gp and BCRP in the intestine can be minimised if the time between administrations is kept apart as long as possible.

### 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.

***Haematopoietic growth factors***

The concurrent use of haematopoietic growth factors and Jakavi has not been studied. It is not known whether the Janus Associated Kinase (JAK) inhibition by Jakavi reduces the efficacy of the haematopoietic growth factors or whether the haematopoietic growth factors affect the efficacy of Jakavi (see section WARNINGS AND PRECAUTIONS).

***Cytoreductive therapies***

The concomitant use of cytoreductive therapies and Jakavi has not been studied. The safety and efficacy of this co-administration is not known (see section WARNINGS AND PRECAUTIONS).

## 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 25mg b.i.d based on AUC.

The use of Jakavi during pregnancy is not recommended. The patient should be advised of the risk to a fetus if 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 passes into the milk of lactating rats. Because of the potential for serious adverse drug reactions in nursing infants from 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 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 Jakavi.

### Infertility
In animal studies, no effects were observed on fertility or reproductive performance of males 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 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

### Pharmacotherapeutic group

ATC code L01EJ01. (Antineoplastic agent, Janus-associated kinase (JAK) inhibitors).

### Mechanism of action

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 (eg. 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

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 TNF-alpha, IL-6, and CRP in patients with MF were decreased following treatment with Jakavi. Patients with MF did not become refractory to the pharmacodynamic effects of Jakavi treatment over time. Similarly, patients with PV also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with Jakavi.

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

### 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 ($V_{D,ss}$) is 75 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%. The mean $V_{D,ss}$ in adolescent and adult acute GvHD patients is 67.5 L whereas in chronic GvHD patients it is 60.9 L. The mean $V_{D,ss}$ is approximately 30 L in pediatric patients with acute or chronic GvHD and with a body surface area (BSA) below 1. 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 enzyme 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 regards to gender and race.

**Population pharmacokinetics**

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. Clearance was 10.4 L/h in adult and adolescent patients with acute GvHD and 7.8 L/h in adolescent and adult patients with chronic GvHD, with 48.7% inter-subject variability. In pediatric patients with acute or chronic GvHD and with a BSA below 1, clearance was between 6.5 L/h and 7 L/h. No relationship was apparent between oral clearance and gender, patient age or race, based on a PopPK evaluation in GvHD patients. At a dose of 10 mg twice daily, exposure was increased in GvHD patients with a low body surface area (BSA). In subjects with a BSA of 1 $m^2$, 1.25 $m^2$ and 1.5 $m^2$, the predicted mean exposure (AUC) was respectively 31%, 22% and 12% higher than the typical adult (1.79 $m^2$).

### Pediatric

The pharmacokinetics of Jakavi in pediatric patients with MF and PV < 18 years of age have not been established.

As in adult patients with GvHD, ruxolitinib was rapidly absorbed after oral administration in pediatric patients with GvHD. Dosing in children between 6 and 11 years at 5 mg twice daily achieved comparable exposure to a dose of 10 mg twice daily in adolescents and adults, confirming the exposure matching approach implemented as part of the extrapolation assumption. In REACH4 and REACH5, Jakavi has not been evaluated in pediatric patients with acute or chronic GvHD below the age of 2 years, therefore physiologically-based pharmacokinetic modeling which accounts for age related aspects in younger patients has been used to predict the exposures in these patients, based on the data from patients aged 2 to 17 years.

Based on a pooled population pharmacokinetic analysis in pediatric patients with acute or chronic GvHD, clearance of ruxolitinib decreased with decreasing BSA. After correcting for the BSA effect, other demographic factors such as age, body weight and body mass index did not have clinically significant effects on the exposure of ruxolitinib.

### Renal impairment

Following a single Jakavi 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 Jakavi 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 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. 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/$mm^3$. Patients with platelet counts ≤100,000/$mm^3$ were not eligible in COMFORT studies. Patients with baseline platelet counts ≥50,000 and <100,000/$mm^3$ were enrolled 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 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 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 percent (76%) 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 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 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 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 9. 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 BAT in COMFORT-II.

