Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ruxolitinib Rowex 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg ruxolitinib (as hydrochloride).

Excipient with known effect
Each tablet contains 71 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off white, round (7.5 mm in diameter), biconvex tablet, debossed with "C24" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Myelofibrosis (MF)

Ruxolitinib Rowex is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.

Polycythaemia vera (PV)

Ruxolitinib Rowex is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.

Graft versus host disease (GvHD)

Acute GvHD
Ruxolitinib Rowex is indicated for the treatment of adults and paediatric patients aged 28 days and older with acute graft versus host disease who have inadequate response to corticosteroids or other systemic therapies (see section 5.1).

Chronic GvHD
Ruxolitinib Rowex is indicated for the treatment of adults and paediatric patients aged 6 months and older with chronic graft versus host disease who have inadequate response to corticosteroids or other systemic therapies (see section 5.1).

4.2 Posology and method of administration

Ruxolitinib Rowex treatment should only be initiated by a physician experienced in the administration of anti-cancer medicinal products.

A complete blood cell count, including a white blood cell count differential, must be performed before initiating therapy with Ruxolitinib Rowex.

Complete blood count, including a white blood cell count differential, should be monitored every 2-4 weeks until Ruxolitinib Rowex doses are stabilised, and then as clinically indicated (see section 4.4).

Posology

Starting dose
Myelofibrosis (MF)
The recommended starting dose of Ruxolitinib Rowex in 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 twice daily
100 000 to 200 000/mm^3	15 mg twice daily
75 000 to less than 100 000/mm^3	10 mg twice daily
50 000 to less than 75 000/mm^3	5 mg twice daily

Polycythaemia vera (PV)
The recommended starting dose of Ruxolitinib Rowex in PV is 10 mg twice daily.

Graft versus host disease (GvHD)
The recommended starting dose of Ruxolitinib Rowex in acute and chronic GvHD is based on age (see Tables 2 and 3):

Table 2 Starting doses in acute graft versus host disease

Age group	**Starting dose**
12 years old and above	10 mg twice daily
6 years to less than 12 years old	5 mg twice daily
28 days to less than 6 years old	8 mg/m^2 twice daily

Table 3 Starting doses in chronic graft versus host disease

Age group	**Starting dose**
12 years old and above	10 mg twice daily
6 years to less than 12 years old	5 mg twice daily
6 months to less than 6 years old	8 mg/m^2 twice daily

These starting doses in GvHD can be administered using either the tablet for patients who can swallow tablets whole or an oral solution that might be available from another marketing authorisation holder.

Ruxolitinib Rowex can be added to corticosteroids and/or calcineurin inhibitors (CNIs).

Dose modifications
Doses may be titrated based on efficacy and safety.

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

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

Treatment should be discontinued 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 haemoglobin is below 8 g/dl. After recovery of blood counts above these levels, dosing may be re-started at 5 mg twice daily and gradually increased based on careful monitoring of complete blood cell count, including a white blood cell count differential.

Dose reductions should be considered if the platelet count decreases during treatment as outlined in Table 4, with the goal of avoiding dose interruptions for thrombocytopenia.

Table 4 Dosing recommendation for MF patients with 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**				
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 reductions should also be considered if haemoglobin decreases below 12 g/dl and is recommended if it decreases below 10 g/dl.

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

Table 5 Dosing recommendations during ruxolitinib therapy for GvHD patients with thrombocytopenia, neutropenia or elevated total bilirubin

Laboratory parameter	**Dosing recommendation**
Platelet count <20 000/mm^3	Reduce Ruxolitinib Rowex by one dose level. If platelet count ≥20 000/mm^3 within seven days, dose may be increased to initial dose level, otherwise maintain reduced dose.
Platelet count <15 000/mm^3	Hold Ruxolitinib Rowex 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 Ruxolitinib Rowex by one dose level. Resume at initial dose level if ANC >1 000/mm^3.
Absolute neutrophil count <500/mm^3	Hold Ruxolitinib Rowex 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 upper limit of normal (ULN): Continue Ruxolitinib Rowex at one lower dose level until ≤3.0 x ULN.
	>5.0 to 10.0 x ULN: Hold Ruxolitinib Rowex up to 14 days until total bilirubin ≤3.0 x ULN. If total bilirubin ≤3.0 x ULN dosing may resume at current dose. If not ≤3.0 x ULN after 14 days, resume at one lower dose level.
	>10.0 x ULN: Hold Ruxolitinib Rowex until total bilirubin ≤3.0 x ULN, then resume at one lower dose level.
Total bilirubin elevation caused by GvHD (liver GvHD)	>3.0 x ULN: Continue Ruxolitinib Rowex at one lower dose level until total bilirubin ≤3.0 x ULN.

Dose adjustment with concomitant strong CYP3A4 inhibitors or dual CYP2C9/3A4 inhibitors
When ruxolitinib is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) the unit dose of ruxolitinib should be reduced by approximately 50%, to be administered twice daily (see section 4.4 and 4.5). The concomitant use of ruxolitinib with fluconazole doses greater than 200 mg daily should be avoided.

Special populations

Renal impairment
No specific dose adjustment is needed in patients with mild or moderate renal impairment.

In patients with severe renal impairment (creatinine clearance less than 30 ml/min) the recommended starting dose based on platelet count for MF, PV and GvHD patients should be reduced by approximately 50% to be administered twice daily. Patients should be carefully monitored with regard to safety and efficacy during ruxolitinib treatment (see section 4.4).

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

The recommended starting dose for PV patients with ESRD on haemodialysis 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 5.2).

There are no data for GvHD patients with ESRD.

Hepatic impairment
In MF patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice daily. Subsequent doses should be adjusted based on careful monitoring of safety and efficacy. The recommended starting dose is 5 mg twice daily for PV patients. Ruxolitinib dose can be titrated to reduce the risk of cytopenia (see section 4.4).

In patients with mild, moderate or severe hepatic impairment not related to GvHD, the starting dose of ruxolitinib should be reduced by 50% (see section 5.2).

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

Elderly patients (≥65 years)
No additional dose adjustments are recommended for elderly patients.

Paediatric population
The safety and efficacy of Ruxolitinib Rowex in children and adolescents aged up to 18 years with MF and PV have not been established. No data are available (see section 5.1).

Treatment discontinuation
Treatment of MF and PV may be continued as long as the benefit-risk assessment remains positive. However the treatment should be discontinued after 6 months if there has been no reduction in spleen size or improvement in symptoms since initiation of therapy.

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

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

Method of administration

Ruxolitinib Rowex is to be taken orally, with or without food.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Pregnancy and lactation.

4.4 Special warnings and precautions for use

Myelosuppression

Treatment with ruxolitinib can cause haematological adverse drug reactions, including thrombocytopenia, anaemia and neutropenia. A complete blood count, including a white blood cell count differential, must be performed before initiating therapy with ruxolitinib. Treatment should be discontinued in MF patients with platelet count less than 50 000/mm^3 or absolute neutrophil count less than 500/mm^3 (see section 4.2).

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 is generally reversible and is usually managed by reducing the dose or temporarily withholding ruxolitinib (see sections 4.2 and 4.8). However, platelet transfusions may be required as clinically indicated.

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

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

Neutropenia (absolute neutrophil count <500) was generally reversible and was managed by temporarily withholding ruxolitinib (see sections 4.2 and 4.8).

Complete blood counts should be monitored as clinically indicated and dose adjusted as required (see sections 4.2 and 4.8).

Infections

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

Tuberculosis has been reported in patients receiving ruxolitinib. Before starting treatment, patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations. This can include medical history, possible previous contact with tuberculosis, and/or appropriate screening such as lung x-ray, tuberculin test and/or interferon-gamma release assay, as applicable. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking ruxolitinib. It is recommended to screen for HBV prior to commencing treatment with ruxolitinib. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

Herpes zoster

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

Progressive multifocal leukoencephalopathy

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

Lipid abnormalities/elevations

Treatment with ruxolitinib 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 dyslipidaemia according to clinical guidelines is recommended.

Major adverse cardiac events (MACE)

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years of age and older with at least one additional cardiovascular risk factor, a higher rate of MACE, defined as cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke, was observed with tofacitinib compared to tumour necrosis factor (TNF) inhibitors.

MACE have been reported in patients receiving ruxolitinib. Prior to initiating or continuing therapy with ruxolitinib, the benefits and risks for the individual patient should be considered particularly in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors.

Thrombosis

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years of age and older with at least one additional cardiovascular risk factor, a dose dependent higher rate of venous thromboembolic events (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE) was observed with tofacitinib compared to TNF inhibitors.

