NOVARTIS

Patient Safety & Pharmacovigilance

Ruxolitinib

INC424

# EU Safety Risk Management Plan

| | |
|---|---|
| Active substance(s) (INN or common name): | Ruxolitinib |
| Product(s) concerned (brand name(s)): | Jakavi |
| Document status: | Final |
| Version number: | 17.0 |
| Data lock point for this RMP | Data cut-off date for GvHD clinical database: Chronic Graft versus Host Disease: CINC424G12201 26 Aug 2024 |
| Date of final sign off | 11-June-2025 |

**Rationale for submitting an updated RMP:**

Compared to the previous European Union (EU) Risk Management Plan (RMP) version 16.3, this version of the RMP (v.17.0) includes:

- The completion of the Study CINC424G12201 (REACH 5) and the removal from the additional pharmacovigilance activities
- The updated exposure and safety data in pooled GvHD pediatric population and in the Chronic GvHD total pediatric population
- The updated post-authorization data as per the PSUR reporting period 23-Feb-2024 to 22-Feb-2025

**Summary of significant changes in this RMP:**

| Part | Major changes in v 17.0 compared to RMP v 16.3 |
|---|---|
| Part I | Updated per the current approved Ruxolitinib SmPC and patient leaflet |
| Part II Module SI | Section 2.1 was updated with current epidemiology data |
| Part II Module SII | Table 3-1: In Juvenile toxicity the reference to ongoing CINC424G12201 was removed |
| Part II Module SIII | Table 4-1 was updated with CINC424G12201 Final CSR<br>Table 4-4, 4-7 and 4-9 “Chronic GvHD Total pediatric patients” data were updated |
| Part II Module SIV | Table 5-1 was updated to reflect the current Ruxolitinib SmPC 2025 |
| Part II Module SV | Ruxolitinib indication and post authorization exposure were updated |
| Part II Module SVI | No change |
| Part II Module SVII | Section 8.2 was updated to reflect no change in Safety concerns<br>Section 8.3, Section 8.3.1, Table 8-2 and Table 8-3 “Chronic GvHD Total pediatric population” data, Table 8-4 pooled pediatric population information were updated<br>Section 8.3.1.2, Table 8-5 Safety database paragraph was updated<br>Section 8.3.2 Table 8-6 evidence and risk were updated with CINC424G12201 final CSR data. |
| Part II Module SVIII | No change |
| Part III | Updated to reflect CINC424G12201 CSR completion<br>Table 10-3 updated to remove CINC424G12201 |
| Part IV | No change |
| Part V | Table 12-2: CINC424G12201 reference was removed |
| Part VI | CINC424G12201 reference was removed and Table 13-5 deleted |
| **Part VII** | |
| Annex 1 | No change |
| Annex 2 | Table 14-1 was removed and Table 14-2 updated |

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| Annex 3 | Reference to studies CINC424F12201 and CINC424G12201 protocols were removed |
| Annex 4 | No change. |
| Annex 5 | No change. |
| Annex 6 | No change. |
| Annex 7 | Brief Statistical Description portion & Supportive Outputs of Annex 7c link updated<br>References list was updated |
| Annex 8 | Updated to reflect the Summary of changes to the RMP v 17.0 |

**Other RMP versions under evaluation**

No RMP versions are currently under evaluation.

**Details of the currently approved RMP:**

Version number: 16.3

Approved with procedure:EMEA/H/C/002464/X/0070/G

Date of approval (opinion date): 13-Jan-2025

**QPPV name:** Dr Justin Daniels, PhD

**QPPV oversight declaration:** The content of this RMP has been reviewed and approved by the marketing authorization holder´s (MAH's) QPPV. The electronic signature is available on file.

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## List of abbreviations

| | |
|---|---|
| ADR | Adverse drug reaction |
| AE | Adverse event |
| aGvHD | Acute graft versus host disease |
| Allo-SCT | Allogeneic stem cell transplantation |
| Allo-HCT | Allogeneic hematopoietic cell transplantation |
| ALT | Alanine aminotransferase |
| AML | Acute myeloid leukemia |
| AMM | Agnogenic myeloid metaplasia |
| ANC | Absolute neutrophil count |
| APC | Antigen presenting cell |
| AR | Assessment report |
| AST | Aspartate aminotransferase |
| AT-MSC | Adipose tissue-derived mesenchymal stromal cell |
| AUC | Area under the curve |
| BAT | Best available therapy |
| BCC | Basal cell carcinoma |
| BP | Blood pressure |
| C7D1 | Cycle 7 Day 1 |
| CI | Confidence interval |
| COPD | Chronic obstructive pulmonary disease |
| cGvHD | Chronic graft versus host disease |
| CMV | Cytomegalovirus |
| CNI | Calcineurin inhibitor |
| COPD | Chronic obstructive pulmonary disease |
| CR | Complete response |
| CrCl | Creatinine clearance |
| CsA | Cyclosporine |
| CSR | Clinical Study Report |
| CT | Clinical trial |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | Cytochrome P450 |
| DLP | Data-lock point |
| ECP | Extracorporeal photopheresis |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| ESA | Erythropoiesis-stimulating agent |
| ET | Essential thrombocythemia |
| EU | European Union |
| FU | Follow-up |
| GI | Gastrointestinal |
| GvHD | Graft versus host disease |

| | |
|---|---|
| GVP | Good Pharmacovigilance Practice |
| HBV | Hepatitis B virus |
| HCP | Health care professional |
| HCT | Hematopoietic cell transplantation |
| HLA | Human leukocyte antigen |
| HR | Hazard Ratio |
| HSCT | Hematopoietic stem cell transplantation |
| HU | Hydroxyurea |
| HZ | Herpes zoster |
| IC50 | Half maximal inhibitory concentration |
| IFN | Interferon |
| IMF | Idiopathic myelofibrosis |
| IR | Incidence rate |
| JAK | Janus kinase family of protein tyrosine kinase |
| JCV | John Cunningham Virus |
| MDS | Myelodysplastic Syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MF | Myelofibrosis |
| MMF | Mycophenolate mofetil |
| MMM | Myelosclerosis with Myeloid Metaplasia |
| MPN | Myeloproliferative neoplasms |
| MSC | Mesenchymal stromal cells |
| MSSD | Maximum safe starting dose |
| MTX | Methotrexate |
| NMSC | Non-melanoma skin cancer |
| NRM | Non-relapse related mortality |
| ORR | Overall response rate |
| PASS | Post authorization safety study |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PD | Pharmacodynamic |
| PET-MF | Post-essential thrombocythemia myelofibrosis |
| PhV | Pharmacovigilance |
| PK | Pharmacokinetic |
| PMF | Primary myelofibrosis |
| PML | Progressive multifocal leukoencephalopathy |
| pp | Post-partum |
| PPV-MF | Post-polycythemia vera myelofibrosis |
| PSUR | Periodic Safety Update Report |
| PT | Preferred term |
| PTY | Patient-treatment years |
| PY | Person year |
| PV | Polycythemia vera |
| RMP | Risk Management Plan |

| | |
|---|---|
| RR | Reporting rate |
| SAE | Serious adverse event |
| SBP | Systolic blood pressure |
| SCC | Squamous cell carcinoma |
| SD | Standard deviation |
| SIR | Standardized incidence ratio |
| SmPC | Summary of Product Characteristics |
| SR | Steroid refractory |
| STAT | Signal transducers and activators of transcription |
| TB | Tuberculosis |
| TNF | Tumor necrosis factor |
| TNF-α | Tumor necrosis factor- alpha |
| TNFR | Tumor necrosis factor receptor |
| TRM | Treatment-related mortality |
| UD | Unrelated donor |
| UK | United Kingdom |
| US/USA | United States of America |
| UTI | Urinary tract infection |
| WBC | White blood cell |

# 1 Part I: Product(s) Overview

**Table 1-1 Part I.1 -Product Overview**

| | |
|---|---|
| **Active substance (INN or common name)** | Ruxolitinib |
| **Pharmacotherapeutic group(s) (ATC Code)** | Antineoplastic agents, protein kinase inhibitors (L01EJ01) |
| **Marketing Authorization Holder** | Novartis Europharm Limited |
| **Medicinal products to which this RMP refers** | 1 |
| **Invented name in the European Economic Area (EEA)** | Jakavi® |
| **Marketing authorization procedure** | Centralized |
| **Brief description of the product** | Chemical class: Ruxolitinib is a protein tyrosine kinase inhibitor (L01EJ01). |
| | Summary of mode of action: Ruxolitinib is a selective inhibitor of the Janus Kinases (JAKs), JAK1 and JAK2 (the half maximal inhibitory concentration [$IC_{50}$] values of 3.3 nM and 2.8 nM for JAK1 and JAK2 enzymes, respectively). These mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. |
| | Important information about its composition: Ruxolitinib inhibits JAK/ signal transducers and activators of transcription (STAT) signaling and cell proliferation of cytokine-dependent cellular models of hematological malignancies, as well as of Ba/F3 cells rendered cytokine-independent by expressing the JAK2V617F mutated protein, with $IC_{50}$ values ranging from 80-320 nM. |
| **Hyperlink to the Product Information** | [Current approved SmPC]<br>Proposed SmPC: Not applicable |
| **Indications in the EEA** | **Current**:<br>Ruxolitinib is indicated:<br>• for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (PMF) (also known as chronic idiopathic myelofibrosis [IMF]), post polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET-MF).<br>• for the treatment of adult patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea (HU).<br>• for the treatment of adults and pediatric patients aged 28 days and older with acute GvHD who have inadequate response to corticosteroids or other systemic therapies.<br>• for the treatment of adults and pediatric patients aged 6 months and older with chronic GvHD who have inadequate response to corticosteroids or other systemic therapies. |