**Table 9 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) | 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 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 Jakavi arm achieved a ≥50% reduction in palpable spleen length.

In COMFORT-II, 28.5% of patients in the Jakavi arm achieved a ≥35% reduction in spleen volume from baseline compared with none (0%) in the BAT 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 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 Jakavi group achieved ≥ 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 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**

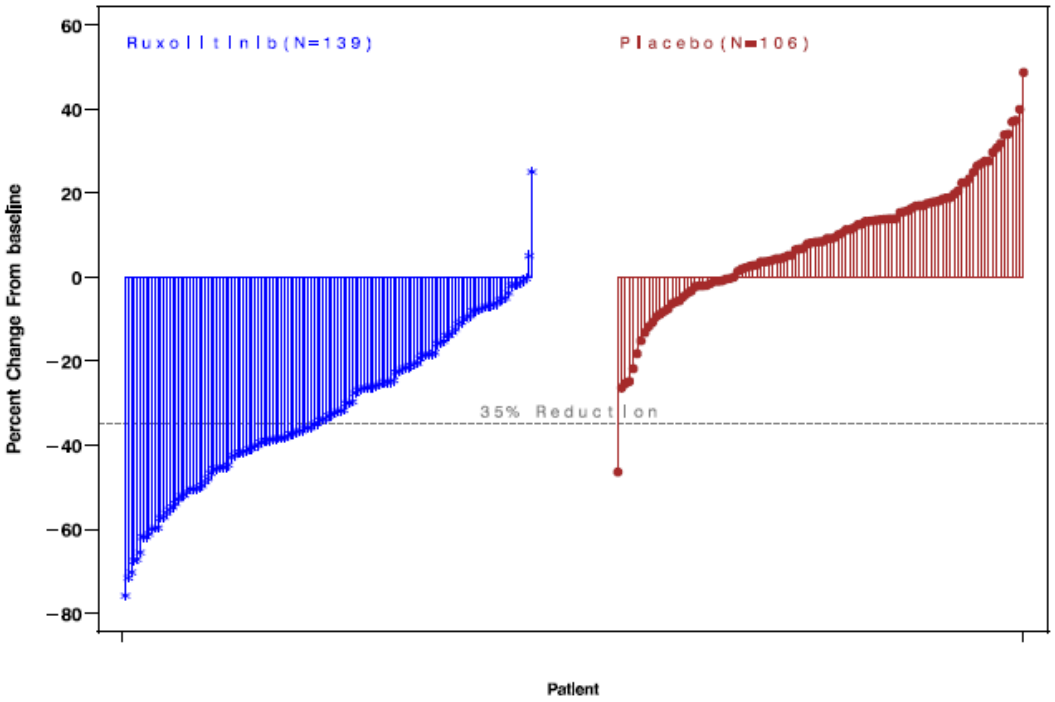
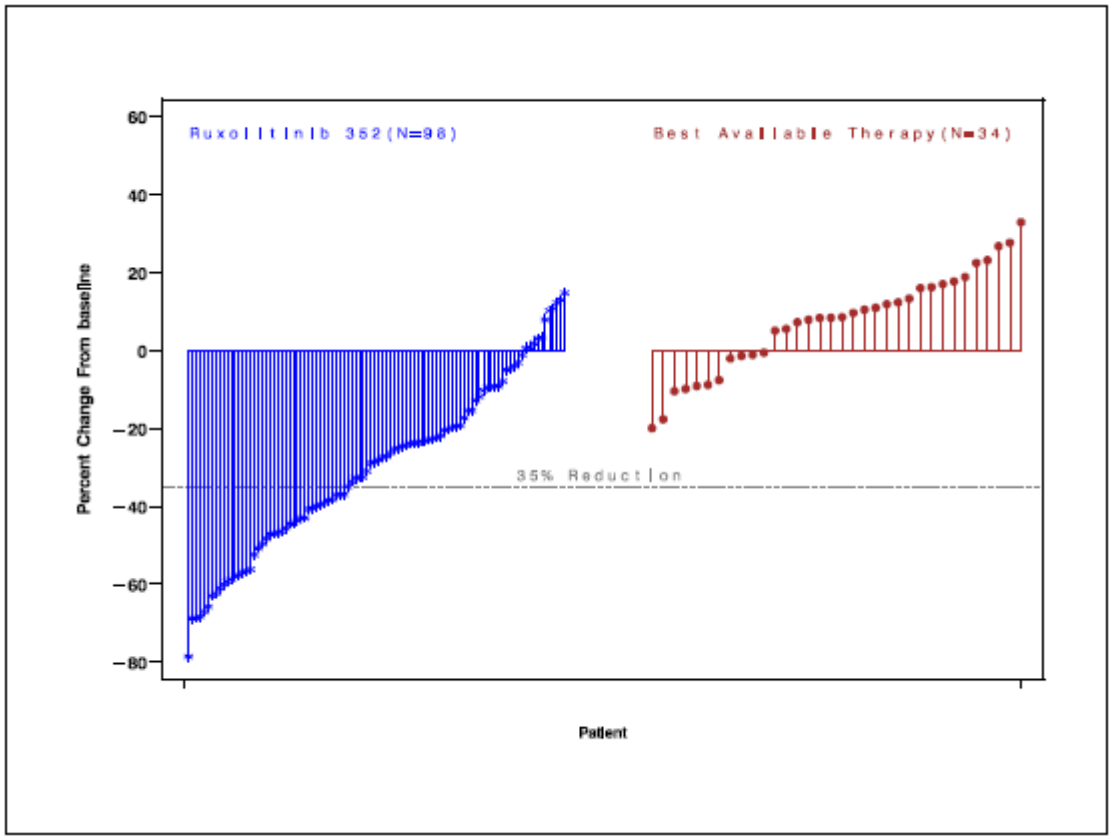