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving ruxolitinib. In patients with MF and PV treated with ruxolitinib in clinical studies, the rates of thromboembolic events were similar in ruxolitinib and control-treated patients.

Prior to initiating or continuing therapy with ruxolitinib, the benefits and risks for the individual patient should be considered, particularly in patients with cardiovascular risk factors (see also section 4.4 "Major adverse cardiovascular events (MACE)").

Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

Second primary malignancies.

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years of age and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma, and non-melanoma skin cancer (NMSC) was observed with tofacitinib compared to TNF inhibitors.

Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including ruxolitinib.

Non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and Merkel cell carcinoma, have been reported in patients treated with ruxolitinib. Most of the MF and PV patients had histories of extended treatment with hydroxyurea and prior NMSC or pre-malignant skin lesions. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Special populations

Renal impairment

The starting dose of ruxolitinib should be reduced in patients with severe renal impairment. For patients with end-stage renal disease on haemodialysis 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 (see section 4.2). Subsequent doses (single dose of 20 mg or two doses of 10 mg given 12 hours apart in MF patients; single dose of 10 mg or two doses of 5 mg given 12 hours apart in PV patients) should be administered only on haemodialysis days following each dialysis session. Additional dose modifications should be made with careful monitoring of safety and efficacy. In GvHD patients with severe renal impairment, the starting dose of Ruxolitinib Rowex should be reduced by approximately 50% (see sections 4.2 and 5.2).

Hepatic impairment

The starting dose of ruxolitinib should be reduced by approximately 50% in MF and PV patients with hepatic impairment. Further dose modifications should be based on the safety and efficacy of the medicinal product. In GvHD patients with hepatic impairment not related to GvHD, the starting dose of ruxolitinib should be reduced by approximately 50% (see sections 4.2 and 5.2).

Patients diagnosed with hepatic impairment while receiving ruxolitinib 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 ruxolitinib and as clinically indicated thereafter once their liver function and blood counts have been stabilised.

Interactions

If ruxolitinib is to be co-administered with strong CYP3A4 inhibitors or dual inhibitors of CYP3A4 and CYP2C9 enzymes (e.g. fluconazole), the unit dose of ruxolitinib should be reduced by approximately 50%, to be administered twice daily (see sections 4.2 and 4.5).

More frequent monitoring (e.g. twice a week) of haematology parameters and of clinical signs and symptoms of ruxolitinib-related adverse drug reactions is recommended while on strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes.

The concomitant use of cytoreductive therapies with ruxolitinib was associated with manageable cytopenias (see section 4.2 for dose modifications during cytopenias).

Withdrawal effects

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

Excipients

Ruxolitinib Rowex contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Interactions resulting in dose reduction of ruxolitinib

CYP3A4 inhibitors
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 ruxolitinib (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 ruxolitinib with strong CYP3A4 inhibitors the unit dose of ruxolitinib should be reduced by approximately 50%, to be administered twice daily.

Patients should be closely monitored (e.g. twice weekly) for cytopenias and dose titrated based on safety and efficacy (see section 4.2).

Dual CYP2C9 and CYP3A4 inhibitors
In healthy subjects co-administration of ruxolitinib (10 mg single dose) with a dual CYP2C9 and CYP3A4 inhibitor, fluconazole, resulted in ruxolitinib C_{max} and AUC that were higher by 47% and 232%, respectively, than with ruxolitinib alone.

50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole). Avoid the concomitant use of ruxolitinib with fluconazole doses greater than 200 mg daily.

Enzyme inducers

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 4.2).

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 ruxolitinib 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 Emax. It is possible that in the individual patient, an increase of the ruxolitinib dose is needed when initiating treatment with a strong enzyme inducer.

Other interactions to be considered affecting ruxolitinib

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 500 mg 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.

Effects of ruxolitinib on other medicinal products

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 systemic exposure of substrates of these transporters, such as dabigatran etexilate, 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.

A study in healthy subjects indicated that ruxolitinib did not inhibit the metabolism of the oral CYP3A4 substrate midazolam. Therefore, no increase in exposure of CYP3A4 substrates is anticipated when combining them with ruxolitinib. Another study in healthy subjects indicated that ruxolitinib does not affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel. Therefore, it is not anticipated that the contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of ruxolitinib in pregnant women.

Animal studies have shown that ruxolitinib is embryotoxic and foetotoxic. Teratogenicity was not observed in rats or rabbits. However, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans (see section 5.3). The potential risk for humans is unknown. As a precautionary measure, the use of Ruxolitinib Rowex during pregnancy is contraindicated (see section 4.3).

Women of childbearing potential/Contraception

Women of child-bearing potential should use effective contraception during the treatment with ruxolitinib. In case pregnancy should occur during treatment with ruxolitinib, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the foetus (see section 5.3).

Breast-feeding

Ruxolitinib Rowex must not be used during breast-feeding (see section 4.3) and breast-feeding should therefore be discontinued when treatment is started. It is unknown whether ruxolitinib and/or its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. Available pharmacodynamic/toxicological data in animals have shown excretion of ruxolitinib and its metabolites in milk (see section 5.3).

Fertility

There are no human data on the effect of ruxolitinib on fertility. In animal studies, no effect on fertility was observed.

4.7 Effects on ability to drive and use machines

Ruxolitinib has no or negligible sedating effect. However, patients who experience dizziness after the intake of ruxolitinib should refrain from driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

Myelofibrosis

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

Haematological adverse drug reactions (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 three most frequent non-haematological adverse drug reactions were bruising (33.3%), other bleeding (including epistaxis, post-procedural haemorrhage and haematuria) (24.3%) and dizziness (21.9%).

The three most frequent non-haematological laboratory abnormalities identified as adverse reactions were increased alanine aminotransferase (40.7%), increased aspartate aminotransferase (31.5%) and hypertriglyceridaemia (25.2%). In phase 3 clinical studies in MF, neither CTCAE grade 3 or 4 hypertriglyceridaemia or increased aspartate aminotransferase, nor CTCAE grade 4 increased alanine aminotransferase or hypercholesterolaemia were observed.

Discontinuation due to adverse events, regardless of causality, was observed in 30.0% of patients.

Polycythaemia vera
The most frequently reported adverse drug reactions were anaemia and increased alanine aminotransferase.

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

The three most frequent non-haematological adverse reactions were weight gain (20.3%), dizziness (19.4%) and headache (17.9%).

The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) identified as adverse reactions were increased alanine aminotransferase (45.3%), increased aspartate aminotransferase (42.6%), and hypercholesterolaemia (34.7%). No CTCAE grade 4 increased alanine aminotransferase or hypercholesterolaemia, and one CTCAE grade 4 increased aspartate aminotransferase were observed.

Discontinuation due to adverse events, regardless of causality, was observed in 19.4% of patients.

Acute GvHD
The most frequently reported adverse drug reactions in REACH2 (adult and adolescent patients) were thrombocytopenia, anaemia, neutropenia, increased alanine aminotransferase and increased aspartate aminotransferase. The most frequently reported adverse drug reactions in the pool of paediatric patients (adolescents from REACH2 and paediatric patients from REACH4) were anaemia, neutropenia, increased alanine aminotransferase, hypercholesterolaemia and thrombocytopenia.

Haematological laboratory abnormalities: identified as adverse drug reactions in REACH2 (adult and adolescent patients) and in the pool of paediatric patients (REACH2 and REACH4) included thrombocytopenia (85.2% and 55.1%), anaemia (75.0% and 70.8%) and neutropenia (65.1% and 70.0%), respectively. Grade 3 anaemia was reported in 47.7% of patients in REACH2 and in 45.8% of patients in the paediatric pool. Grade 3 and 4 thrombocytopenia were reported in 31.3% and 47.7% of patients in REACH2 and in 14.6% and 22.4% of patients in the paediatric pool, respectively. Grade 3 and 4 neutropenia were reported in 17.9% and 20.6% of patients in REACH2 and in 32.0% and 22.0% of patients in the paediatric pool, respectively.

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

The most frequent non-haematological laboratory abnormalities identified as adverse drug reactions in REACH2 (adult and adolescent patients) and in the pool of paediatric patients (REACH2 and REACH4) were increased alanine aminotransferase (54.9% and 63.3%), increased aspartate aminotransferase (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 alanine aminotransferase was reported in 17.6% of patients in REACH2 and 27.3% of patients in the paediatric pool

Discontinuation due to adverse events, regardless of causality, was observed in 29.4% of patients in REACH2 and in 21.6% of patients in the paediatric pool.