<table>
<tr><td></td><td>Proposed: Not applicable</td></tr>
<tr><td>Dosage in the EEA</td><td>
Current: Myelofibrosis and Polycythemia vera<br>
Starting dose:<br>
The recommended starting dose of ruxolitinib in MF is based on platelet counts (see Table below):
<table>
<tr><th>Platelet count</th><th>Starting dose</th></tr>
<tr><td>Greater than 200000/mm$^3$</td><td>20 mg orally b.i.d.</td></tr>
<tr><td>100000 to 200000/mm$^3$</td><td>15 mg orally b.i.d.</td></tr>
<tr><td>75000 to less than 100000/mm$^3$</td><td>10 mg orally b.i.d.</td></tr>
<tr><td>50000 to less than 75000/mm$^3$</td><td>5 mg orally b.i.d.</td></tr>
</table>
The recommended starting dose of ruxolitinib in PV is 10 mg given orally b.i.d.<br>
Dose modifications:<br>
Doses may be titrated based on safety and efficacy. Treatment should be discontinued for platelet counts less than 50000/mm$^3$ or absolute neutrophil counts (ANC) less than 500/mm$^3$. In PV, treatment should also be interrupted when hemoglobin is below 8 g/dl. After recovery of blood counts above these levels, dosing may be re-started at 5 mg b.i.d. and gradually increased based on careful monitoring of complete blood cell count, including a white blood cell (WBC) count differential.<br><br>
Current: Graft versus host disease<br>
Starting dose:<br>
Starting doses in acute graft versus host disease:
<table>
<tr><th>Age Group</th><th>Starting dose</th></tr>
<tr><td>12 years old and above</td><td>10 mg orally twice daily.</td></tr>
<tr><td>6 years to less than 12 years old</td><td>5 mg orally twice daily.</td></tr>
<tr><td>28 days to less than 6 years old</td><td>8 mg/m² orally twice daily.</td></tr>
</table>
Starting doses in chronic graft versus host disease:
<table>
<tr><th>Age Group</th><th>Starting dose</th></tr>
<tr><td>12 years old and above</td><td>10 mg orally twice daily.</td></tr>
<tr><td>6 years to less than 12 years old</td><td>5 mg orally twice daily.</td></tr>
<tr><td>6 months to less than 6 years old</td><td>8 mg/m² orally twice daily.</td></tr>
</table>
These starting doses in GvHD can be administered using either the tablet for patients at or above 6 years old who can swallow tablets or the oral solution<br>
Dose modifications:<br>
Dose reductions and temporary interruptions 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.
</td></tr>
</table>

| | |
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| | One dose level reduction step is recommended (10 mg b.i.d. to 5 mg b.i.d. or 5 mg b.i.d. to 5 mg once daily). In patients who are unable to tolerate ruxolitinib at a dose of 5 mg once daily, treatment should be interrupted.<br>In GvHD, tapering of ruxolitinib may be considered in patients with a response and after having discontinued corticosteroids. A 50% dose reduction of ruxolitinib every 2 months is recommended. If signs or symptoms of GvHD reoccur during or after the taper of ruxolitinib, re-escalation of treatment should be considered. |
| | **Proposed**: Not applicable |
| **Pharmaceutical form(s) and strengths** | **Current**: 5 mg, 10 mg, 15 mg and 20 mg tablets. Oral solution, 5 mg/mL. Different strengths may be available outside the EU. |
| | **Proposed**: Not applicable |
| **Will the product be subject to additional monitoring in the EU?** | No |

# 2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

## 2.1 Indication: Myelofibrosis

Myelofibrosis, including PMF, PPV-MF, PET-MF.

The modern nomenclature for agnogenic myeloid metaplasia (AMM), myelosclerosis with myeloid metaplasia (MMM) and IMF discussed in this section is PMF, a myeloproliferative neoplasm (MPN) characterized by stem cell-derived clonal myeloproliferation (Tefferi 2020). When there was no published epidemiologic information available for PPV-MF and PET-MF, data for PV and essential thrombocythemia (ET) was included.

### Incidence:

PMF

According to the Orphanet database, the global PMF incidence estimate is approximately 1 per 100,000 persons (Orphanet 2023). Additionally, in a study in Sweden with a study period of 2000-2014, the nationwide crude incidence of PMF was 0.54 (95% CI 0.50-0.58) per 100,000 PY, and the age-standardized incidence was 0.52 (95% CI 0.48-0.56) per 100,000 PY (Hultcrantz et al 2020).

Outside of the EU, in a study in the US (study period 2012-2016), the annual incidence of PMF was 0.48 (95% CI 0.46-0.50) per 100,000 PY (Verstovsek et al 2022). In Calgary, Alberta, Canada, (study period 2011-2015), the crude incidence of PMF was 0.56 (95% CI 0.40-0.76) per 100,000 PY, and the age-standardized incidence was 0.80 (95% CI 0.76-0.84) per 100,000 PY (Canada, Heppner et al 2019). Omine (2006) reported the annual incidence of PMF in Japan as 1 per 100,000 population.

PPV-MF and PET-MF:

Phekoo et al 2006 identified 826 cases of chronic myeloproliferative disease diagnosed in South East England between Jan-1999 and Dec-2000. Among these cases, there were 61 (7%) cases of IMF, 185 (22%) cases of PV, 4 (0.5%) cases of myelofibrotic transformation of PV, 297 (36%) cases of primary thrombocythemia (also known as ET) and 10 (9%) cases of myelofibrotic transformation of ET. The incidence estimates were 0.37/100,000 for IMF, 1.08/100,000 for PV and 1.65/100,000 for ET.

A retrospective study performed in a population-based registry in the Cote d'Or area, France, from 1980 to 2007 (Girodon et al 2009) found annual disease-specific incidence estimates per 100,000 population of 0.5 for IMF, 2.0 for ET and 0.9 for PV.

A study based on data from the North American Association of Cancer Registries and the Surveillance, Epidemiology and End Results Program during 2001-2004 found the IR for MMM of 0.21 per 100,000 PY, ET – of 0.51 per 100,000 PY and PV – of 1.01 per 100,000 PY (Rollison et al 2008).

### Prevalence:

Limited published population-based data on the prevalence of MF have been identified , however, the Orphanet database does provide a global PMF prevalence estimate range of 1 to 9 per 100,000 persons (Orphanet 2023).

Only 1 European study reported the population-based number of prevalent cases of myeloproliferative disorders using 48 years of Swedish nationwide cancer registry data (Landgren et al 2008). In 2005, it identified in Sweden 1172 prevalent cases of MF, 2838 prevalent cases of ET and 6217 prevalent cases of PV. Based on the population in Sweden as of 01-Jan-2006 (Eurostat 2011) of 904,7752, the prevalence proportions can be estimated as 13 per 100,000 for MF, 31 per 100,000 for ET and 69 per 100,000 for PV.

In the US, an analysis of Connecticut medical claims data estimated the prevalence of ET and PV in the US to be 136,000 patients (71,000 with ET and 65,000 with PV) as of 2003. In Connecticut, the 2003 age standardized prevalence proportions were 24 per 100,000 and 22 per 100,000 populations for ET and PV, respectively (Ma et al 2008).

### Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age and gender:

PMF: According to a US based study, the median age at diagnosis of PMF in the US was 70 years (IQR 61-78 years), and 59.6% of PMF patients were male (40.4% female) (Verstovsek et al 2022). The median age at diagnosis in New Zealand was 70 years (IQR 59-80 years), and 65.1% of PMF patients were male (34.9% female). Maori and Pacific Islander PMF patients were significantly younger at diagnosis than European PMF patients ($p < 0.001$) (Varghese et al 2021).

PPV-MF and PET-MF: According to several studies, the median age at diagnosis of MF (including PMF, PPV-MF and PET-MF), patients in Europe ranged from 68 years to 69.7 years. (The proportion of MF patients that were male in Europe ranged from 59% to 63.5% (Garcia-Fortes et al 2022, Hernandez-Boluda et al 2022, Mead et al 2022). In the rest of the world, the proportion of MF patients that were male ranged from 49.7% to 55.3% (Saliba et al 2020a, Saliba et al 2020b, Yassin et al 2020).

Inter-ethnic/race variations:

It has been reported that the frequency of myeloproliferative disorders varies substantially depending on race and ethnic origin.

PMF: European race and ethnicity studies are scarce, however, in the US, a study reported 82.5% of PMF patients White, 8.2% Black, 7.3% Asian/Pacific Islander, 0.5% American Indian/Alaska Native, and 1.5% Unknown race (Verstovsek et al 2022).

In New Zealand, 77.6% of PMF patients were European, 9.9% were Maori and 6.6% were Pacific Islander. Maori and Pacific Islander PMF patients were significantly younger at diagnosis than European PMF patients ($p < 0.001$) (Varghese et al 2021).

PPV-MF and PET-MF:

A study based on data from the North American Association of Cancer Registries and the Surveillance, Epidemiology and End Results Program during 2001-2004 reported the IR (per 100,000) for chronic myeloproliferative disorders stratified by race and ethnicity as follows (Rollison et al 2008):

- White –1.99
- Black – 2.09
- Asian/Pacific Islander – 1.38
- American Indian/Alaska Native – 0.75
- Hispanic – 1.46
- Non-Hispanic –2.07

Lastly, in a study by Ruiz-Arguelles et al 2002 that reviewed data on 8069 individuals treated in a hematologic center in Mexico City, Mexico found that AMM, primary thrombocythemia and PV were significantly less prevalent in Mexican than in Caucasian populations ($p < 0.1$).

### Risk factors for the disease

Risk factors for MF include:

- Age: the IR of myeloproliferative disorders increase with age with mean age at diagnosis of 52 to 72 (Chaiter et al 1992, Mesa et al 1999, Girodon et al 2009, Abdulkarim et al 2011).
- Exposure to certain chemicals: MF has been linked to exposure to industrial chemicals such as toluene (Bosch et al 1989) and benzene (Tondel et al 1995).
- Another blood cell disorder: a portion of people with MF develop the condition as a complication of ET or PV.
- The Orphanet database notes "an increased prevalence" of PMF in Ashkenazi Jews (Orphanet 2023)

### The main existing treatment options:

The only potentially curative therapy for MF currently is allogeneic stem cell transplantation (alloSCT). Drug therapy is indicated by the presence of symptoms due to anemia, splenomegaly, extramedullary hematopoiesis, or constitutional symptoms and includes androgens, erythropoiesis-stimulating agents (ESAs), immunomodulators (lenalidomide and thalidomide), prednisone and HU. None of these agents is approved for the treatment of MF. Splenectomy or splenic irradiations are performed to treat symptoms related to splenomegaly (AbdelWahab and Levine 2009). In 2012, ruxolitinib was approved in the EU for the treatment of disease related splenomegaly or symptoms in adult patients with PMF, PPVMF or PETMF.

### Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The disease entity of PMF is characterized by an evolution from an initial prefibrotic stage revealing hypercellular bone marrow with absent or minimal reticulin fibrosis to an overt fibrotic phase with marked reticulin or collagen fibrosis of the bone marrow. About 30% of patients are asymptomatic at the time of diagnosis. In the initial prefibrotic phase, the only relevant finding may be marked thrombocytosis and borderline anemia and/or splenomegaly.

Constitutional symptoms may include fatigue, dyspnea, weight loss, night sweats, low-grade fever and bleeding. Nearly 50% of patients present with splenomegaly. The principal causes of death in patients with MF include infection, thrombohemorrhagic events and leukemic transformation.