Figure 2 shows a waterfall plot of the percent change from baseline in spleen volume at Week 48 in COMFORT-II. Among the 98 patients in the Jakavi arm who had both baseline and Week 48 spleen volume evaluations, the median reduction in spleen volume at Week 48 was 28%. Among the 34 patients in the BAT 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 10.

**Table 10** **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 COMFORT- 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 to 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 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 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 Jakavi to placebo at 24 weeks and COMFORT-II compared Jakavi to BAT at 48 weeks. At baseline for both studies, EORTC QLQ-C30 individual subscale scores for the Jakavi and comparator arms were similar. At Week 24 in COMFORT-I, the 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 Jakavi and placebo, respectively, p <0.0001). At week 24 and week 48, the 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 Jakavi 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 Jakavi 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 Jakavi 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 Jakavi 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 defined based on the European LeukemiaNet (ELN) international working group published criteria. A total of 110 patients were randomized to the Jakavi 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 Jakavi arm had PV diagnosis for a median of 8.2 years and had previously received

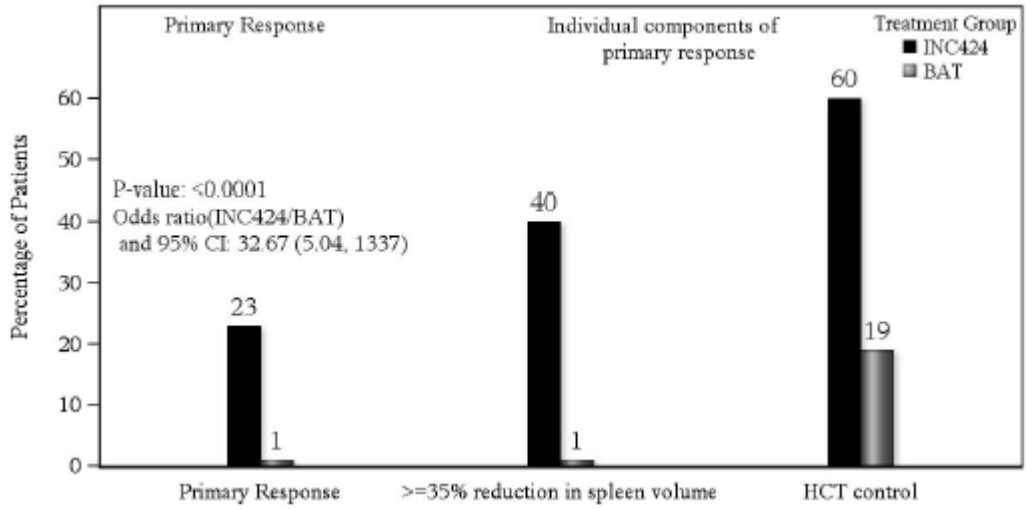
hydroxyurea for a median of approximately 3 years. Most patients (> 80%) had received at least two phlebotomies in the last 24 weeks prior to screening. Comparative data regarding long-term survival and incidence of disease complications is missing.

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 arm 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). HCT control was achieved in 60% of patients in the Jakavi arm compared to 18.75% 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-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 Jakavi 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 Jakavi -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 Jakavi-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 11).

**Table 11 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 Jakavi 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.

### Acute graft-versus-host disease in adolescents and adults

The clinical efficacy of Jakavi in patients 12 years of age and older with GvHD has been investigated in REACH2, a phase 3, open-label, randomised, multicentre study and in REACH1, a phase 2 open-label, single-arm, multicentre study of Jakavi for treatment of patients with steroid-refractory aGvHD Grades 2 to 4 (Mount Sinai Acute GvHD International Consortium (MAGIC) criteria) occurring after allogeneic hematopoietic stem cell transplantation.

In REACH1, Jakavi was administered at 5 mg twice daily, and the dose could be increased to 10 mg twice daily after 3 days in the absence of toxicity. Seventy-one patients were enrolled

in the study. These patients had a median age of 58 years (range 18-73 years), 49.3% were male and the majority of participants were White/Caucasian (93.0%)

In REACH1, 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), Very good Partial Response (VGPR) or a partial response (PR) (as per the CIBMTR modifications to the IBMTR response index).

The key secondary endpoint was six-month duration of response (DOR), defined as the time from first response until GvHD progression or death assessed when all participants who are still on study complete the Day 180 visit.

The REACH1 study achieved the predetermined threshold for a positive study outcome (lower limit of the 95% CI for Day 28 ORR ≥ 40%). Forty participants (56.3% [95% CI: 44.0, 68.1]) demonstrated a response at Day 28, including 19 participants (26.8%) who achieved a CR, 6 participants who achieved a VGPR (8.5%) and 15 participants who achieved a PR (21.1%).

In REACH2, 309 patients with grade II to IV corticosteroid-refractory, acute GvHD were randomised 1:1 to Jakavi or BAT. Patients were stratified by severity of acute GvHD at the time of randomisation. 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. The starting dose of Jakavi was 10 mg twice daily.

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 Jakavi or BAT, patients could have received standard allogeneic stem cell transplantation supportive care including anti-infective medicinal products and transfusion support. Ruxolitinib was added to continued use of corticosteroids and/or calcineurin inhibitors (CNIs) such as cyclosporine or tacrolimus and/or topical or inhaled corticosteroid therapies per institutional guidelines.

Patients who received one prior systemic treatment other than corticosteroids and CNI for acute GvHD were eligible for inclusion in the study. In addition to corticosteroids and CNI, prior systemic medicinal product for acute GvHD was allowed to continue only if used for acute GvHD prophylaxis (i.e. started before the acute GvHD diagnosis) as per common medical practice.