Chronic GvHD
The most frequently reported adverse drug reactions in REACH3 (adult and adolescent patients) were anaemia, hypercholesterolemia and increased aspartate aminotransferase. The most frequently reported adverse drug reactions in the pool of paediatric patients (adolescents from REACH3 and paediatric patients from REACH5) were neutropenia, hypercholesterolaemia and increased alanine aminotransferase.

Haematological laboratory abnormalities identified as adverse drug reactions in REACH3 (adult and adolescent patients) and in the pool of paediatric patients (REACH3 and REACH5) included 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 patients in REACH3 and in 17.0% of patients in the paediatric pool. Grade 3 and 4 neutropenia were reported in 9.5% and 6.7% of patients in REACH3 and in 17.3% and 11.1% of patients in the paediatric pool, respectively. 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 patients in the paediatric pool, respectively.

The most frequent non-haematological adverse drug reactions in REACH3 (adult and adolescent patients) and in the pool of paediatric patients (REACH3 and REACH5) were hypertension (15.0% and 14.5%) and headache (10.2% and 18.2%), respectively.

The most frequent non-haematological laboratory abnormalities identified as adverse drug reactions in REACH3 (adult and adolescent patients) and in the pool of paediatric patients (REACH3 and REACH5) were hypercholesterolaemia (52.3% and 54.9%), increased aspartate aminotransferase (52.2% and 45.5%) and increased alanine aminotransferase (43.1% and 50.9%). The majority were grade 1 and 2, however grade 3 laboratory abnormalities reported in the pool of paediatric patients included increased alanine aminotransferase (14.9%) and increased aspartate aminotransferase (11.5%).

Discontinuation due to adverse events, regardless of causality, was observed in 18.1% of patients in REACH3 and in 14.5% of patients in the paediatric pool.

Tabulated list of adverse reactions

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

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

The safety of ruxolitinib 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 initially randomised to ruxolitinib (n=152) and patients who received ruxolitinib after crossing over from the best available therapy (BAT) arm (n=49). The median exposure upon which the adverse drug reaction frequency categories were based was 8.9 weeks (range 0.3 to 66.1 weeks). In the pool of paediatric patients ≥2 years of age (6 patients in REACH2 and 45 patients in REACH4), the median exposure was 16.7 weeks (range 1.1 to 48.9 weeks).

The safety of ruxolitinib 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 initially randomised to ruxolitinib (n=165) and patients who received ruxolitinib after crossing over from BAT (n=61). The median exposure upon which the adverse drug reaction frequency categories were based was 41.4 weeks (range 0.7 to 127.3 weeks). In the pool of paediatric patients ≥2 years of age (10 patients in REACH3 and 45 patients in REACH5), the median exposure was 57.1 weeks (range 2.1 to 155.4 weeks).

In the clinical study programme the severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1=mild, grade 2=moderate, grade 3=severe, grade 4=life-threatening or disabling, grade 5=death.

Adverse drug reactions from clinical studies in MF and PV (Table 6) and in acute and chronic GvHD (Table 7) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: 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); not known (cannot be estimated from the available data).

Table 6 Frequency category of adverse drug reactions reported in the phase 3 studies in MF and PV

Adverse drug reaction	Frequency category for MF patients	Frequency category for PV patients
Infections and infestations		
Urinary tract infections[d]	Very common	Very common
Herpes zoster[d]	Very common	Very common
Pneumonia	Very common	Common
Sepsis	Common	Uncommon
Tuberculosis	Uncommon	Not known[e]
HBV reactivation	Not known[e]	Uncommon
Blood and lymphatic system disorders[a,d]		
Anaemia[a]		
CTCAE[c] grade 4 (<6.5g/dl)	Very common	Uncommon
CTCAE[c] grade 3 (<8.0 – 6.5 g/dl)	Very common	Common
Any CTCAE[c] grade	Very common	Very common
Thrombocytopenia[a]		
CTCAE[c] grade 4 (<25 000/mm^3)	Common	Uncommon
CTCAE[c] grade 3 (50 000 – 25 000/mm^3)	Very common	Common
Any CTCAE[c] grade	Very common	Very common

Neutropenia[a]		
CTCAE[c] grade 4 (<500/mm^3)	Common	Uncommon
CTCAE[c] grade 3 (<1 000 – 500/mm^3)	Common	Uncommon
Any CTCAE[c] grade	Very common	Common
Pancytopenia[a,b]	Common	Common
Bleeding (any bleeding including intracranial, and gastrointestinal bleeding, bruising and other bleeding)	Very common	Very common
Bruising	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
Metabolism and nutrition disorders		
Hypercholesterolaemia[a] any CTCAE[c] grade	Very common	Very common
Hypertriglyceridaemia[a] any CTCAE[c] grade	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		
Elevated lipase, any CTCAE[c] grade	Very common	Very common
Constipation	Very common	Very common
Flatulence	Common	Common
Hepatobiliary disorders		
Increased alanine aminotransferase[a]		
CTCAE[c] grade 3 (> 5x – 20 x ULN)	Common	Common
Any CTCAE[c] grade	Very common	Very common
Increased aspartate aminotransferase[a]		
Any CTCAE[c] grade	Very common	Very common
Vascular disorders		
Hypertension	Very common	Very common

[a] Frequency is based on new or worsened laboratory abnormalities compared to baseline.
[b] Pancytopenia is defined as haemoglobin level <100 g/l, platelet count <100x10^9/l, and neutrophil count <1.5x10^9/l (or low white blood cell count of grade 2 if neutrophil count is missing), simultaneously in the same lab assessment
[c] Common Terminology Criteria for Adverse Events (CTCAE) version 3.0; grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening
[d] These adverse drug reactions are discussed in the text.
[e] Adverse drug reactions derived from post-marketing experience

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 clinical studies in MF the total symptom score for MF symptoms gradually returned to baseline value within 7 days after dose discontinuation (see section 4.4).

Table 7 Frequency category of adverse drug reactions reported in clinical studies in GvHD

	Acute GvHD (REACH2)	**Acute GvHD (Paediatric pool)**	**Chronic GvHD (REACH3)**	**Chronic GvHD (Paediatric pool)**
Adverse drug reaction	**Frequency category**	**Frequency category**	**Frequency category**	**Frequency category**
Infections and infestations				

CMV infections	Very common	Very common	Common	Common
CTCAE[3] grade ≥3	Very common	Common	Common	N/A[5]
Sepsis	Very common	Common	-[6]	-[6]
CTCAE grade ≥3[4]	Very common	Common	-[6]	-[6]
Urinary tract infections	Very common	Common	Common	Common
CTCAE grade ≥3	Common	Common	Common	Common
BK virus infections	-[6]	-[6]	Common	Common
CTCAE grade ≥3	-[6]	-[6]	Uncommon	N/A[5]
Blood and lymphatic system disorders				
Thrombocytopenia[1]	Very common	Very common	Very common	Very common
CTCAE grade 3	Very common	Very common	Common	Common
CTCAE grade 4	Very common	Very common	Very common	Very common
Anaemia[1]	Very common	Very common	Very common	Very common
CTCAE grade 3	Very common	Very common	Very common	Very common
Neutropenia[1]	Very common	Very common	Very common	Very common
CTCAE grade 3	Very common	Very common	Common	Very common
CTCAE grade 4	Very common	Very common	Common	Very common
Pancytopenia[1,2]	Very common	Very common	-[6]	-[6]
Metabolism and nutrition disorders				
Hypercholesterolaemia[1]	Very common	Very common	Very common	Very common
CTCAE grade 3	Common	N/A[5]	Common	Common
CTCAE grade 4	Common	N/A[5]	Uncommon	Common
Weight gain	-[6]	-[6]	Common	Common
CTCAE grade ≥3	-[6]	-[6]	N/A[5]	Common
Nervous system disorders				
Headache	Common	Common	Very common	Very common
CTCAE grade ≥3	Uncommon	N/A[5]	Common	Common
Vascular disorders				
Hypertension	Very common	Very common	Very common	Very common
CTCAE grade ≥3	Common	Very common	Common	Common
Gastrointestinal disorders				
Increased lipase[1]	-[6]	-[6]	Very common	Very common
CTCAE grade 3	-[6]	-[6]	Common	Common
CTCAE grade 4	-[6]	-[6]	Uncommon	Common
Increased amylase[1]	-[6]	-[6]	Very common	Very common
CTCAE grade 3	-[6]	-[6]	Common	Common
CTCAE grade 4	-[6]	-[6]	Common	N/A[5]
Nausea	Very	Common	-[6]	-[6]