Transformation to acute leukemia is associated with a dismal outcome and has been estimated to occur in 3.9% to 20% patients. The overall prognosis depends on the stage of the disease at diagnosis. The median survival time is 3 to 7 years when the diagnosis is made in the fibrotic stage, with 10- and 15 year relative survival rates of 72% and 59%, respectively, when the disease is diagnosed in the early prefibrotic stage (Abdel-Wahab and Levine 2009, Thiele 2009).

PMF: In European studies, the incidence of second non-hematological malignancies in PMF patients was 31.6 per 1,000 PY (Saliba et al 2020a), the incidence of venous thromboembolism was 11.24 per 1,000 PY , and the incidence of arterial thromboembolism was 20.78 per 1,000 PY (Saliba et al 2020b).

In the US, the 5-year overall mortality rate in PMF patients was 51%, and for the most recent years (2012-2016) the median survival time was 3.8 years (IQR 3.5-4.2) (Verstovsek et al 2022). In Singapore, among PMF patients the 1-year OS was 89.1%, 2-year OS was 59.2% and 5-year OS was 46.7%, and the median survival time was 4.6 years (Htun et al 2022). In New Zealand, the overall mortality rate for PMF patients over a median 2.0 years follow up was 44.7% (Varghese et al 2021).

PPV-MF and PET-MF:

Phekoo et al (2006) reported the 3-year survival for IMF as 48%, for PV as 80% and for primary thrombocythemia as 81%. Mesa et all 1999 analyzed the survival of AMM and ET patients and found a 3-year survival of 52.4% for AMM and 5- and 10 year survival of 74.4% and 61.3%, respectively for ET. Anía et al 1994 found the median survival following PV diagnosis of 7.2 years. The probability of surviving at least 5 and 10 years was estimated to be 0.56 and 0.39, respectively.

Cervantes et al (2009) developed a prognostic scoring system for PMF based on 1054 patients consecutively diagnosed with PMF at 7 participating centers. Overall median survival was 69 months (95% CI: 61, 76). Multivariate analysis of parameters obtained at diagnosis identified age greater than 65 years, presence of constitutional symptoms, hemoglobin level less than 10 g/dL, leukocyte count greater than $25x10^9$/L and circulating blast cells 1% or greater as predictors of shortened survival. Based on the presence of 0 (low risk), 1 (intermediate risk - 1), 2 (intermediate risk - 2) or greater than or equal to 3 (high risk) of these variables, 4 risk groups with no overlap in their survival curves were delineated; respective median survivals were 135, 95, 48 and 27 months ($p < 0.001$).

Patients with MPN are more susceptible than matched controls from the general population to infectious diseases. Hultcrantz et al (2015a) observed a risk of infection among 9655 patients with MPNs 2-fold that observed for 38660 matched controls (hazard ratio [HR]: 1.9; 95% CI: 1.8-2.0). This higher risk of infection is also associated with a higher risk of death due to infection. Patients with PMF showed the highest cumulative incidence of death at 10 years

after diagnosis (10.4%, 95% CI: 6.7-14.2; results for 70-79 years old age group) among MPNs (Hultcrantz et al 2015b).

Hultcrantz et al (2015b) reported also a higher risk of cardiovascular and cerebrovascular diseases death in MPN patients of all ages when compared with matched controls (HR for both conditions ranging from 8.7 in 18-49 years old to 1.4 in >80 years; all statistically significant differences). The 10-years cumulative incidence in PMF patients aged 70-79 years old was 12.3% (95% CI: 8.6-16.1) for cardiovascular disease and 2.4% (95% CI: 0.9-3.9) for cerebrovascular (data for other age groups by type of MPN not presented).

### Important co-morbidities:

The most common comorbidities (frequency occurring in > 20% of patients) among MF (PMF, PPV-MF or PET-MF) were: hypertension (42.2% to 59.8%), diabetes (18.5% to 26.0%) (Saliba et al 2020a, Saliba et al 2020b, Garcia-Fortes et al 2022, Hernandez-Boluda et al 2022), hypercholesterolemia (23.9%) (Hernandez-Boluda et al 2022), vascular disease (32.0% to 32.4%) (Saliba et al 2020a, Saliba et al 2020b), smoking-active or ever (21.5% to 34.9%) (Hernandez-Boluda et al 2022) chronic renal failure (20.1%-20.4%), and PV (22.0% to 22.9%) (Saliba et al 2020a, Saliba et al 2020b). No studies were identified reporting the frequencies of comorbidities in PMF only patients.

**Table 2-1 Co-morbidity of target population, per indication**

| | Incidence | Prevalence | Mortality |
|---|---|---|---|
| **Population: co-morbidities in Primary Myelofibrosis** | | | |
| Splenomegaly | NA | 89-100% at diagnosis | NA |
| Hepatomegaly | NA | 50% at diagnosis | NA |
| Anemia | NA | 50-70% at diagnosis | Hb ≤10g/dL associated with 3-5X shorter survival |
| Bleeding | NA | 25% | final cause of death in 2.7% (N=517) |
| Infections | NA | NA | final cause of death in 5-15% (N=517, N=133) |
| **Population: co-morbidities in Polycythemia vera** | | | |
| Splenomegaly | NA | 56% at diagnosis | HR=2.15<br>p=0.0037<br>N=150 |
| Arterial thrombotic events | 4% /year | NA | NA |
| Venous thrombotic events | 2.2%/year | NA | NA |
| Bleeding complications | 1.7%/year | NA | NA |
| **Population: co-morbidities in Essential Thrombocythemia** | | | |
| Splenomegaly | NA | 30-50% at diagnosis | NS |
| Hepatomegaly | NA | 15-20% at diagnosis | NA |

| | | | |
|---|---|---|---|
| Arterial thrombotic events | 3.4%/year | NA | NA |
| Venous thrombotic event | 0.7%/year | NA | NA |
| Bleeding complications | 1.6%/year | NA | NA |

**Source:** Visani et al 1990, Dupriez et al 1996, Barosi and Hoffman 2005, Abdel-Wahab and Levine 2009, Thiele 2009, Abdulkarim et al 2011.
Hb: Hemoglobin, HR – Hazard ratio, N – Total number, NA – Not available, NS – No statistically significant effect.

## 2.2 Indication: Polycythemia vera

### Incidence:

A literature and disease registry database review observed that the incidence of PV varies.

The Orphanet 2024 database provides a range of global estimates for annual PV incidence from 1 per 38.314 people (Orphanet 2024. In Europe, a recent study conducted in Sweden reported the national crude PV incidence rate over the study period 2000-2014 as 1.52 per 100 000 PY (95% CI 1.45-1.59), and the age-standardized PV incidence rate to be 1.48 per 100,000 PY (95% CI 1.42-1.54) (Hultcrantz et al 2020, Croatian, Southwest Germany, Sweden) Moulard et al 2013, Maynadié et al 2011, Johansson et al 2004, OscaGelis et al 2013, Phekoo et al 2006.

Also in the EU, in a recent publication of the Registry of Hematologic Malignancies in France, the PV IR during the period 1980-2004 was 0.6 cases per 100,000 inhabitants year (Maynadié et al 2011) and in Göteborg (Sweden), a retrospective medical record review of patients with suspicion of a MPN yielded an IR adjusted to the European standard population of 1.97 cases per 100,000 inhabitants year- (Johansson et al 2004). In Girona (Spain), the IR adjusted to the European standard population, based on data from the population-based Girona Cancer Registry, was 1.08 cases per 100,000 inhabitants-year (Osca-Gelis et al 2013) and, similarly, in South East-England (UK), the review of the patients with a myeloid malignancy diagnosis gave as a result an IR standardized to the European standard population of 1.08 cases per 100,000 inhabitantsyear- (Phekoo et al 2006). and, similarly, in South East-England (UK), the review of the patients with a myeloid malignancy diagnosis gave as a result an IR standardized to the European standard population of 1.08 cases per 100,000 in habitants year (Phekoo et al 2006).).

In the US and Canada, PV incidence ranged from 0.44 per 100,000 PY to 1.55 per 100,000 PY (Heppner et al 2019, Le et al 2019, Verstovsek et al 2022). In particular, one study using SEER 18 data (study period 2002-2016) reported the annual PV incidence rate to be 1.57 per 100,000 PY (95% CI 1.55-1.60), and in the most recent years (2012-2016) the annual PV incidence rate was 1.55 per 100,000 PY (95% CI 1.51-1.59) (Verstovsek et al 2022). Additionally, geographic variability on PV incidence was observed in a published global literature review. The lowest IR observed in this review was in Japan (0.02 cases per 100000 PY), while the highest was observed in Göteborg (Sweden) (2.8 cases per 100000 PY). Other countries included in this review were: Australia, France, Israel, Sweden (the city of Malmö), UK and the US (Kutti and Ridell 2001).

Based on the reviewed literature, the overall incidence of PV in the EU and in the US ranges between 0.4 and 2.8 cases per 100,000 PY and globally is 208 per 100,000 PY.

### Prevalence:

The 2024 Orphanet estimate for global PV prevalence is 10 to 5 per 100,000 persons, with a range from 10 to 50 per 100,000 persons (Orphanet 2024).

The Finnish National Cancer Registry reported an annual total prevalence of 4 per 100,000 for men and 3 per 100,000 for women (Moulard et al 2013). In Göteborg (Sweden), in a retrospective medical record review of patients with suspicion of a MPN, the observed PV prevalence was 35 cases per 100000 (Johansson et al 2006). In Italy, the PV prevalence estimated through the evaluation and 5--year follow-up of the first 10000 persons enrolled in the Vicenza Thrombophilia and Atherosclerosis was 30 per 100000 (95% CI: 6, 87) (Ruggeri et al 2003).

In the US, in a study based on data from Ingenix Impact National Managed Care Integrated Health Care Information Solutions (IHCIS) and MarketScan databases, the prevalence of PV in 2010 was 57.2 (IHCIS) and 48.2 (MarketScan) per 100,000 (Mehta et al 2014). Also, in the US, in a study based on health claims data from major commercial insurance payers in Connecticut and the Center for Medicare and Medicaid Services, the PV age-standardized to the US population prevalence observed in 2003 was 22.06 per 100,000 (Ma et al 2008).

The prevalence of HU resistance or intolerance in PV patients was reported in two European based studies as 12% to 20% although the authors note that if European Leukemia Net (ELN) criteria for hydroxyurea resistance are used, rates of resistance appear to be higher (38.2%) (Devos et al 2018, van de Ree-Pellikaan et al 2019). In a study in Thailand the prevalence of hydroxyurea resistance or intolerance using ELN and modified ELN criteria was 8.6% (Chiaranairungrot et al 2022).

### Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age and Gender

Polycythemia vera is very rare in children and is diagnosed very seldom before 30 years of age, the incidence increases with advanced age and median age at diagnosis is approximately 70 years (Johansson 2006). When PV frequency is analyzed stratifying by sex, differences on the PV distribution between females and males are observed in some studies, with usually a higher incidence among males.

In Europe, the median age of PV patients ranged from 62.3 to 74 years (Crodel et al 2022, Benevolo et al 2021, Darba et al 2022, Devos et al 2018, van de Ree-Pellikaan et al 2019), from 62.5 to 67 years in the US (Grunwald et al 2018, Paranagama et al 2018, Parasuraman et al 2018, Verstovsek et al 2023, Verstovsek et al 2022),and from 60 to 67 years in the rest of the world (Chiaranairungrot et al 2022, Komatsu et al 2020, Yassin et al 2020).

In a study based on health claims data from major commercial insurance payers in Connecticut and the Center for Medicare and Medicaid Services, the estimated PV prevalence increased from 0.31 cases per 100,000 in the 0-34 age group to 237.57 cases per 100,000 in those aged 85 or older (Ma et al 2008). The low frequency of PV in young ages was also observed in a multicenter study conducted in Italy, Austria and the US which followed 1545 patients. In this study, the percentage of patients under 40 and 50 years was 10% and 24% respectively without

relevant differences between sexes (females 10/23% and males 10/26%) (Tefferi 2013). Also, in a study conducted in South East-England (UK), 39% of patients were under 65 years (Phekoo et al 2006).

The proportion of PV patients that were male ranged from 45.7% to 52.8% in Europe (Crodel et al 2022, Darba et al 2022, Benevolo et al 2021, van de Ree-Pellikaan et al 2019, Devos et al 2018), from 51.3% to 65.9% in the US (Grunwald et al 2018, Paranagama et al 2018, Parasuraman et al 2018, Verstovsek et al 2023, Verstovsek et al 2022), and from 56.9% to 62.9% in the rest of the world (Chiaranairungrot et al 2022, Komatsu et al 2020, Yassin et al 2020).

However, not all studies show a higher incidence in males. In a retrospective medical record study conducted in Göteborg (Sweden), the overall annual gender specific IR for PV were 2.40 per 100000 males and 3.08 per 100000 females inhabitants year (Johansson et al 2004). In South East-England (UK), no significant differences by gender were observed. The male to female ratio was 1.11 (95% CI: 0.73, 1.69) and PV IR (standardized to the standard European population) were 1.13 and 1.01 per 100000 inhabitants year respectively (Phekoo et al 2006).

Race and Ethnicity

In the US, the proportion of PV patients belonging to each racial/ethnic group was as follows: White, 64% to 89.1%, Black/African American, 5% to 6.9%, Asian/Pacific Islander, 1% to 6.1%, American Indian/Alaska Native, 0.5%, mixed race, 3%, Unknown/Other race, 1% to 23%, Hispanic ethnicity, 3.9% to 5%, and non-Hispanic ethnicity, 91.4% (Verstovsek et al 2023, Verstovsek et al 2022, Grunwald et al 2018).

Risk factors for the disease:

One study of a PV cluster in Canada indirectly confirms previous research showing that Ashkenazi Jewish ethno-religious identity and older age are risk factors for PV (Le et al 2019).

The Orphanet database reports that the somatic Janus Kinase 2 (JAK2)-V617F mutation is present in the vast majority (95%) of PV patients, and that PV is most common in adults aged > 50 years (Orphanet 2023).

In 2005, several groups reported a single, acquired point mutation (V617F) in the JAK2 gene which is present in more than 95% of PV patients (Campbell and Green 2006). This JAK2 mutation is not in the germ line but, rather, is acquired, although the factors which lead to this mutation are unknown (Baxter et al 2005, Zhao et al 2005, Zhao et al 2005, Zhao et al 2005). In addition, JAK2 exon 12 mutations are relatively specific to JAK2V617F negative PV and mutational frequency among all patients with PV is estimated at 3% (Tefferi and Vainchenker 2011). Despite the evidence that JAK2 mutation is acquired, a systematic review of 61 papers which recruited patients with at least 2 family members diagnosed with MPN (PV represented 50%) concluded that 3 potential origins of MPN may exist: sporadic, familial associated with a genetic heterogeneity or multifactorial inheritance and autosomal dominant inheritance with variable penetrance (Ranjan et al 2013).

Other risk factors identified included:

Overweight (Body mass index [BMI] $\geq$ 25): frequency 46.5% (Benevolo et al 2021)

- Smoking (not otherwise specified): frequency 15.4% to 26.1% (Crodel et al 2022, Benevolo et al 2021)
- Ever smoked: frequency 48.1% (Grunwald et al 2018)
- Former smoking: frequency 30% (van de Ree-Pellikaan et al 2019)

### The main existing treatment options:

The therapeutic goal for PV patients is to alleviate symptoms, reduce risk of cardiovascular events and decrease and/or minimize the risks of progression to MF, myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) (Finazzi and Barbui 2008). In the initial phases of the disease, phlebotomy is a cornerstone treatment with the objective of maintaining hematocrit <45%, a cut-off that has been shown to be associated with a lower risk of cardiovascular death and major thrombosis Marchioli et al 2013 (Marchioli et al 2013).

Risk stratification plays an important role in the initial selection of therapy and is derived from risk factors identified from previous various studies. Current risk stratification in PV is designed to estimate the likelihood of thrombotic complications. Age of 60 years or older and history of thrombosis are the 2 risk factors used to classify patients into low risk (zero risk factors) and high risk (1 or 2 risk factors) groups. In addition, because of the potential risk for bleeding, low-risk patients with extreme thrombocytosis (platelet count greater than $1000x10^9$/L) are considered separately (Tefferi and Vainchenker 2011).

In low-risk patients and without extreme thrombocytosis (age <60 years or absence of history of thrombosis) the preferred approach is low-dose aspirin plus phlebotomy and in those with extreme thrombocytosis (platelets >$1000x10^9$/L), low-dose aspirin provided ristocetin cofactor activity is higher than 30% plus phlebotomy are the preferred approach. In high-risk patients (age 60 years or history of or presence of thrombosis) and those with persistent hematological abnormalities, clinical symptoms, poor compliance with or intolerance of phlebotomy, the recommended treatment includes low-dose aspirin, phlebotomy and cytoreductive agents. Although not approved in all countries, HU is the most common first-line cytoreductive therapy used in PV. In those cases where PV is refractory or the patient is intolerant to HU, the therapeutic management would be low-dose aspirin, phlebotomy and other agents such interferon (IFN)-α (if age lower than 65 years) or busulfan (if age 65 years or older). Other therapeutic options include pipobroman, chlorambucil, 32P (radioactive isotope of phosphorus) (Najean and Rain 1997, Finazzi et al 2005, Kiladjian et al 2011, Tibes and Mesa 2013, Tefferi 2013). In 2015, ruxolitinib was approved in EU for PV patients who are resistant to or intolerant of HU.

### Natural history of the indicated condition in the untreated population, including mortality and morbidity:

In Europe, the incidence proportion of thrombolic complications after diagnosis was 14.3% over an unknown follow up period (Crodel et al 2022), the incidence proportion of thrombotic vascular events was 9.3% over median 4.1 years follow up (van de Ree-Pellikaan et al 2019), and the incidence rate of progression to post-polycythemia vera myelofibrosis (PPV-MF) was 0.8 per 100 PY (Benevolo et al 2021). In the US, the incidence proportion of at least one thrombotic event subsequent to treatment initiation was 16% over a median 2.2 years follow up (Verstovsek et al 2023), and the incidence proportion of at least one thrombotic event after

hydroxyurea treatment initiation was 16.3% over 1 year follow up (Parasuraman et al 2018). In one global study, the incidence rate of major bleeding events in PV patients ranged from 0.3 to 5.3 per 100 PY, and the annual incidence proportion of bleeding events of all types in PV patients ranged from 0.1% to 5.64% (Nicol et al 2021). In the rest of the world, the incidence proportion of disease progression (to myelofibrosis or AML) was 2.1% over mean 2.4 years follow up, the incidence proportion of myelofibrosis was 1.7% over an unknown follow up interval, the incidence proportion of acute myeloid leukemia (AML) transformation was 1.7% over an unknown follow up interval, the incidence proportion of thrombosis ranged from 5.2% over an unknown follow up interval to 16.5% over mean 2.4 years follow up, and the incidence proportion of bleeding ranged from 3.1% over mean 2.4 years follow up to 10.3% over an unknown follow up interval, and the incidence proportion of nonhematologic malignancies was 3.3 over mean 2.4 years follow up (Chiaranairungrot et al 2022, Komatsu et al 2020).

In a multinational study conducted in 7 centers from Italy, Austria and the US and which follow-up 1545 PV patients, palpable splenomegaly, pruritus and vasomotor symptoms were each expressed by about a third of the patients at the time of diagnosis. During follow-up, leukemic transformations were observed in 50 (3%) patients, progression to MF in 138 (9%), arterial thrombosis in 184 (12%), venous thrombosis in 137 (9%), major hemorrhage in 24 out of 572 (4.2%) (Tefferi et al 2013).

In Europe, the hospital in-patient mortality rate from PV was 13.2%, and was higher in patients aged ≥ 60 years compared to patients aged < 60 years (15.9% vs. 1.0%) (Darba et al 2022), and the overall mortality rate among PV patients was 9.2% over median 6.1 years follow up (Benevolo et al 2021). In the US, the 5-year mortality rate for PV patients diagnosed from 2012-2016 was 11.1%, and the median survival time was 12.0 years (95% CI 11.7-12.4) (Verstovsek et al 2022). In the rest of the world, the overall PV mortality rate was 4.3% over a mean 2.4 years follow up (Komatsu et al 2020).

In a study of 1638 patients with PV from 12 European countries, the overall mortality rate was 3.7 deaths/100 patients per year - 1.2 times higher than that expected in the general population. Factors adversely affecting survival were age over 65 and a positive history of thrombotic events (Marchioli et al 2005). Moreover, a multivariable analysis among 1545 patients with contemporary PV showed that survival was adversely affected by older age, leukocytosis, venous thrombosis and abnormal karyotype (Tefferi et al 2013).