Patients on BAT could cross over to ruxolitinib after day 28 if they met the following criteria:

- Failed to meet the primary endpoint response definition (complete response [CR] or partial response [PR]) at day 28; OR
- Lost the response thereafter and met criteria for progression, mixed response, or no response, necessitating new additional systemic immunosuppressive treatment for acute GvHD, AND
- Did not have signs/symptoms of chronic GvHD.

Tapering of 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 Jakavi and BAT arms, respectively.

The reasons for patients' insufficient response to corticosteroids in the Jakavi and BAT arms 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 acute GvHD were skin (54.0%) and lower gastrointestinal tract (68.3%). More patients in the 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 Jakavi arm and 49.0% 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 a CR or PR at day 28 and maintained a CR or PR at day 56.

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 $p<0.0001$, two-sided, OR: 2.64; 95% CI: 1.65, 4.22).

There was also a higher proportion of complete responders in the 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 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 Jakavi and BAT arms, 2.6% and 8.4% had disease progression, respectively.

Overall results are presented in Table 12.

**Table 12 Overall response rate at day 28 in REACH2**

| | **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 (2-sided) | 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 based on the primary data analysis (data cut-off date: 25-Jul-2019). Durable ORR at day 56 was 39.6% (95% CI: 31.8, 47.8) in the 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=0.0007). The proportion of patients with a CR was 26.6% in the Jakavi arm versus 16.1% in the BAT arm. Overall, 49 patients (31.6%) originally randomised to the BAT arm crossed over to the Jakavi arm.

### Chronic graft-versus-host disease in adolescents and adults

In REACH3, 329 patients with moderate or severe corticosteroid-refractory, chronic GvHD were randomised 1:1 to Jakavi 10 mg twice daily (n=165) or BAT (n=164). Patients were stratified by severity of chronic GvHD at the time of randomisation. 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 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 randomisation including systemic corticosteroids and CNIs (cyclosporine or tacrolimus). Topical or inhaled corticosteroid therapy was allowed to be continued per institutional guidelines.

Patients randomised to the BAT arm were allowed to cross over to the Jakavi arm after the Cycle 7 Day 1 visit (Week 24). Tapering of 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 Jakavi and the BAT arms, respectively.

Patients' insufficient response to corticosteroids in the Jakavi and BAT arm were characterised by i) a lack of response or disease progression after corticosteroid treatment for at least 7 days at 1 mg/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 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 Jakavi arm and 49% in the BAT arm) and corticosteroids+CNIs (41% patients in the 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.

REACH3 met its primary objective. ORR at week 24 was higher in the 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 13.