	common			
CTCAE grade ≥3	Uncommon	N/A[5]	-[6]	-[6]
Constipation	-[6]	-[6]	Common	Common
CTCAE grade ≥3	-[6]	-[6]	N/A[5]	N/A[5]
Hepatobiliary disorders				
Increased alanine aminotransferase[1]	Very common	Very common	Very common	Very common
CTCAE grade 3	Very common	Very common	Common	Very common
CTCAE grade 4	Common	N/A[5]	Uncommon	Common
Increased aspartate aminotransferase[1]	Very common	Very common	Very common	Very common
CTCAE grade 3	Common	Common	Common	Very common
CTCAE grade 4	N/A[5]	N/A[5]	Uncommon	N/A[5]
Musculoskeletal and connective tissue disorders				
Increased blood creatine phosphokinase[1]	-[6]	-[6]	Very common	Very common
CTCAE grade 3	-[6]	-[6]	Common	N/A[5]
CTCAE grade 4	-[6]	-[6]	Common	N/A[5]
Renal and urinary disorders				
Increased blood creatinine[1]	-[6]	-[6]	Very common	Common
CTCAE grade 3	-[6]	-[6]	Common	N/A[5]
CTCAE grade 4	-[6]	-[6]	N/A[5]	N/A[5]

[1] Frequency is based on new or worsened laboratory abnormalities compared to baseline.
[2] Pancytopenia is defined as haemoglobin level <100 g/l, platelet count <100 x 10^9/l, and neutrophil count <1.5 x 10^9/l (or low white blood cell count of grade 2 if neutrophil count is missing), simultaneously in the same laboratory assessment.
[3] CTCAE Version 4.03.
[4] Grade ≥3 sepsis includes 20 (10%) grade 5 events in REACH2. There were no grade 5 events in the paediatric pool.
[5] Not applicable: no cases reported
[6] "-": not an identified adverse drug reaction in this indication

Description of selected adverse drug reactions

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

In patients receiving ruxolitinib 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 ruxolitinib -treated MF patients and 37.7% of placebo-treated MF patients received red blood cell transfusions during randomised treatment. In the COMFORT-II study the rate of packed red blood cell transfusions was 53.4% in the ruxolitinib arm and 41.1% in the best available therapy arm.

In the randomised period of the pivotal studies, anaemia was less frequent in PV patients than in MF patients (40.8% versus 82.4%). In the PV population, the CTCAE grade 3 and 4 events were reported in 2.7%, while in the MF patients the frequency was 42.56%.

In the phase 3 acute (REACH2) and chronic (REACH3) GvHD studies, anaemia (all grades) was reported in 75.0% and 68.6% of patients, CTCAE grade 3 was reported in 47.7% and 14.8% of patients, respectively. In paediatric patients with acute and chronic GvHD, anaemia (all grades) was reported in 70.8% and 49.1% of patients, CTCAE grade 3 was reported in 45.8% and 17.0% of patients, respectively.

Thrombocytopenia

In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 000/mm^3 was 14 days. During the randomised period, platelet transfusions were administered to 4.7% of patients receiving ruxolitinib and to 4.0% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving ruxolitinib 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 ruxolitinib had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet count >200 000/mm^3 (64.2% versus 38.5%).

In the randomised period of the pivotal studies, the rate of patients experiencing thrombocytopenia was lower in PV (16.8%) patients compared to MF (69.8%) patients. The frequency of severe (i.e. CTCAE grade 3 and 4) thrombocytopenia was lower in PV (2.7%) than in MF (11.6%) patients.

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

Neutropenia
In the phase 3 clinical studies in MF, in patients who developed grade 3 or 4 neutropenia, the median time to onset was 12 weeks. During the randomised period, dose holding or reductions due to neutropenia were reported in 1.0% of patients, and 0.3% of patients discontinued treatment because of neutropenia.

In the randomised period of the phase 3 studies in PV patients, neutropenia was reported in 1.6% of patients exposed to ruxolitinib compared to 7% in reference treatments. In the ruxolitinib arm one patient developed CTCAE grade 4 neutropenia. An extended follow-up of patients treated with ruxolitinib showed 2 patients reporting CTCAE grade 4 neutropenia.

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

Bleeding
In the phase 3 pivotal studies in MF bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 32.6% of patients exposed to ruxolitinib 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 ruxolitinib 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 ruxolitinib compared with the reference treatments (21.3% versus 11.6%). Intracranial bleeding was reported in 1% of patients exposed to ruxolitinib and 0.9% exposed to reference treatments. Gastrointestinal bleeding was reported in 5.0% of patients exposed to ruxolitinib 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 ruxolitinib and 10.3% treated with reference treatments.

During the long-term follow-up of phase 3 clinical studies in MF, the cumulative frequency of bleeding events increased proportionally to the increase in the follow-up time. Bruising events were the most frequently reported bleeding events (33.3%). Intracranial and gastrointestinal bleeding events were reported in 1.3% and 10.1% of patients respectively.

In the comparative period of phase 3 studies in PV patients, bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 16.8% of patients treated with ruxolitinib, 15.3% of patients receiving best available therapy in RESPONSE study and 12.0% of patients receiving best available therapy in RESPONSE 2 study. Bruising was reported in 10.3% of patients treated with ruxolitinib, 8.1% of patients receiving best available therapy in RESPONSE study and 2.7% of patients receiving best available therapy in RESPONSE 2 study. No intracranial bleeding or gastrointestinal haemorrhage events were reported in patients receiving ruxolitinib. One patient treated with ruxolitinib 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 8.7% of patients treated with ruxolitinib, 6.3% of patients treated with best available therapy in RESPONSE study and 6.7% of patients treated with best available therapy in RESPONSE 2 study.

During the long-term follow-up of phase 3 studies in PV, the cumulative frequency of bleeding events increased proportionally to the increase in the follow-up time. Bruising events were the most frequently reported bleeding events (17.4%). Intracranial and gastrointestinal bleeding events were reported in 0.3% and 3.5% of patients respectively.

In the comparative period of the phase 3 acute GvHD study (REACH2), bleeding events were reported in 25.0% and 22.0% of patients in the ruxolitinib and BAT arms respectively. The sub-groups of bleeding events were generally similar between treatment arms: bruising events (5.9% in ruxolitinib vs. 6.7% in BAT arm), gastrointestinal events (9.2% vs. 6.7%) and other haemorrhage events (13.2% vs. 10.7%). Intracranial bleeding events were reported in 0.7% of patients in the BAT arm and in no patients in the ruxolitinib arm. In paediatric patients, the frequency of bleeding events was 23.5%. Events reported in ≥5% of patients were cystitis haemorrhagic and epistaxis (5.9% each). No intracranial bleeding events were reported in paediatric patients.

In the comparative period of the phase 3 chronic GvHD study (REACH3), bleeding events were reported in 11.5% and 14.6% of patients in the ruxolitinib and BAT arms respectively. The sub-groups of bleeding events were generally similar between treatment arms: bruising events (4.2% in ruxolitinib vs. 2.5% in BAT arm), gastrointestinal events (1.2% vs. 3.2%) and other haemorrhage events (6.7% vs. 10.1%). In paediatric patients, the frequency of bleeding events was 9.1%. The reported events were epistaxis, haematochezia, haematoma, post-procedural haemorrhage, and skin haemorrhage (1.8% each). No intracranial bleeding events were reported in patients with chronic GvHD.

Infections
In the phase 3 pivotal studies in MF, grade 3 or 4 urinary tract infection was reported in 1.0% of patients, herpes zoster in 4.3% and tuberculosis in 1.0%. In phase 3 clinical studies sepsis was reported in 3.0% of patients. An extended follow-up of patients treated with ruxolitinib showed no trends towards an increase in the rate of sepsis over time.

In the randomised period of the phase 3 studies in PV patients, one (0.5%) CTCAE grade 3 and no grade 4 urinary tract infection was reported. The rate of herpes zoster was similar in PV (4.3%) patients and MF (4.0%) patients. There was one report of CTCAE grade 3 post-herpetic neuralgia amongst the PV patients. Pneumonia was reported in 0.5% of patients treated with ruxolitinib compared to 1.6% of patients in reference treatments. No patients in the ruxolitinib arm reported sepsis or tuberculosis.

During long-term follow-up of phase 3 studies in PV, frequently reported infections were urinary tract infections (11.8%), herpes zoster (14.7%) and pneumonia (7.1%). Sepsis was reported in 0.6% of patients. No patients reported tuberculosis in long-term follow-up.