The HAEMACARE project (to which 48 cancer registries in 20 European countries are contributing) reported an overall 5-year relative survival for PV patients (N=1382) of 84.8% (95% CI: 81.5-87.5), with a trend to decrease across age groups: 15-49 years 94.9% (95% CI: 89.7-97.5), 50-69 years 86.4% (95% CI: 82.3-89.6) and 70 years or older 79.4% (95% CI: 73.1-84.4) (Maynadié et al 2013). In the US, the estimated PV 3-year survival was 80% (95% CI: 73, 86) and it was higher in those younger than 65-year-old compared with those aged 65 years or older (90% [95% CI: 78-95] versus (vs.) 76% [95% CI: 66-83]; p=0.015). No differences were observed between males and females (Phekoo et al 2006). A recent study showed that median survival of PV patients (14.1 years) was significantly shorter (p <0.001) than that of the age- and sex-matched US population (Tefferi et al 2013).

Over time, PV may progress to MF (PPV-MF), MDS, or acute leukemia. In a study of 396 patients, the 15-year risk of progression of PV to MF or AML was estimated to be 6% and

7%, respectively (Passamonti et al 2004). The rate of leukemia-related mortality in PV patients is 36 times higher than that expected in the general population (Marchioli et al 2005) and splenomegaly at the time of diagnosis of PV is associated with an increased risk of development of MF or AML and shorter survival (Abdulkarim et al 2011). However, PV evolution may differ according to the type of treatment. The overall impact of HU or pipobroman treatments was assessed based on long-term data from the randomized clinical trial (CT) French Polycythemia Study Group / French Intergroup of Myeloproliferative Neoplasms after a median follow-up of 16.3 years. The cumulative incidence of AML/MDS for the total cohort of patients was 9.8%, 23.6% and 33.9% at 10, 15 and 20 years, respectively. Within the intention to treat population, the cumulative incidence of AML/MDS in the HU treatment arm was 6.6%, 16.5% and 24.2% at 10, 15 and 20 years, respectively. The corresponding values in the pipobroman treatment arm were 13.1%, 34.1% and 52.1%, respectively (p=0.004). Similar results were observed when the analyses were performed according to the main treatment actually received by patients. In the case of progression to MF, the cumulative incidence in the intention to treat analysis at 10, 15 and 20 years for patients in the HU treatment arm was 12.6%, 19.4% and 26.9%, respectively, which was comparable to the pipobroman arm at 7.8%, 15.7% and 27%, respectively (p=0.07). However, when the analyses were performed based on the treatment actually received by patients, MF was significantly higher in patients treated with HU (Kiladjian et al 2011).

Polycythemia vera patients are also at increased risk of non-hematologic malignancies including gastrointestinal (GI), lung, non-melanoma skin cancers (NMSC) and others, as shown in a large Danish population-based cohort study which reported a standardized incidence ratio (SIR) for developing a non-hematologic cancer of 1.4 (95% CI: 1.3, 1.5) for PV patients (N=4625). The non-hematologic cancers among PV patients stratified by type with a higher incidence when compared with the general population were: cancer of the esophagus (SIR: 2.4; 95% CI: 1.4, 4.0), liver (SIR: 2.2; 95% CI: 1.1, 3.9), lung (SIR: 1.9; 95% CI: 1.6, 2.2), prostate (SIR: 1.3; 95% CI: 1.0, 1.6), kidney (SIR: 1.9; 95% CI: 1.1, 3.0), urinary tract (SIR: 1.4; 95% CI: 1.1, 1.9), malignant melanoma (SIR: 1.7; 95% CI: 1.0, 2.7) and NMSC (SIR: 1.7; 95% CI: 1.4, 1.9) (Frederiksen et al 2011). Another study based on data from the Swedish Cancer Registry which included 3530 PV patients, reported also an increased risk of secondary malignancies after PV diagnosis. However, among the non-hematologic cancers in Frederiksen et al (2011) with an increased incidence when compared with the general population, only in the case of kidney and skin similar results were observed in the Swedish study (Fallah et al 2011).

Similar results were observed in the US based on SEER data. Khanal et al (2015) reported an increased risk of second primary malignancies in PV patients when compared with the general population. Second primary malignancies occurred at a SIR of 1.29 (95% CI 1.16-1.43) with an absolute excess risk of 42.49 per 10000 population.

The association between long-term HU therapy and development of numerous, often aggressive, cutaneous carcinomas is documented in the literature (Antonioli et al 2012, Best and Petitt 1998, Callot-Mellot et al 1996, Sanchez-Palacios and Guitart 2004, Best and Petitt 1998, Callot-Mellot et al 1996, Sanchez-Palacios and Guitart 2004). The frequency of NMSC was estimated in a retrospective study of 3411 of Ph-negative MPN patients treated with HU (963 PV, 1,912 ET, 357 PMF, 93 PPV MF and 86 PET-MF). In this study, dysplastic pre-carcinomatous lesions (actinic keratosis) were found in 7 patients: 5 PV, 1 ET and 1 PMF.

Three patients temporarily interrupted or reduced HU treatment with an improvement of lesions but no complete resolution; in the 4 patients who continued HU, worsening of lesions was reported in 1 and transformation to squamous cell carcinoma (SCC) occurred in 3. Basal cell carcinoma (BCC) was diagnosed by skin biopsy in 3 patients: 2 PV and 1 ET (Antonioli et al 2012).

All these early and late complications make PV a condition with significant morbidity and mortality (Passamonti et al 2004, Tefferi 2013, Tefferi et al 2013, Vaidya et al 2009).

### Important co-morbidities:

Important co-morbidities in PV have been presented with incidence, prevalence and mortality in Table 2-1.

Additional co-morbidities frequencies (occurring in > 20% of PV patients) were as follows:

- Hypertension: frequency 34.8% to 70.6% and Hypercholesterolemia / hyperlipidemia / dyslipidemia: frequency 8.5% to 30.4% (Benevolo et al 2021, Chiaranairungro et al 2022, Komatsu et al 2020, van de Ree-Pellikaan et al 2019, Grunwald et al 2018, Paranagama et al 2018, Parasuraman et al 2018).Chronic pain: frequency 12.9% to 23.1% (Paranagama et al 2018, Parasuraman et al 2018).
- Cardiovascular conditions / comorbidities: frequency 26.2% to 45.7% (Komatsu et al 2020, Yassin et al 2020).

## 2.3 Indication: Graft versus host disease

Graft versus host disease is an immunologically mediated disease resulting from a complex interaction between donor and recipient immunity, involving donor T cell responses to host antigens and the dysregulation of inflammatory cytokine cascade. Graft versus host disease has been classically categorized into 2 main clinical forms namely acute graft versus host disease (aGvHD) and chronic graft versus host disease (cGvHD) using a cut-off of 100 days post-transplant. However, the signs and symptoms of these 2 categories may occur outside this period or may occur, although infrequently, at the same time in the same patient (overlap syndrome), requiring a complex and comprehensive evaluation of clinical findings rather than a set time period to make an accurate diagnosis. The aGvHD is measured by evaluation of 3 target organ systems: the skin, liver and GI tract (Jagasia et al 2018, Schoemans et al 2018). The most frequently involved organs in patients with cGvHD are skin, mouth, and liver, with less frequent involvement of eye, lung, GI tract, joint/fascia, and genital tract (Lee 2017). Given current trends of transplants from UDs, incidence of GvHD is expected to increase in the next years (Ferrara et al 2009).

About 35%-50% of hematopoietic stem cell transplant (HSCT) recipients will develop acute Graft versus host disease (GVHD). Given the number of transplants performed, it is estimated that about 5500 patients/year will develop acute GVHD (Orphanet 2023).

### Incidence:

**aGvHD:**

In the US, the cumulative incidence of aGvHD in patients after allo-HSCT ranged from 23% (Barba et al 2017) to 44.6% (Johnson et al 2019). Grade 24 aGvHD- incidence ranged between 16% (Barba et al 2017) and 47% (Al-Kadhimi et al 2014) in sibling donor allo-HSCT- patients. The incidence of severe (grade 34) aGvHD- ranged from 5% (Barba et al 2017) to 37% (in UDs) (Al-Kadhimi et al 2014). In the EU, the cumulative incidence of aGvHD in patients after allo-HSCT- ranged from 10% (Germany,Grube et al 2016) to 72% (Italy, Castagnola et al 2014). Grade 24 aGvHD- was reported ranging from 32% (France, Saillard et al 2014 and Denmark, Minculescu et al 2018) to 40% (Spain, Pérez-Simon et al 2008) of the allo-HSCT- patients. The incidence of severe (grade 3-4) aGvHD- ranged from 4% (Germany, Ayuk et al 2015) to 33% (France, Orvain et al 2017). The incidence of SR aGvHD ranged from 6% (Denmark, Minculescu et al2018) to 19% (Italy, Castagnola et al 2014). In studies conducted outside of EU and US, the 2 year cumulative incidence of late aGvHD in patients after allo-HSCT- was reported at 3.2% in Japan (Ohwada et al 2020), while the global incidence of grade 34 aGvHD- decreased from 28% to 25% between 1995 and 2007 (Arai et al 2015).

The incidence of aGvHD in children under age 12 years undergoing HSCT was described in seven observational studies. Table 2-2describes the results of these studies. In children under age 12 years undergoing HSCT, the 100-day cumulative incidence (CuI) of grade II to IV aGvHD was 62.3% in a study in Europe, 41% in global populations, and 44% in studies conducted in specific countries outside of EU (Table 2-2).

**Table 2-2 Incidence of aGvHD in children under age 12 years**

| Region | Grade | CuI or IP | Follow up | Reference |
|---|---|---|---|---|
| Europe | Grade II-IV | 62.26% | 100-day | Szmit et al (2019) |
| | Grade III-IV | 10% | NR | Fagioli et al (2013) |
| Global | Grade II-IV | 13%-41% | 100-day | Rangarajan et al (2021), Qayed et al (2018), Locatelli et al (2013) |
| | Grade III-IV | 3%-9% | 100-day | Qayed et al (2018) |
| Rest of world | Grade II-IV | 44% | 100-day | Yoshida et al (2020) |
| | Grade III-IV | 22% | 100-day | Yoshida et al (2020) |
| | Grade III-IV | 8.7% | Median 9.6 y | Khan et al (2022) |

aGvHD: acute graft vs. host disease, CuI: cumulative incidence, IP: incidence proportion, NR: not reported, y: years

### cGvHD:

Al-Kadhimi et al (2014) evaluated the clinical outcomes of 414 consecutive patients who underwent allo-HSCT from sibling or UD at Karmanos Cancer Center in Detroit, Michigan. In this study the 2-year cumulative incidence of cGvHD was 47% and 53% in the sibling and UD groups, respectively. In Europe, the cumulative incidence of cGvHD was reported from 39% (Germany, Duncker et al 2000) to 70% (Spain, Pérez-Simon et al 2008). The cumulative incidence of cGvHD was between 22% at 5 year (Japan, Kondo et al 2001) and 52% at 1.5 year after allo-HSCT in countries outside of EU (Taiwan, Chen et al 2017).