**Table 13 Overall response rate at Cycle 7 Day 1 in REACH3**

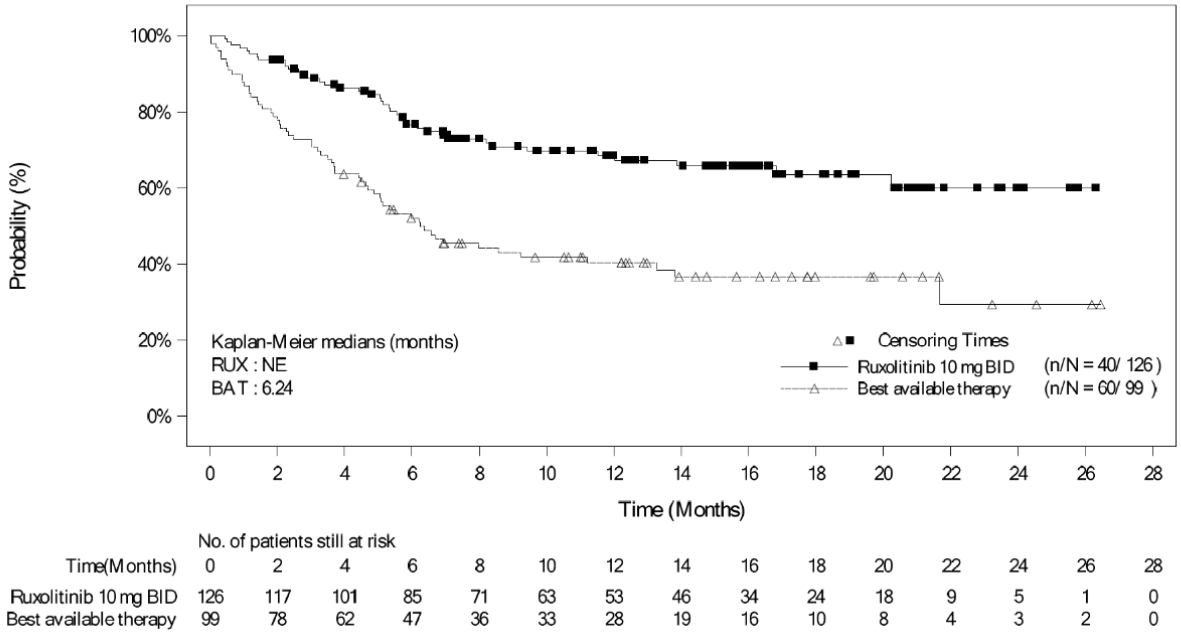
| | Jakavi N = 165 | | BAT N = 164 | |
|---|---|---|---|---|
| | n (%) | 95% CI | n (%) | 95% CI |
| Overall Response | 82 (49.7) | 41.8, 57.6 | 42 (25.6) | 19.1, 33.0 |
| OR (95% CI) | 2.99 (1.86, 4.80) | | | |
| p-value | p < 0.0001 | | | |
| Complete Response | 11 (6.7) | | 5 (3.0) | |
| Partial Response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

Best overall response (BOR) is 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 Jakavi arm (76.4%) than in the BAT arm (60.4%).

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

Duration of response was evaluated in patients who achieved a complete or partial response at or before Cycle 7 Day 1 (BOR). DOR was defined as "time from first response until cGVHD progression, death, or systemic therapies for cGVHD". The Median duration of response was not reached in Jakavi arm and was 6.2 months (95% CI: 4.7 to 13.3) in the BAT arm. The estimated probability of maintaining BOR with 95% CIs was higher in the Jakavi arm (76.58%; 95% CI: 67.87, 88.22) compared to the BAT arm (52.11%; 95% CI: 41.78, 61.45) at 6 months. Similar trends in probability were observed at 12 months and 18 months.

**Figure 4 Kaplan Meier estimate of Duration of Response**




## Pediatric population

In GvHD pediatric patients above 2 years of age, the safety and efficacy of Jakavi are supported by evidence from the randomised phase 3 studies REACH2 and REACH3 and from the open-label, single-arm phase 2 studies REACH4 and REACH5 (see DOSAGE REGIMEN AND ADMINISTRATION section for information on pediatric use).

### *Pediatric acute graft-versus-host disease*

In REACH4, 45 pediatric patients with grade II-IV acute GvHD were treated with Jakavi added to corticosteroids to assess the safety, efficacy, and pharmacokinetics of Jakavi. Patients were enrolled into 4 groups based on age:

- Group 1 (Age ≥12 years to <18 years, N=18),
- Group 2 (Age ≥6 years to <12 years, N=12),
- Group 3 (Age ≥2 years to <6 years N=15),
- Group 4 (Age ≥28 days to <2 years N=0).

The doses used in each group are listed in Table 14. Patients were treated for 24 weeks or until discontinuation. Jakavi was administered as either a 5 mg tablet or a capsule/oral solution for pediatric patients <12 years.

Patients were allowed to have received prior systemic treatment for acute GvHD or had treatment-naïve acute GvHD. In addition to Jakavi, patients could have received standard allogeneic stem cell transplantation supportive care including anti-infective medicinal products and transfusion support. Continued use of systemic corticosteroids, calcineurin inhibitors (CNIs) (cyclosporine or tacrolimus), and/or topical corticosteroid therapies was allowed per institutional guidelines. Tapering of Jakavi was allowed after the Day 56 visit.