In the phase 3 acute GvHD study (REACH2), during the *comparative period*, urinary tract infections were reported in 9.9% (grade ≥3, 3.3%) of patients in the ruxolitinib arm compared to 10.7% (grade ≥3, 6.0%) in the BAT arm. CMV infections were reported in 28.3% (grade ≥3, 9.3%) of patients in the ruxolitinib arm compared to 24.0% (grade ≥3, 10.0%) in the BAT arm. Sepsis events were reported in 12.5% (grade ≥3, 11.1%) of patients in the ruxolitinib arm compared to 8.7% (grade ≥3, 6.0%) in the BAT arm. BK virus infection was reported only in the ruxolitinib arm in 3 patients with one grade 3 event. During *extended follow-up* of patients treated with ruxolitinib, urinary tract infections were reported in 17.9% (grade ≥3, 6.5%) of patients and CMV infections were reported in 32.3% (grade ≥3, 11.4%) of patients. CMV infection with organ involvement was seen in very few patients; CMV colitis, CMV enteritis and CMV gastrointestinal infection of any grade were reported in four, two and one patients, respectively. Sepsis events, including septic shock, of any grade were reported in 25.4% (grade ≥3, 21.9%) of patients. Urinary tract infections and sepsis events were reported with lower frequency in paediatric patients with acute GvHD (9.8% each) compared to adult and adolescent patients. CMV infections were reported in 31.4% of paediatric patients (grade 3, 5.9%).

In the phase 3 chronic GvHD study (REACH3), during the *comparative period*, urinary tract infections were reported in 8.5% (grade ≥3, 1.2%) of patients in the ruxolitinib arm compared to 6.3% (grade ≥3, 1.3%) in the BAT arm. BK virus infection was reported in 5.5% (grade ≥3, 0.6%) of patients in the ruxolitinib arm compared to 1.3% in the BAT arm. CMV infections were reported in 9.1% (grade ≥3, 1.8%) of patients in the ruxolitinib arm compared to 10.8% (grade ≥3, 1.9%) in the BAT arm. Sepsis events were reported in 2.4% (grade ≥3, 2.4%) of patients in the ruxolitinib arm compared to 6.3% (grade ≥3, 5.7%) in the BAT arm. During *extended follow-up* of patients treated with ruxolitinib, urinary tract infections and BK virus infections were reported in 9.3% (grade ≥3, 1.3%) and 4.9% (grade ≥3, 0.4%) of patients, respectively. CMV infections and sepsis events were reported in 8.8% (grade ≥3, 1.3%) and 3.5% (grade ≥3, 3.5%) of patients, respectively. In paediatric patients with chronic GvHD, urinary tract infections 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. CMV infections occurred in 7.3% (no grade ≥3) of patients.

Elevated lipase

In the randomised period of the RESPONSE study, the worsening of lipase values was higher in the ruxolitinib arm compared to the control arm, mainly due to the differences among grade 1 elevations (18.2% vs 8.1%). Grade ≥2 elevations were similar between treatment arms. In RESPONSE 2, the frequencies were comparable between the ruxolitinib and the control arm (10.8% vs 8%). During long-term follow-up of phase 3 PV studies, 7.4% and 0.9% of patients reported grade 3 and grade 4 elevation of lipase values. No concurrent signs and symptoms of pancreatitis with elevated lipase values were reported in these patients.

In phase 3 studies in MF, high lipase values were reported in 18.7% and 19.3% of patients in the ruxolitinib arms compared to 16.6% and 14.0% in the control arms in COMFORT-I and COMFORT-II studies, respectively. In patients with elevated lipase values, no concurrent signs and symptoms of pancreatitis were reported.

In the *comparative period* of the phase 3 acute GvHD study (REACH2), new or worsened lipase values were reported in 19.7% of patients in the ruxolitinib arm compared to 12.5% in the BAT arm; corresponding grade 3 (3.1% vs 5.1%) and grade 4 (0% vs 0.8%) increases were similar. During *extended follow-up* of patients treated with ruxolitinib, increased lipase values were reported in 32.2% of patients; grade 3 and 4 were reported in 8.7% and 2.2% of patients respectively. Elevated lipase was reported in 20.4% of paediatric patients (grade 3 and 4: 8.5% and 4.1%, respectively).

In the *comparative period* of the phase 3 chronic GvHD study (REACH3), new or worsened lipase values were reported in 32.1% of patients in the ruxolitinib arm compared to 23.5% in the BAT arm; corresponding grade 3 (10.6% vs 6.2%) and grade 4 (0.6% vs 0%) increases were similar. During *extended follow-up* of patients treated with ruxolitinib, increased lipase values were reported in 35.9% of patients; grade 3 and 4 were observed in 9.5% and 0.4% of patients, respectively. Elevated lipase was reported with lower frequency (20.4%, grade 3 and 4: 3.8% and 1.9%, respectively) in paediatric patients.

Increased systolic blood pressure
In the phase 3 pivotal clinical studies in MF 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 (MF patients) the mean increase from baseline in systolic BP was 0-2 mmHg on ruxolitinib 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 MF patients.

In the randomised period of the pivotal study in PV patients, the mean systolic blood pressure increased by 0.65 mmHg in the ruxolitinib arm versus a decrease of 2 mmHg in the BAT arm.

Special populations

Paediatric patients
A total of 106 patients aged 2 to <18 years with GvHD were analysed for safety: 51 patients (45 patients in REACH4 and 6 patients in REACH2) in acute GvHD studies and 55 patients (45 patients in REACH5 and 10 patients in REACH3) in the chronic GvHD studies. The safety profile observed in paediatric patients who received treatment with ruxolitinib was similar to that observed in adult patients.

Elderly
A total of 29 patients in study REACH2 and 25 patients in REACH3 aged >65 years and treated with ruxolitinib were analysed for safety. Overall, no new safety concerns were identified and the safety profile in patients >65 years old is generally consistent with that of patients aged 18-65 years old.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

There is no known antidote for overdoses with ruxolitinib. 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, anaemia and thrombocytopenia. Appropriate supportive treatment should be given.

Haemodialysis is not expected to enhance the elimination of ruxolitinib.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EJ01

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 signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function.

MF and PV are myeloproliferative neoplasms known to be associated with dysregulated JAK1 and JAK2 signalling. 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 signalling regardless of JAK2V617F mutation status. Activating mutations in JAK2 (V617F or exon 12) are found in >95% of PV patients.

Ruxolitinib inhibits JAK-STAT signalling and cell proliferation of cytokine-dependent cellular models of haematological malignancies, as well as of Ba/F3 cells rendered cytokine-independent by expressing the JAK2V617F mutated protein, with IC_{50} ranging from 80-320 nM.

JAK-STAT signalling pathways play a role in regulating the development, proliferation, and activation of several immune cell types important for GvHD pathogenesis.

Pharmacodynamic effects

Ruxolitinib inhibits cytokine-induced STAT3 phosphorylation in whole blood from healthy subjects, MF patients 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 TNFα, IL-6 and CRP in subjects with MF were decreased following treatment with ruxolitinib. MF patients did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with PV also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with ruxolitinib.

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

Clinical efficacy and safety

Myelofibrosis

Two randomised phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with MF (primary MF, post-polycythaemia vera MF or post-essential thrombocythaemia MF). In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate-2 or high risk based on the International Working Group (IWG) Consensus Criteria. The starting dose of ruxolitinib was based on platelet count. Patients with platelet counts ≤100 000/mm^3 were not eligible for enrolment in COMFORT studies but 69 patients were enrolled in the EXPAND study, a Phase Ib, open label, dose-finding study in patients with MF (primary MF, post-polycythaemia vera MF or post-essential thrombocythaemia MF) and baseline platelet counts ≥50 000 and <100 000/mm^3.

COMFORT-I was a double-blind, randomised, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. The primary efficacy endpoint was proportion of subjects achieving ≥35% reduction from baseline in spleen volume at week 24 as measured by Magnetic Resonance Imaging (MRI) or Computed Tomography (CT).

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

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

Secondary endpoints included proportion of patients achieving a ≥35% reduction of spleen volume from baseline at week 24 and duration of maintenance of a ≥35% reduction from baseline spleen volume.

In COMFORT-I and COMFORT-II, patient baseline demographics and disease characteristics were comparable between the treatment arms.