The incidence of cGvHD in children under age 12 years undergoing HSCT was described in five observational studies. Table 2-3describes the results of these studies. The 1-year CuI of any

grade cGvHD ranged from 10-23% in global populations, and the 2-year CuI of any grade cGvHD was 35% in countries outside of EU.

**Table 2-3 Incidence of cGvHD in children under age 12 years**

| Region | Severity | CuI or IP | Follow up | Reference |
|---|---|---|---|---|
| Global | Any | 10%-23% | 1-y | Rangarajan et al (2021), Qayed et al (2018) |
| | Any | 27% | 3-y | Rangarajan et al (2021) |
| | Any | 15% | 5-y | Locatelli et al (2013) |
| Rest of world | Any | 35% | 2-y | Yoshida et al (2020) |
| | Any | 12.8% | Median 9.6 y | Khan et al (2022) |
| | Extensive | 18.7% | NR | Yoshida et al (2020) |

cGvHD: chronic graft vs. host disease, CuI: cumulative incidence, IP: incidence proportion, NR: not reported, y: years

## Prevalence:

No studies were identified describing the prevalence of chronic or acute GvHD in children under 12 years of age.

According to Orphanet 2023, prevalence of GvHD overall is 1-9 per 100 000.

**aGvHD:**

In Europe, one study reported that the prevalence of aGvHD in children under age 18 years after HSCT ranged from 21,100 per 100,000 persons to 32,100 per 100,000 persons (Kutnik et al 2019).

**cGvHD:**

In the EU, a single center prospective study was conducted in Italy; at 6 months after allo-HSCT, the prevalence of cGvHD was 57%, at 1-year, the prevalence was 40%, while at the second year 28% of the patients had cGvHD (Berchicci et al 2018). In Sweden, the prevalence of cGvHD was 74% in women after HSCT (Knutsson et al 2014). In Europe, one study reported the prevalence of cGvHD in children under age 18 years after HSCT ranged from 6,900 per 100,000 persons to 14,100 per 100,000 persons (Kutnik et al 2019).

## Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

**aGvHD:**

In Turkey, among children under age 18 years with aGvHD, the median (range) age at HSCT was 4.8 years (1.2-15.4), and 26.3% of patients with aGvHD were female (Demirdag et al 2021). In Poland, among patients under age 21 years with aGvHD, 23.7% of aGvHD patients were age $\leq$ 5 years, 54.7% of patients with aGvHD were age 5-15 years, and 37.4% of patients with aGvHD were female (Szmit et al 2019).

The most consistently reported factors significantly associated with an increased risk of grades 2-4 aGvHD were recipient HLA mismatching with the donor, alloimmunization of the donor, the use of a female donor for male recipients, and older patient age (Flowers et al 2011).

**Risk factors for aGvHD in children under age 18 years undergoing HSCT**

In Europe, risk factor for aGvHD included later neutrophil engraftment day (per day) (adjusted OR 1.11, 95% CI 1.01-1.21), busulfan (vs. cyclophosphamide) conditioning regimen (adjusted HR 2.13, 95% CI 1.03-4.39), and busulfan plus cyclophosphamide (vs. total body irradiation plus cyclophosphamide) conditioning regimen (adjusted RR 2.1, 95% CI 1.3-3.2) (De Berranger et al 2014, Demirdag et al 2021, Chiesa et al 2020)

In the US and Canada, peripheral blood transplant (vs. bone marrow transplant) was a risk factor for aGvHD (aHR 1.48, 95% CI 1.19-1.81) (Keesler et al 2018). In global studies, factors associated with aGvHD included age 2-12 years at transplant (vs. age 13-17 years) (aHR 0.42, 95% CI 0.26-0.70), cyclosporine prophylaxis regimen with or without other agents (vs. cyclosporine with methotrexate) (aHR 3.21, 95% CI 1.77-5.83), higher Karnofsky score (aHR 0.36, 95% CI 0.19-0.65), and more recent year of transplant (>2009 vs. < 2004, and 2005-2008 vs < 2004) (aHR 0.24 [95% CI 0.11-0.53] and aHR 0.36 [95% CI 0.20-0.65], respectively) (Qayed et al 2018).

In the rest of the world, factors associated with aGvHD included human leukocyte antigen (HLA) mismatch (vs. without mismatch) (aHR 1.74, 95% CI 1.20-2.52) (Marinho et al 2015), anti-thymocyte globulin (ATG) use as conditioning regimen (vs. non-use) (aHR 0.58, 95% CI 0.40-0.86) (Marinho et al 2015).

**cGvHD**

In Turkey, among children under age 18 years with cGvHD, the median (range) age at HSCT was 9.2 years (2.5-14.5), and 15.4% of patients with cGvHD were female (Demirdag et al 2021).

In Germany, Ayuk et al (2015) conducted a single-center retrospective analysis of 201 patients with cGvHD. Median followup was 41 months (range 25 to 62 months). Median patient age was 54 years (range 1875 years); median donor age was 40 years (range 16–18 years). The proportion of males was 55% in patients and 61% in donors. Another study in Germany (Grube et al 2016) reported a mean age of 48 years (range 1669 years) in 243 cGvHD patient who underwent alloSCT in a singlecenter retrospective study. The proportion of males was 62%. Kondo et al (2001) reported demographical characteristics of 55 Japanese children with cGvHD; 65% were boys, the median age at onset was 9 years (range 0 to 15 years).

**Risk factors for cGvHD in children under age 18 years undergoing HSCT**

In Europe, some studies conducted in pediatric have identified the following risk factors for GvHD: source of transplant (peripheral blood vs. other) (aOR 9.97, 95% CI 1.04-95.55) (Demirdag et al 2021), female-to-male transplant (vs. other sex match) (aOR 8.51, 95% CI 1.32-54.84) (Demirdag et al 2021), age at transplant (per 10 years) (aHR 1.35, 95% CI 1.05-1.75) (Chiesa et al 2020), and Bu-Cy200 conditioning regimen (vs. TBI-Cy) (aRR 2.0, 95% CI 1.3-3.2) (De Berranger et al 2014). In the US and Canada, risk factors for cGvHD included matched unrelated donor (vs. matched related donor) (aHR 5.3, 95% CI 1.18-23.9) (Srinivasan et al 2022) and peripheral blood transplant (vs. bone marrow) (aHR 1.92, 95% CI 1.55-2.39) (Keesler et al 2018). In global studies, factors associated with cGvHD included age at transplant (2-12 years vs. 13-17 years) (aHR 0.32, 95% CI 0.19-0.54), tacrolimus based prophylaxis regimen (vs. cyclosporine with methotrexate) (aHR 2.35, 95% CI 1.18-4.70), cyclosporine

(CSA)-based prophylaxis regimen (vs. cyclosporine with methotrexate) (aHR 2.40, 95% CI 1.22-4.70), and use of a donor younger than the recipient (aHR 0.43, 95% CI 0.26-0.72) (Qayed et al 2018). In the rest of the world, risk factors for cGvHD included peripheral blood transplant (vs. bone marrow) (aHR 1.89, 95% CI 1.04-3.42) (Rocha et al 2021), mother donor (vs. other donor) (aHR 3.06, 95% CI 1.69-5.55) (Rocha et al 2021), previous aGvHD (vs. none) (aHR 5.64, 95% CI 2.06-15.40) (Tavares et al 2020) and HLA disparity 4/6 (vs. matched 6/6) (aRR 2.99, 95% CI 1.42-6.30) (Atsuta et al 2013).

## The main existing treatment options:

### Prophylactic therapy for GvHD

Current GvHD prophylaxis and treatment are only partially effective, with an increased risk for infections, disease relapse, and longterm adverse effects. Data suggest that use of T cell directed immunosuppressants potentially inhibits tolerance induction, at least in part by suppressing regulatory T cell homeostasis. Cytokines and chemokines are the major players in GvHD and blockade of tumor necrosis factor (TNF)α, interleukin6, and CC chemokine receptor type 5 has been tested based on data from mouse models. Recent progress in the understanding of signaling pathway and molecular targeting enables targeting the redundant effect of multiple cytokines. Thus, better understanding and a more targeted approach of signaling pathways in T cells with a newer class of immunomodulatory approaches could lead to more effective control of GvHD (Harris et al 2012).

The standard prophylaxis in myeloablative conditioning is CsA and short course of methotrexate (MTX). For transplantations with reduced intensity conditioning the standard prophylaxis is CsA and mycophenolate mofetil (MMF). The recommended prophylaxis in cord blood transplantation is CsA and MMF, with dosing and duration of administration as for transplantations with reduced intensity conditioning. Antithymocyte globulin has been shown to reduce cGvHD and improve the quality of life in transplantations from a UD. Frequently prophylactic medications are continued after GvHD diagnosis (Ruutu et al 2014).

### Treatment of graft versus host disease

Steroids, with their potent antilymphocyte and antiinflammatory activity, are the gold standard for treatment of GvHD. Many centers treat mild GvHD of the skin (grade 1) with topical steroids alone, but for more severe skin GvHD and any degree of visceral GvHD involvement, high dose systemic steroids are usually initiated (Ferrara et al 2009). More than 50% of patients with grade 2 to 4 aGvHD do not show adequate response to corticosteroids and often become steroid resistant, refractory or fail to taper corticosteroids. Second line therapy is generally recommended for patients whose disease was not resolved, had progressed, and not improved after certain duration of treatment with high-dose steroids, and who do not tolerate steroids (Jamil and Mineishi 2015). Treatments that are currently used for grade 24 SRaGvHD include: antithymocyte globulin, extracorporeal photopheresis (ECP), mesenchymal stromal cells (MSC), low dose MTX, MMF, mammalian target of rapamycin inhibitors (everolimus or sirolimus), etanercept, or infliximab. No clear consensus exist on the best second line agent as response rates are usually limited. Due to the small number of well designed, randomized clinical studies in the treatment of GvHD, no clear benefit of therapeutic agents was demonstrated with second line treatments in larger studies. Therefore, the choice of second line

agent is based on the patient characteristics, potential safety concerns, possible interactions with concomitant medications, convenience, cost, and physician experience (Hill et al 2018, Martin et al 2012).