Male and female patients accounted for 62.2% (n=28) and for 37.8% (n=17) patients, respectively. Twenty-seven patients (60.0%) had underlying malignancy, most frequently leukemia (26 patients, 57.8%).

Among the 45 pediatric patients enrolled in REACH4, 13 (28.9%) had treatment naïve acute GvHD and 32 (71.1%) had SR-acute GvHD. At baseline 64.4% of patients had grade II, 26.7% had grade III and 8.9% had grade IV acute GvHD.

The ORR at Day 28 (primary efficacy endpoint) in REACH4 was 84.4% (90% CI: 72.8, 92.5) in all patients, with CR in 48.9% of patients and PR in 35.6% of patients.

Rate of durable ORR at Day 56 (measured by the proportion of patients who achieved a CR or a PR at Day 28 and maintained a CR or a PR at Day 56) was 66.7% in all REACH4 patients.

In REACH2, responses were observed at Day 28 in 4 out of 5 adolescent patients with acute GvHD (3 had a CR and 1 had a PR) in the Jakavi arm and in 3 out of 4 adolescent patients (3 had a CR) in the BAT arm.

The ORR from all Jakavi pediatric patients (adolescent from REACH2 and pediatric patients from REACH4) are presented in Table 14.

**Table 14 Overall response rate at Day 28 in acute graft-versus-host pediatric patients**

| | **REACH4** | | | **REACH2** | **REACH4 and 2** |
|---|---|---|---|---|---|
| | ≥12 y - <18 y<br>Jakavi<br>10 mg bid<br>n (%) | ≥6 y - <12 y<br>Jakavi<br>5 mg bid<br>n (%) | All patients<br>n (%) | ≥12 y - < 18 y<br>Jakavi<br>10 mg bid<br>n (%) | Total pediatric subjects<br>n (%) |
| | N=18 | N=12 | N=45 | N=5 | N=50 |
| ORR<br>Day 28 | 15 (83.3) | 10 (83.3) | 38 (84.4) | 4 (80.0) | 42 (84.0) |
| ORR<br>90% CI | (62.3, 95.3) | (56.2, 97.0) | (72.8, 92.5) | (34.3, 99.0) | (73.0, 91.8) |
| CR | 8 (44.4) | 4 (33.3) | 22 (48.9) | 3 (60.0) | 25 (50.0) |
| PR | 7 (38.9) | 6 (50.0) | 16 (35.6) | 1 (20.0) | 17 (34.0) |

***Pediatric chronic graft-versus-host disease***

In REACH5, 45 pediatric patients with moderate or severe chronic GvHD were treated with Jakavi added to corticosteroids to assess safety, efficacy, and pharmacokinetics of Jakavi. Patients were enrolled into 4 groups based on age:

- Group 1 (Age ≥12 years to <18 years, N=22),
- Group 2 (Age ≥6 years to <12 years, N=16),
- Group 3 (Age ≥2 years to <6 years, N=7),

- Group 4 (Age ≥28 days to <2 years, N=0).

The doses used in each group are listed in Table 15 and patients were treated for 39 cycles/156 weeks or until discontinuation. Jakavi was administered as either a 5 mg tablet or an oral solution for pediatric patients <12 years.

Patients were allowed to have received prior systemic prophylactic therapy for chronic GvHD or had treatment-naive chronic GvHD. In addition to Jakavi, patients could have received standard allogeneic stem cell transplantation supportive care including anti-infective medicinal products and transfusion support. Continued use of topical corticosteroid therapies was allowed per institutional guidelines. Tapering of Jakavi was allowed after the Cycle 7, Day 1 visit.

Male and female patients accounted for 64.4% (n=29) and for 35.6% (n=16) of patients, respectively. Thirty patients (66.7%) had a pre-transplant disease history of underlying malignancy, most frequently leukemia (27 patients, 60%).