Table 8 Percentage of patients with ≥35% reduction from baseline in spleen volume at week 24 in COMFORT-I and at week 48 in COMFORT-II (ITT)

	COMFORT-I		COMFORT-II	
	ruxolitinib (N=155)	Placebo (N=153)	ruxolitinib (N=144)	Best available therapy (N=72)
Time points	Week 24		Week 48	
Number (%) of subjects with spleen volume reduced by ≥35%	65 (41.9)	1 (0.7)	41(28.5)	0
95% confidence intervals	34.1, 50.1	0, 3.6	21.3, 36.6	0.0, 5.0
p-value	<0.0001		<0.0001	

A significantly higher proportion of patients in the ruxolitinib group achieved ≥35% reduction from baseline in spleen volume (Table 8) regardless of the presence or absence of the JAK2V617F mutation (Table 9) or the disease subtype (primary MF, post-polycythaemia vera MF, post-essential thrombocythaemia MF).

Table 9 Percentage of patients with ≥35% reduction from baseline in spleen volume by JAK mutation status (safety set)

	COMFORT-I				COMFORT-II			
	ruxolitinib		Placebo		ruxolitinib		Best available therapy	
JAK mutation status	Positive (N=113) n (%)	Negative (N=40) n (%)	Positive (N=121) n (%)	Negative (N=27) n (%)	Positive (N=110) n (%)	Negative (N=35) n (%)	Positive (N=49) n (%)	Negative (N=20) n (%)
Number (%) of subjects with spleen volume reduced by ≥35%	54 (47.8)	11 (27.5)	1 (0.8)	0	36 (32.7)	5 (14.3)	0	0
Time point	After 24 weeks				After 48 weeks			

The probability of maintaining spleen response (≥35% reduction) to ruxolitinib for at least 24 weeks was 89% in COMFORT-I and 87% in COMFORT-II; 52% maintained spleen responses for at least 48 weeks in COMFORT-II.

In COMFORT-I, 45.9% subjects in the ruxolitinib group achieved a ≥50% improvement from baseline in the week 24 total symptom score (measured using MFSAF diary v2.0), as compared to 5.3% in the placebo group (p<0.0001 using chi-square test). The mean change in the global health status at week 24, as measured by EORTC QLQ C30 was +12.3 for ruxolitinib and -3.4 for placebo (p<0.0001).

In COMFORT-I, after a median follow-up of 34.3 months, the death rate in patients randomised to the ruxolitinib arm was 27.1% versus 35.1% in patients randomised to placebo; HR 0.687; 95% CI 0.459-1.029; p=0.0668.

In COMFORT-I, after a median follow–up of 61.7 months, the death rate in patients randomised to the ruxolitinib arm was 44.5% (69 of 155 patients) versus 53.2% (82 of 154) in patients randomised to placebo. There was a 31% reduction in the risk of death in the ruxolitinib arm as compared to placebo (HR 0.69; 95% CI 0.50-0.96; p=0.025).

In COMFORT-II, after a median follow-up of 34.7 months, the death rate in patients randomised to ruxolitinib was 19.9% versus 30.1% in patients randomised to best available treatment (BAT); HR 0.48; 95% CI 0.28-0.85; p=0.009. In both studies, the lower death rates noted in the ruxolitinib arm were predominantly driven by the results obtained in the post polycythaemia vera and post essential thrombocythaemia subgroups.

In COMFORT-II, after a median follow-up of 55.9 months, the death rate in patients randomised to the ruxolitinib arm was 40.4% (59 of 146 patients) versus 47.9% (35 of 73 patients) in patients randomized to best available therapy (BAT). There was a 33% reduction in risk of death in the ruxolitinib arm compared to the BAT arm (HR 0.67; 95% CI 0.44-1.02; p=0.062).

Polycythaemia vera
A randomised, 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. 110 patients were randomised to the ruxolitinib arm and 112 patients to the BAT arm. The starting dose of ruxolitinib was 10 mg twice daily. Doses were then adjusted in individual patients based on tolerability and efficacy with a maximum dose of 25 mg twice daily. BAT was selected by the investigator on a patient-by-patient basis and included hydroxyurea (59.5%), interferon/pegylated interferon (11.7%), anagrelide (7.2%), pipobroman (1.8%) and observation (15.3%).

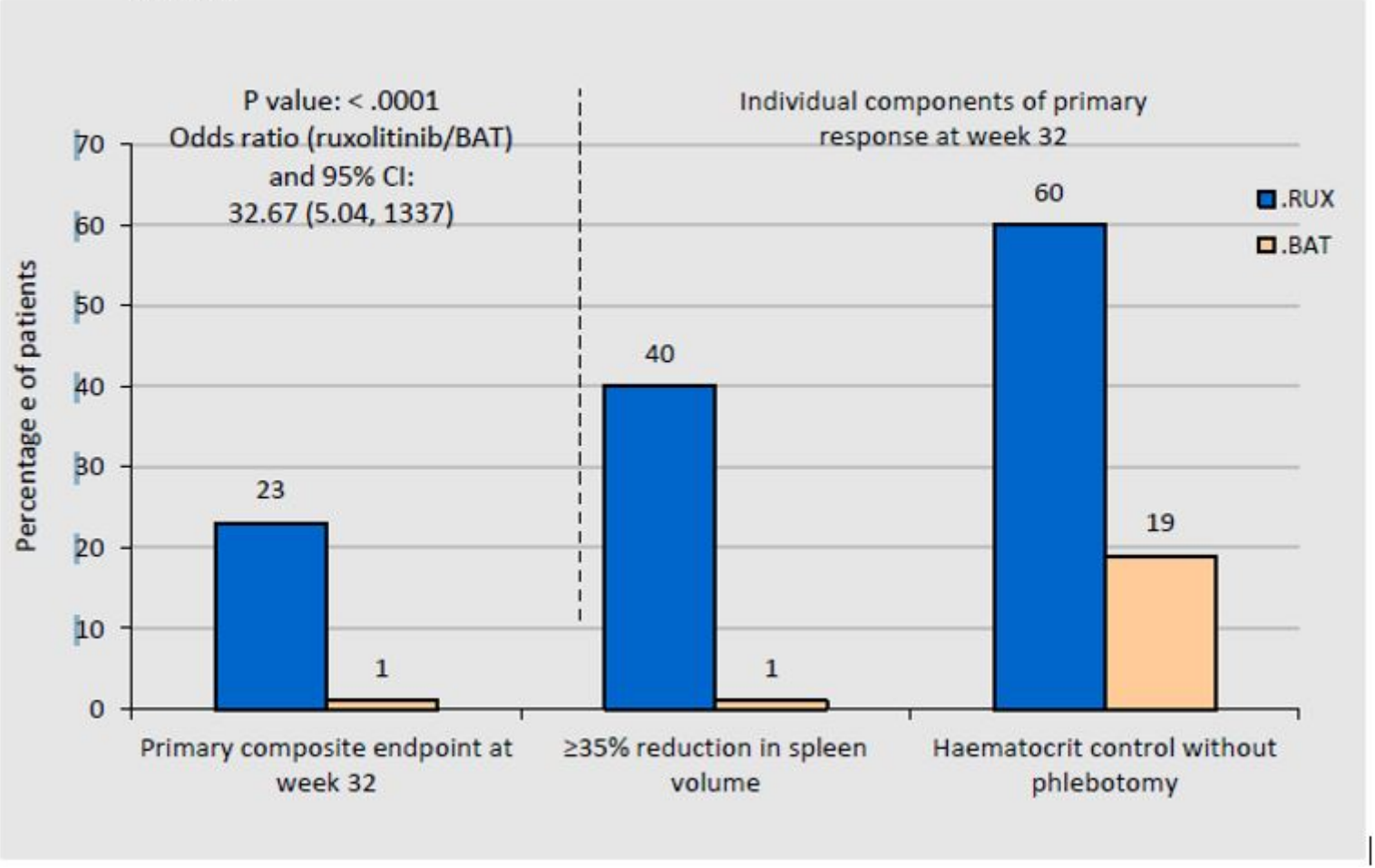
Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years.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

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

The study met its primary objective and a higher proportion of patients in the ruxolitinib group achieved the primary composite endpoint and each of its individual components. Significantly more patients treated with ruxolitinib (23%) achieved a primary response (p<0.0001) compared to BAT (0.9%). Haematocrit control was achieved in 60% of patients in the ruxolitinib arm compared to 18.8% in the BAT arm and a ≥35% reduction in spleen volume was achieved in 40% of patients in the ruxolitinib arm compared to 0.9% in the BAT arm (Figure 1).