An increasingly common treatment for GvHD is ECP. During ECP, the patient's WBCs are collected by apheresis, incubated with the DNAintercalating agent, 8methoxypsoralen, exposed to ultraviolet light, and returned to the patient. Extracorporeal photopheresis is known to induce cellular apoptosis, which has strong anti-inflammatory effects in a number of systems, including prevention of rejection of solid organ grafts (Barr et al 1998). Another interesting strategy to treat GvHD is the blockade of the inflammatory cytokine TNFα. The TNF-α can activate APCs, recruit effector cells and cause direct tissue damage. In animal models, TNFα plays a central role in GvHD of the GI tract, which is central to the "cytokine storm" and plasma levels of tumor necrosis factor receptor (TNFR I ; a surrogate marker for TNFα) rise in patients before the clinical manifestations of GvHD appear (Reddy and Ferrara 2003). Etanercept reported a clinical response rate of 46% (6/13) in patients with SRaGvHD, with the higher responses seen in patients with GI involvement (64%; 7/11). Subsequent studies found response rates to be around 5055% and little to no improvement in overall survival (Park et al 2014, De Jong et al 2017).

### Treatment of acute graft versus host disease

A Phase II trial of etanercept, a solubilized TNFR II, showed significant efficacy when added to systemic steroids as primary therapy for aGvHD. Seventy percent of patients had complete resolution of all GvHD symptoms within 1 month, with 80% complete responses (CR) in the GI tract and the skin. The authors also showed that plasma levels of TNFR I were a significant biomarker for clinical GvHD (Levine et al 2008).

### Treatment of chronic graft versus host disease

Treatment for cGvHD depends on the severity of the disease and the number of organs affected. Patients with mild cGvHD with skin involvement are likely to respond to topical steroid treatment. Systemic corticosteroids with or without addition of other immunosuppressive agents are the most widely used firstline therapy for patients with moderate to severe cGvHD. Approximately 50% of patients do not respond or have inadequate control of disease with steroid treatment and require addition of another systemic therapy, or fail to taper corticosteroids (Axt et al 2019, Inamoto 2014, Garnett et al 2013). For patients with cGvHD who do not respond to steroids or are unable to taper steroids, the prognosis remains poor with a 5-year survival rate of 50 to 70%, necessitating the addition of other agents (Wolff et al 2011, Mawardi et al 2019).

Second line treatment should be considered in patients who do not have adequate response to corticosteroids or do not tolerate corticosteroids and in those that cannot taper off steroids (Wolff et al 2011). According to the global treatment guidelines, various treatments with different modes of actions are accepted. The most common secondline agents globally used in clinical practice included ECP, low dose MTX, MMF, sirolimus, everolimus, infliximab, rituximab, imatinib, pentostatin, and ibrutinib. In addition, therapeutic agents including calcineurin inhibitors (CNIs), proteasome inhibitors, and tyrosine kinase inhibitors were included in the treatment guidelines. These agents may be used alone or in combinations with steroids.

No consensus was reached so far regarding the best agent to be used for the treatment of patients who failed corticosteroids (Ruutu et al 2014, Penack et al 2020).

## Natural history of the indicated condition in the untreated population, including mortality and morbidity:

### Natural history of graft versus host disease in pediatric population

The most common manifestations of acute and or chronic GvHD in children under age 18 years reported in Europe, US and Canada and international studies were in the skin (frequency 60.6-69.8%), gut (frequency 14.1-77%), lung (17.1-38.8%) and liver (frequency 1.5-45%) (Chandar et al 2022, Salamonowicz-Bodzioch et al 2022, Verbeek et al 2022, Faraci et al 2020, Bresters et al 2017, Gassas et al 2013 ).

Common complications of GvHD in children under age 18 years undergoing HSCT in Europe included infections (frequency 80%), bronchiolitis obliterans syndrome (frequency 17.3%), thrombotic microangiopathy (frequency 16%), cytopenia (frequency 14.8%), and renal insufficiency (frequency 12.3%) (Verbeek et al 2022). Among children undergoing HSCT, GvHD was a risk factor for the following complications in Europe: endocrinopathies, iatrogenic Cushing disease, gastrointestinal infection, invasive fungal infection, alopecia and hepatobiliary dysfunction (Guemes et al 2022, Salamonowicz-Bodzioch et al 2022, Hazar et al 2019, Bresters et al 2017, Thorvaldson et al 2016 ).

### Mortality of acute GvHD among pediatric patients

In Turkey, the 1-y mortality rate among children under the age of 18 years with aGvHD was 41% (Verbeek et al 2022), and the 1-y and 5-y OS rates were 61.1% and 55.0% (Demirdag et al 2021). In the rest of the world, the 5-y OS rate was 58.1% for any grade aGvHD (Mitsui et al 2020), and the 3-y OS rate was 76.3% for grade II, 66.9% for grade III, and 42.5% for grade IV aGvHD (Kato et al 2019); the 3-y NRM rate was 11.0% for grade II, 20.6% for grade III, and 55.3% for grade IV aGvHD (Kato et al 2019); and the 3-y relapse-free survival (RFS) rate was 72.2% for grade II, 62.6% for grade III, and 43.5% for grade IV aGvHD (Kato et al 2019).

### Mortality of chronic GvHD among pediatric patients

One international study described survival and mortality rates in children with cGvHD under age 12 years (Yoshida et al 2020). The 5-year (y) overall survival (OS) for children with cGvHD was 89% (95% confidence interval [CI] 74-96), the 5-y event-free survival (EFS) for children with cGvHD was 82% (95% CI 65-92), and the 5-y transplant-related mortality (TRM) in children with cGvHD was 3% (95% CI 0-13) (Yoshida et al 2020).

In Turkey, the 1-y, 3-y and 5-y OS rates in children under the age of 18 years with cGvHD were 92.3%, 83.1% and 71.2% (Demirdag et al 2021). In the rest of the world, the median survival time in children with cGvHD following HSCT for high-risk acute leukemia was 160.3 days (Chandar et al 2022); the 3-y NRM was 10.4% in children with cGvHD and 15.4% in children with extensive cGvHD (Kato et al 2019); the 3-y RFS was 75.2% in children with cGvHD and 73.5% in children with extensive cGvHD (Kato et al 2019); and the 3-y OS was 79.3% in children with cGvHD and 76.1% in children with extensive cGvHD (Kato et al 2019); and the

5-y OS in children with cGvHD ranged from 67.6% to 72.2% (Mitsui et al 2020, Hamidieh et al 2019).

### Natural history of acute graft versus host disease in adult population

Based on studies reporting cumulative incidence of NRM between 3 to 12 months, the lowest frequency was 11% (FU 6 months) among patients with aGvHD confirmed by biopsy and treated with intra-arterial steroid infusions (Japan, Nishimoto et al 2015), while the highest incidence was 77.6% (FU 12 months) in patients with SR aGvHD (Germany, Von Dalowski et al 2016). For a follow up period of 4-years, the cumulative incidence of NRM was 82.3% in SR-aGvHD patients in Spain (García-Cadenas et al 2017). For a follow up time of 6 months to 5-years, the cumulative incidence of TRM varied between 17.6% (FU 12 months) in aGvHD patients receiving ECP as the second/third line treatment (Greece, Sakellari et al 2018) to 58% (FU 12 months) among patients with grade 3 or 4 aGvHD recruited between 1997 and 2006 (US, El-Jawahri et al 2016). The proportion of patients with aGvHD as cause of death ranged from 5.3% (FU 6 months) among patients with aGvHD confirmed by biopsy (Japan, Nishimoto et al 2015) to 66.7% (FU ≤35.1 months) among SR-aGvHD patients (US, Roddy et al 2016).

### Mortality of acute graft versus host disease in adult population

The overall mortality rate of aGvHD ranges widely, with up to 100% mortality (FU <9 months) reported in alloSCT patients treated with etanercept for SRaGvHD (The Netherlands, De Jong et al 2017). Fifteen months to 3-year overall mortality rate varied between 36.6% (FU 3 years) in patients with confirmed aGvHD colon tissues (South Korea, Park et al 2014) to 89% (FU 15 months) in patients with SR GI aGvHD (global: Floisand et al 2019).

### Natural history of chronic graft versus host disease in adult patients

For a follow up time of 2 to 4years, the cumulative incidence of NRM varied between 19% (FU 2 years, France, Saillard et al 2014 ) to 36% (FU 3 years) in cGvHD patients (International, Arai et al 2015). For a follow up of ≥5 years, the cumulative incidence of NRM ranged from 9.5% (FU 5 years) among cGvHD patients (Germany, Ayuk et al 2015) to 44% (FU 5 years) in high risk group of cGvHD patients (US, Arora et al 2015). Among cGvHD patients (all severities), Grube et al (2016) reported the incidence of TRM at 35% for an almost 15 years follow up.

### Mortality of chronic graft versus host disease in adult population

The overall mortality rate in cGvHD patients is ranging between 2.6% (FU 6 months) in SR patients (EU and US, Zeiser et al 2015) and 26.9% (FU median 41 months) (Germany, Ayuk et al 2015). One to 12 months overall mortality rate ranged between 2.6% (FU 6 months) in SR cGvHD patients (EU and US, Zeiser et al 2015) to 21.4% (FU 12 months) in those with cGvHD treated with AT-MSCs (Italy, Jurado et al 2017). For a FU of ≥2 years, the overall mortality ranged from 14.3% (FU <9 years) among cGvHD children (Kuwait, Nanda et al 2018) to 26.9% (FU <5.2 years) in cGvHD patients secondary to allo-SCT (Germany, Ayuk et al 2015).

### Important co-morbidities of GvHD in adult patients:

In adult GvHD subjects, comorbidities are key factors in determining risks of grade 3-4 aGvHD and the prognosis of patients diagnosed with aGvHD (Sorror et al 2014). Despite this, the prevalence of comorbid illness in patients with GvHD, and the influence of comorbidity burden upon subsequent functional and survival outcomes, is not well described. Most of the studies are describing the infection related comorbidities only (Wood et al 2013). In the US, Sorror et al (2014) assessed whether the comorbidities can provide prognostic information about development of aGvHD. The study enrolled 2985 patients treated with HSCT for hematological malignant or non-malignant diseases, and comorbidity prevalence at HSCT were calculated. The most prevalent comorbidities were moderate pulmonary (27%), mild hepatic (16%), severe pulmonary (14%), and psychiatric disorders (11%) (Sorror et al 2014).

In cGvHD, a study in the US estimated comorbidity prevalence at HSCT and at cGvHD enrollment including 239 adult patients (Wood et al 2013). The assessed prevalence of comorbidities is described in Table 2-4.