Among the 45 pediatric patients enrolled in REACH5, 17 (37.8%) were treatment naïve chronic GvHD patients and 28 (62.2%) had SR-chronic GvHD. The disease was severe in 62.2% of patients and moderate in 37.8% of patients. Thirty-one (68.9%) patients had skin involvement, eighteen (40.0%) had mouth involvement, and fourteen (31.1%) had lung involvement.

The ORR at Cycle 7 Day 1 (primary efficacy endpoint) was 40.0% (90% CI: 27.7, 53.3) in REACH5 pediatric patients (Table 15).

The best overall response (BOR) defined as the proportion of patients who achieved overall response (CR or PR) at any time up to Cycle 7 Day 1 or up to the start of additional systemic therapy for chronic GvHD was 82.2% (90% CI: 70.2, 90.8) in all REACH5 pediatric patients.

In REACH3, responses were observed at Cycle 7 Day 1 in 3 out of 4 adolescent patients with chronic GvHD (all had PR) in the Jakavi arm and in 2 out of 8 adolescent patients (both had PR) in the BAT arm.

The ORR from all Jakavi pediatric patients (adolescent from REACH3 and pediatric patients from REACH5) are presented in Table 15.

**Table 15 Overall response rate at cycle 7 day 1 in chronic graft-versus-host pediatric patients**

| | **REACH5** | | | **REACH3** | **REACH5 and 3** |
|---|---|---|---|---|---|
| | ≥12 y - <18 y<br>Jakavi<br>10 mg bid<br>n (%) | ≥6 y - <12 y<br>Jakavi<br>5 mg bid<br>n (%) | All patients<br><br><br>n (%) | ≥12 y - <18 y<br>Jakavi<br>10 mg bid<br>n (%) | Total pediatric<br>patients<br><br><br>n (%) |
| | N=22 | N=16 | N=45 | N=4 | N=49 |
| ORR<br>Cycle 7 Day 1 | 8 (36.4) | 8 (50.0) | 18 (40.0) | 3 (75.0) | 21 (42.9) |

| | | | | | |
|---|---|---|---|---|---|
| ORR (90% CI)<br><br>Cycle 7 Day 1 | (19.6, 56.1) | (27.9, 72.1) | (27.7, 53.3) | (24.9, 98.7) | (30.8, 55.6) |
| CR | 1 (4.5) | 2 (12.5) | 4 (8.9) | 0 | 4 (8.2) |
| PR | 7 (31.8) | 6 (37.5) | 14 (31.1) | 3 (75.0) | 17 (34.7) |

## NON-CLINICAL SAFETY DATA

Ruxolitinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity and reproductive toxicity studies and in a carcinogenicity study. Target organs associated with the pharmacological action of ruxolitinb in repeated 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 dose of 25 mg twice daily. No effects were noted in an evaluation of the neuropharmacological 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.

Ruxolitinib decreased foetal weight and increased post-implantation loss in animal studies. There was no evidence of a teratogenic effect in rats and rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans. No effects were noted on fertility. In a pre- and post-natal development study, a slightly prolonged gestation period, reduced number of implantation sites, and reduced number of pups delivered were observed. In the pups, decreased mean initial body weights and short period of decreased mean body weight gain were observed. 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.

Reproductive toxicity data are quoted in PREGNANY, 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.

# PHARMACEUTICAL INFORMATION

## Incompatibilities

Not applicable.

## Storage

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. Store in original packaging.

### Presentation 1

Tablets are packed in PVC/PCTFE blisters with Alu foil of 14 tablets, in a box of 56 tablets.
Tablets are packed in PVC/PCTFE blisters with Alu foil in a box of 14 tablets

### Presentation 2

Tablets are packed in PVC/PE/PVdC blisters with Alu foil of 14 tablets, in a box of 56 tablets.
Tablets are packed in PVC/PE/PVdC blisters with Alu foil in a box of 14 tablets.

Not all pack sizes or presentations are marketed

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