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

Figure 1 Patients achieving the primary endpoint and components of the primary endpoint at week 32



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

Treatment benefit perception was measured by the Patient Global Impression of Change (PGIC) questionnaire. 66% of patients treated with ruxolitinib compared to 19% treated with BAT reported an improvement as early as four weeks after beginning treatment. Improvement in perception of treatment benefit was also higher in patients treated with ruxolitinib 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 randomisation. 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 10).

Table 10 Durability of primary response in the RESPONSE study

	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 randomised, open label, active-controlled phase 3b study (RESPONSE 2) was conducted in 149 PV patients who were resistant to, or intolerant of, hydroxyurea but without palpable splenomegaly. The primary endpoint defined as the proportion of patients achieving HCT control (absence of phlebotomy eligibility) at week 28 was met (62.2% in the ruxolitinib arm versus

18.7% in the BAT arm). The key secondary endpoint defined as the proportion of patients achieving complete haematological remission at week 28 was also met (23.0% in the ruxolitinib arm versus 5.3% in the BAT arm).

Graft-versus-host disease
Two randomised phase 3, open-label, multi-centre studies investigated ruxolitinib in patients 12 years of age and older with acute GvHD (REACH2) and chronic GvHD (REACH3) after allogeneic haematopoietic stem cell transplantation (alloSCT) and insufficient response to corticosteroids and/or other systemic therapies. The starting dose of ruxolitinib was 10 mg twice daily.

Acute graft-versus-host disease
In REACH2, 309 patients with grade II to IV corticosteroid-refractory, acute GvHD were randomised 1:1 to ruxolitinib 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.

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

In addition to ruxolitinib 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 ruxolitinib was allowed after the day 56 visit for patients with treatment response.

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

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

The reasons for patients' insufficient response to corticosteroids in the ruxolitinib 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 ruxolitinib arm had acute GvHD involving skin (60.4%) and liver (23.4%), compared to the BAT arm (skin: 47.7% and liver: 16.1%).

The most frequently used prior systemic acute GvHD therapies were corticosteroids+CNIs (49.4% in the ruxolitinib 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 ruxolitinib 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 ruxolitinib arm (34.4%) compared to BAT arm (19.4%).

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

Among the non-responders at day 28 in the ruxolitinib and BAT arms, 2.6% and 8.4% had disease progression, respectively.

Overall results are presented in Table 11.

Table 11 Overall response rate at day 28 in REACH2

	Ruxolitinib 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. Durable ORR at day 56 was 39.6% (95% CI: 31.8, 47.8) in the ruxolitinib 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 ruxolitinib arm versus 16.1% in the BAT arm. Overall, 49 patients (31.6%) originally randomised to the BAT arm crossed over to the ruxolitinib arm.

Chronic graft-versus-host disease
In REACH3, 329 patients with moderate or severe corticosteroid-refractory, chronic GvHD were randomised 1:1 to ruxolitinib or BAT. 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 ruxolitinib or BAT, patients could have received standard allogeneic stem cell transplantation supportive care including anti-infective medicinal products and transfusion support. Continued use of corticosteroids and CNIs such as cyclosporine or tacrolimus and topical or inhaled corticosteroid therapies were allowed per institutional guidelines.

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

Patients on BAT could cross over to ruxolitinib on day 169 and thereafter due to disease progression, mixed response, or unchanged response, due to toxicity to BAT, or due to chronic GvHD flare.

Efficacy in patients that transition from active acute GvHD to chronic GvHD without tapering off corticosteroids and any systemic treatment is unknown. Efficacy in acute or chronic GvHD after donor lymphocyte infusion (DLI) and in patients who did not tolerate steroid treatment is unknown.

Tapering of ruxolitinib was allowed after the day 169 visit.

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

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

Patients' insufficient response to corticosteroids in the ruxolitinib 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 ruxolitinib arm, compared to 69% and 41% in the BAT arm.

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

The primary endpoint was the ORR on day 169, 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 National Institutes of Health (NIH) criteria.

A key secondary endpoint was failure free survival (FFS), a composite time to event endpoint, incorporating the earliest of the following events: i) relapse or recurrence of underlying disease or death due to underlying disease, ii) non-relapse mortality, or iii) addition or initiation of another systemic therapy for chronic GvHD.

REACH3 met its primary objective. At the time of primary analysis (data cut-off date: 08-May-2020), the ORR at week 24 was higher in the ruxolitinib 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, two-sided, OR: 2.99; 95% CI: 1.86, 4.80). Results are presented in Table 12.

Among the non-responders at day 169 in the ruxolitinib and BAT arms, 2.4% and 12.8% had disease progression, respectively.

Table 12 Overall response rate at day 169 in REACH3

	Ruxolitinib 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 (2-sided)	p<0.0001			
Complete response	11 (6.7)		5 (3.0)	
Partial response	71 (43.0)		37 (22.6)	

The key secondary endpoint, FFS, demonstrated a statistically significant 63% risk reduction of ruxolitinib versus BAT (HR: 0.370; 95% CI: 0.268, 0.510, p<0.0001). At 6-months, the majority of FFS events were "addition or initiation of another systemic therapy for cGvHD" (probability of that event was 13.4% vs 48.5% for the ruxolitinib and the BAT arms, respectively). Results for "relapse of underlying disease" and non-relapse mortality (NRM) were 2.46% vs 2.57% and 9.19% vs 4.46%, in the ruxolitinib and the BAT arms, respectively. No difference of cumulative incidences between treatment arms was observed when focusing on NRM only.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing ruxolitinib in all subsets of the paediatric population for the treatment of MF and PV. In GvHD paediatric patients above 2 years of age, the safety and efficacy of ruxolitinib 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 section 4.2 for information on paediatric use). The single-arm design does not isolate the contribution of ruxolitinib to overall efficacy.

Acute graft versus host disease

In REACH4, 45 paediatric patients with grade II to IV acute GvHD were treated with ruxolitinib and corticosteroids +/- CNIs to assess the safety, efficacy and pharmacokinetics of ruxolitinib. Patients were enrolled into 4 groups based on age (Group 1 [≥12 years to < 18 years, N=18], Group 2 [≥6 years to < 12 years, N=12], Group 3 [≥2 years to <6 years, N=15] and Group 4 [≥28 days to <2 years, N=0]).
The doses tested were 10 mg twice daily for Group 1, 5 mg twice daily for Group 2 and 4 mg/m^2 twice daily for Group 3 and patients were treated for 24 weeks or until discontinuation. Ruxolitinib was administered as either a 5 mg tablet or a capsule/oral solution for paediatric patients <12 years.

Patients were enrolled with either steroid-refractory or treatment-naïve disease status. Patients were considered steroid refractory as per institutional criteria or per physician decision in case institutional criteria were not available and were permitted to have received no more than one additional prior systemic treatment for acute GvHD in addition to corticosteroids. Patients were considered treatment naïve if they had not received any prior systemic treatment for acute GvHD (except for a maximum 72 hours prior systemic corticosteroid therapy of methylprednisolone or equivalent after the onset of acute GvHD). In addition to ruxolitinib, patients were treated with systemic corticosteroids and/or CNI (cyclosporine or tacrolimus) and topical corticosteroid therapies were also allowed per institutional guidelines. In REACH4, 40 patients (88.9%) received concomitant CNIs. Patients could also have received standard allogeneic stem cell transplantation supportive care including anti-infective medicinal products and transfusion support. Ruxolitinib was to be discontinued in case of lack of response to acute GvHD treatment at day 28

Tapering of ruxolitinib was allowed after the day 56 visit.

Male and female patients accounted for 62.2% (n=28) and for 37.8% (n=17) of patients, respectively. Overall, 27 patients (60.0%) had underlying malignancy, most frequently leukaemia (26 patients, 57.8%). Among the 45 paediatric patients enrolled in REACH4, 13 (28.9%) had treatment-naïve acute GvHD and 32 (71.1%) had steroid-refractory 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 overall response rate (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. In terms of pre-treatment status, the ORR at day 28 was 90.6% in steroid refractory (SR) patients.

Rate of durable ORR at day 56 (key secondary endpoint) measured by the proportion of patients who achieved a CR or PR at day 28 and maintained a CR or PR at day 56 was 66.7% in all REACH4 patients, and 68.8% in SR patients.

Chronic graft versus host disease
In REACH5, 45 paediatric patients with moderate or severe chronic GvHD were treated with ruxolitinib and corticosteroids +/- CNIs to assess safety, efficacy and pharmacokinetics of ruxolitinib treatment. Patients were enrolled into 4 groups based on age (Group 1 [≥12 years to < 18 years, N=22], Group 2 [≥6 years to < 12 years, N=16], Group 3 [≥2 years to < 6 years, N=7] and Group 4 [≥28 days to < 2 years, N=0]). The doses tested were 10 mg twice daily for Group 1, 5 mg twice daily for Group 2 and 4 mg/m^2 twice daily for Group 3 and patients were treated for 39 cycles/156 weeks or until discontinuation. Ruxolitinib was administered as either a 5 mg tablet or an oral solution for paediatric patients <12 years.

Patients were enrolled with either steroid-refractory or treatment-naïve disease status. Patients were considered steroid refractory as per institutional criteria or per physician decision in case institutional criteria were not available and were permitted to have received additional prior systemic treatment for chronic GvHD in addition to corticosteroids. Patients were considered treatment naïve if they had not received any prior systemic treatment for chronic GvHD (except for a maximum 72 hours prior systemic corticosteroid therapy of methylprednisolone or equivalent after the onset of chronic GvHD). In addition to ruxolitinib, patients continued use of systemic corticosteroids and/or CNI (cyclosporine or tacrolimus) and topical corticosteroid therapies were also allowed per institutional guidelines. In REACH5, 23 patients (51.1%) received concomitant CNIs. Patients could also have received standard allogeneic stem cell transplantation supportive care including anti-infective medicinal products and transfusion support. Ruxolitinib was to be discontinued in case of lack of response to chronic GvHD treatment day 169.

Tapering of ruxolitinib was allowed after the day 169 visit.

Male and female patients accounted for 64.4% (n=29) and for 35.6% (n=16) of patients, respectively, with 30 patients (66.7%) with pre-transplant disease history of underlying malignancy, most frequently leukaemia (27 patients, 60%).

Among the 45 paediatric patients enrolled in REACH5, 17 (37.8%) were treatment-naïve chronic GvHD patients and 28 (62.2%) were SR chronic GvHD patients. 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%) had mouth involvement, and fourteen (31.1%) had lung involvement.

The ORR at day 169 (primary efficacy endpoint) was 40% (90% CI: 27.7, 53.3) in all REACH5 paediatric patients, and 39.3% in SR patients.

5.2 Pharmacokinetic properties

Absorption

Ruxolitinib is a Biopharmaceutical Classification System (BCS) class 1 compound, 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 human mass balance study, oral absorption of ruxolitinib, as ruxolitinib or metabolites formed under first-pass, is 95% or greater. Mean ruxolitinib C_{max} and total exposure (AUC) increased proportionally over a single dose range of 5-200 mg. There was no clinically relevant change in the pharmacokinetics of ruxolitinib upon administration with a high-fat meal. The mean C_{max} was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) on dosing with a high-fat meal.

Distribution

The mean volume of distribution at steady state is approximately 75 litres in MF and PV patients, 67.5 litres in adolescent and adult acute GvHD patients and 60.9 litres in adolescent and adult chronic GvHD patients. The mean volume of distribution at steady state is approximately 30 litres in paediatric patients with acute or chronic GvHD and with a body surface area (BSA) below 1 m^2 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

Ruxolitinib is mainly metabolised by CYP3A4 (>50%), with additional contribution from CYP2C9. Parent compound is the predominant entity in human plasma, representing approximately 60% of the drug-related material in circulation. Two major and active metabolites are present in plasma representing 25% and 11% of parent AUC. These metabolites have one half to one fifth of the parent JAK-related pharmacological activity. The sum total of all active metabolites contributes 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. *In vitro* data indicate that ruxolitinib may inhibit P-gp and BCRP.

Elimination

Ruxolitinib is mainly eliminated through metabolism. The mean elimination half-life of ruxolitinib is approximately 3 hours. Following a single oral dose of [$_{14}$C]-labelled ruxolitinib in healthy adult subjects, elimination was predominately through metabolism, with 74% of radioactivity excreted in urine and 22% via faeces. Unchanged parent substance accounted for less than 1% of the excreted total radioactivity.

Linearity/non-linearity

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

Special populations

Effects of age, gender or race
Based on studies in healthy subjects, no relevant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race.

Population pharmacokinetics
In a population pharmacokinetic evaluation in MF patients, no relationship was apparent between oral clearance and patient age or race. The predicted oral 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, based on a population pharmacokinetic evaluation in PV patients. Clearance

was 10.4 l/h in adolescent and adult patients with acute GvHD and 7.8 l/h in adolescent and adult patients with chronic GvHD, with a 49% inter-subject variability. In paediatric patients with acute or chronic GvHD and with a BSA below 1 m^2, clearance was between 6.5 and 7 l/h. No relationship was apparent between oral clearance and gender, patient age or race, based on a population pharmacokinetic evaluation in GvHD patients. At a dose of 10 mg twice daily, exposure was increased in GvHD patients with a low 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).

Paediatric population
The pharmacokinetics of ruxolitinib in paediatric patients <18 years old with MF and PV have not been established.

As in adult patients with GvHD, ruxolitinib was rapidly absorbed after oral administration in paediatric patients with GvHD. Dosing in children between 6 and 11 years old at 5 mg twice daily achieved comparable exposure to a dose of 10 mg twice daily in adolescents and adults with acute and chronic GvHD, confirming the exposure matching approach implemented as part of the extrapolation assumption. In children between 2 and 5 years old with acute and chronic GvHD, the exposure matching approach suggested a dose of 8 mg/m^2 twice daily

Ruxolitinib has not been evaluated in paediatric patients with acute or chronic GvHD below the age of 2 years, therefore modelling which accounts for age-related aspects in younger patients has been used to predict the exposure in these patients, based on the data from adult patients.

Based on a pooled population pharmacokinetic analysis in paediatric 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
Renal function was determined using both Modification of Diet in Renal Disease (MDRD) and urinary creatinine. Following a single ruxolitinib dose of 25 mg, the exposure of ruxolitinib was 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 were most markedly increased in the subjects with severe renal impairment. It is unknown whether the increased metabolite exposure is of safety concern. A dose modification is recommended in patients with severe renal impairment and end-stage renal disease (see section 4.2). Dosing only on dialysis days reduces the metabolite exposure, but also the pharmacodynamic effect, especially on the days between dialysis.

Hepatic impairment
Following a single ruxolitinib dose of 25 mg in patients with varying degrees of hepatic impairment, 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. There was no clear relationship between AUC and 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 of approximately 50% is recommended for MF and PV patients with hepatic impairment (see section 4.2).

In GvHD patients with hepatic impairment not related to GvHD, the starting dose of ruxolitinib should be reduced by 50%.

5.3 Preclinical 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 ruxolitinib 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.

In juvenile rat studies, administration of ruxolitinib resulted in effects on growth and bone measures. Reduced bone growth was observed at doses ≥5 mg/kg/day when treatment started on postnatal day 7 (comparable to human newborn) and at ≥15 mg/kg/day when treatment started on postnatal days 14 or 21 (comparable to human infant, 1–3 years). Fractures and early termination of rats were observed at doses ≥30 mg/kg/day when treatment was started on postnatal day 7. Based on

unbound AUC, the exposure at the NOAEL (no observed adverse effect level) in juvenile rats treated as early as postnatal day 7 was 0.3-fold that of adult patients at 25 mg twice daily, while reduced bone growth and fractures occurred at exposures that were 1.5- and 13-fold that of adult patients at 25 mg twice daily, respectively. The effects were generally more severe when administration was initiated earlier in the postnatal period. Other than bone development, the effects of ruxolitinib in juvenile rats were similar to those in adult rats. Juvenile rats are more sensitive than adult rats to ruxolitinib toxicity.

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. Ruxolitinib was not mutagenic or clastogenic. Ruxolitinib was not carcinogenic in the Tg.rasH2 transgenic mouse model.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose, microcrystalline (PH 101) (E 460)
Povidone (K29/32)
Hydroxypropyl cellulose (E 463)
Sodium starch glycolate (type A)
Cellulose, microcrystalline (PH 102) (E 460)
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Alu/PVC/PE/PVDC blisters containing 14, 28, 56, 60, 140 or 168 tablets or Alu/PVC/PE/PVDC perforated unit dose blisters containing 14 x 1, 28 x 1, 56 x 1, 60 x 1, 140 x 1 or 168 x 1 tablets, or

Alu/PVC/PE/PVDC calendar blisters containing 14, 28, 56, 60, 140, or 168 tablets or Alu/PVC/PE/PVDC calendar perforated unit dose blisters containing 14 x 1, 28 x 1, 56 x 1, 60 x 1, 140 x 1 or 168 x 1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd

Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/353/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd October 2026

10 DATE OF REVISION OF THE TEXT