**Table 2-4 Prevalence of comorbidities in chronic graft versus host disease in adult patients**

| Comorbidity | Prevalence at HSCT | Prevalence at cGvHD |
|---|---|---|
| COPD, ARDS, or Emphysema | 59.4% | 69.5% |
| Upper gastrointestinal disease | 30.5% | 51.9% |
| Obesity and/or BMI >30 | 24.7% | 16.3% |
| Depression | 21.3% | 23.8% |
| Prior solid tumor | 13% | 13% |
| Diabetes types I and II | 9.6% | 17.2% |
| Hepatic, mild | 7.5% | 22.6% |
| Infection | 6.3% | 13.4% |
| Anxiety or panic disorders | 5.9% | 8.8% |
| Arthritis (rheumatoid and osteoarthritis) | 4.6% | 6.7% |
| Angina | 4.2% | 4.6% |
| Asthma | 4.2% | 4.2% |
| Neurological disease | 4.2% | 9.6% |
| Osteoporosis | 3.3% | 46.9% |
| Arrhythmia | 2.1% | 4.2% |
| Congestive heart failure | 2.1% | 0.8% |
| Inflammatory bowel disease | 1.7% | 1.7% |
| Heart attack | 1.3% | 1.3% |
| Degenerative disk disease | 0.8% | 2.5% |
| Heart valve disease | 0.4% | 1.3% |
| Stroke or TIA | 0.4% | 0.4% |
| Visual impairment | 0% | 0.4% |
| Hearing impairment | 0% | 0.4% |
| Hepatic impairment, moderate/ severe | 0% | 10.5% |

| Comorbidity | Prevalence at HSCT | Prevalence at cGvHD |
|---|---|---|
| Moderate/severe renal impairment | 0% | 3.8% |
| Peripheral vascular disease | 0% | 0.4% |

ARDS=Acute respiratory distress syndrome; BMI=Body mass index; COPD=Chronic obstructive pulmonary disorder; cGvHD=Chronic graft versus host disease; HSCT=Hematopoietic stem cell transplantation; TIA=Transient ischemic attack.

**Source:** Wood et al 2013.

Note: Prevalence is calculated using the data mentioned in the source, Wood et al 2013..

### Important co-morbidities among pediatric patients

No studies were identified describing the frequency of comorbidities in children with aGvHD or cGvHD under 18 years of age.

### Infections in adult patients

In the identified observational studies, the incidence proportion of any infection ranged from 48% in patients with sclerotic skin cGvHD (France, Jachiet et al 2014) to 92.1% in patients with GI aGvHD (US, Johnson et al 2019). When the infection was reported according to the type, the most frequent infection was bacterial with the incidence proportion ranging up to 54.4% in GIaGvHD patients (Johnson et al 2019). One-year cumulative incidence of bacterial infection ranged from 35.3% in GvHD patients treated with MSCs (Belarus, Stoma et al 2018) to 73.5% in those with grade 2–4 SR aGvHD treated with inolimomab or etanercept (Spain, GarcíaCadenas et al 2017). Viral infection was the second most frequent infection with an incidence proportion ranging from 23.8% in aGvHD patients treated with inolimomab and etanercept (the Netherlands, Van Groningen et al 2016) to 58.6% in patients treated with vedolizumab for SR GI aGvHD (US, Floisand et al 2019). One year cumulative incidence of viral infection ranged from 20.6% in GvHD patients treated with MSCs (Belarus, Stoma et al 2018) to 67.5% in those with grade 2–4 SRaGvHD treated with inolimomab or etanercept (Spain, García-Cadenas et al 2017). Two year cumulative incidence of viral infection was 51.8% among patients with GI SR aGvHD or aGvHD resistant to another line of immunosuppressive drug after corticosteroids and treated with alemtuzumab (France, Meunier et al 2014). Fungal infection was the least frequent infection with the incidence proportion ranging from as low as 4.2% in patients with GI SR aGvHD or aGvHD resistant to another line of immunosuppressive drug after corticosteroids and treated with alemtuzumab (France, Meunier et al 2014) to 35.8% in aGvHD patients (US, Johnson et al 2019). One year cumulative incidence of fungal infection ranged between 14.2% (Spain, GarcíaCadenas et al 2017) to 20.6% (Belarus, Stoma et al 2018) whereas 2year cumulative incidence was 7.8% in patients with aGvHD grade 2–4 or extensive chronic GvHD under one high or a combination of immunosuppressive treatment (Germany,, Christen et al 2019).

# 3 Part II Safety specification Module SII: Non-clinical part of the safety specification

**Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:**

| Key Safety findings (from non-clinical studies) | Relevance to human usage |
|---|---|
| **Effects on lymphoid organs and bone marrow**<br>Reversible lymphoid depletion in bone marrow and lymphoid organs in rats and dogs were noted. In addition, in dogs, demodectic mange, bacterial pneumonia and viral-induced papillomas were seen. The emergence of demodectic mange mites in dogs is likely a result of the pharmacologic inhibition of eosinophils by ruxolitinib (Adachi and Alam 1998, van der Bruggen et al 1995, Pazdrak et al 1995). The bacterial pneumonia and viral-induced papillomas most likely reflect a response to the immunosuppressive effects of ruxolitinib in dogs. | Pharmacologically mediated immunosuppression may result in an increased susceptibility to infections.<br>Effects on hematology parameters can be monitored in patients with dose adjustments as necessary. |
| **Hematologic Changes**<br>Reversible hematological effects included decreases in red blood cells, reticulocytes, eosinophils and lymphocytes. | Risk of decreases in red blood cells (RBC) mass parameters and WBC and their clinical consequences.<br>Effects on hematology parameters can be monitored in patients with dose adjustments as necessary. |
| **Gastrointestinal Tract**<br>In the 4-week dog toxicity study, minimal inflammation of the ileum only was seen in only 1 of 8 dogs given 10 mg/kg/day. At a dose of 20 mg/kg, erosion with inflammation of the ileum was observed in 2 of 8 dogs; whereas inflammation without erosion was seen in 2 dogs at this dose. Lesions of the GI tract were not observed in dogs given 3 mg/kg/day or in dogs following a 4-week recovery period. Similar lesions were not observed at any dose in the 6-month dog study (doses <10 mg/kg/day) or at any dose in the 12-month dog study (doses <6 mg/kg/day). | Flatulence is a common adverse drug reaction (ADR) in the MF population and constipation is a common ADR in the PV population (Section 4.8 of the SmPC).<br>As previously reviewed and concluded in PSUR 06, review of CT data in PSUR 06 did not identify severe GI events as safety concerns. This fact along with the low incidence of findings localized to the ileum at high doses in an early dog toxicology study, the absence of GI findings in the definitive longer term dog toxicology studies and absence of GI findings in definitive rat studies, suggests a low level of clinical relevance.<br>As a result, in PSUR 06, Novartis proposed to remove the GI events as key safety findings from non-clinical studies from Section 3 'Non-clinical part of the safety specification' of the RMP (v 8.0). |
| **Effects on the heart**<br>Minimal heart fibrosis was seen in females in 6 of 15 female rats in a 13-week toxicity study at doses ≥150 mg/kg. The 150 mg/kg/day dose is associated with an unbound area under the curve (AUC)0-τ of >16 µM*h which is 57-fold the unbound AUC0-τ at the maximum recommended 25 mg b.i.d. clinical dose. Safety margin at the no effect level for this finding is 20-fold. | The effects observed in female rats are not deemed to be clinically relevant due to their occurrence at very high exposures. |

| Key Safety findings (from non-clinical studies) | Relevance to human usage |
|---|---|
| **Effects on the adrenal**<br>Minimal adrenal cortical atrophy in 7 of 15 male rats was noted at the highest dose administered, 60 mg/kg/day, in the 6-month study. Precise mechanisms for adrenocortical atrophy in males were not identified. This finding was not noted in dog studies of up to 1 year in duration. | The effects observed in rats only are not deemed to be clinically relevant. |
| **Effects on prostate and estrus cycle**<br>In the 6-month dog toxicity study (and not in the 12-month toxicity study), prostatic hypoplasia/atrophy was noted. All male dogs with prostatic hypoplasia/atrophy in the 6-month study had normal testes with active spermatogenesis. Male dogs in the high dose group (6 mg/kg/day) in the 12-month study had similar Cmax and AUC values as the mid-dose group (5 mg/kg/day) in the 6-month study but did not have the prostatic microscopic finding. In female dogs given doses of 0.5 to 10 mg/kg/day, a small number were noted to be in the diestrus phase of the estrus cycle vs. anestrus/proestrus for control animals in the 6-month study. As noted, these findings were not replicated in the 52-week dog study.<br>Both findings were deemed of unlikely relationship to ruxolitinib. | The effects are not deemed to be clinically relevant. Nonclinical findings in the 6-month dog study were deemed of uncertain relationship to ruxolitinib and were not observed in the definitive dog toxicology study. Good laboratory practice (GLP) reproductive toxicology studies in rat did not reveal any effects on estrus cycling. |
| **Embryofetal toxicity**<br>No signs of teratogenicity. Ruxolitinib was embryolethal and produced fetotoxicity (increases in post-implantation loss and reduced fetal weights). Ruxolitinib is transferred into the milk in lactating rats with a milk/plasma concentration ratio of approximately 13. | Potentially embryotoxic and fetotoxic in humans. Potentially excreted into breast milk. See SmPC. 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 (SmPC). |
| **Juvenile toxicity**<br>Administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. Ruxolitinib was administered daily by oral gavage at doses from 1.5 to 75 mg/kg/day from Day 7 (the human equivalent of a newborn) to 63 post-partum (pp), 15 mg/kg/day from Day 14 (the human equivalent of 1 year of age) to 63 pp and 5, 15 and 60 mg/kg/day from Day 21 (the human equivalent of 2-3 years of age) to 63 pp. Doses ≥30 mg/kg/day (1200 ng*h/mL based on unbound AUC) resulted in fractures and early termination of the groups when treatment started on Day 7 pp. Reduced bone growth was observed at doses ≥5 mg/kg/day (≥150 ng*h/mL based on unbound AUC) when treatment started on Day 7 pp and at ≥15 mg/kg/day (≥150 ng*h/mL based on unbound AUC) when treatment started on Day 14 pp or Day 21 pp. Based on unbound | No safety concerns regarding growth and development have been identified in the GvHD pediatric studies. However, long-term safety in pediatric patients is considered as missing information. |

| Key Safety findings (from non-clinical studies) | Relevance to human usage |
|---|---|
| AUC, fractures and reduced bone growth occurred at exposures 13- and 1.5- fold the exposure in adult patients at the maximum recommended dose of 25 mg b.i.d., respectively. The effects were generally more severe when administration was initiated earlier in the postnatal period. Other than the effects on bone development, the toxicity profile in juvenile rats was comparable to that observed in adult rats. | |
| **Safety Pharmacology**<br>Adverse decreases in blood pressure (BP) 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 Cmax) at the non-adverse level in the dog and rat studies were 15.7-fold and 10.4-fold greater, respectively, than the maximum human recommended 25 mg b.i.d. dose. | There were no clinically significant findings in a thorough QT study in healthy volunteers [INCB 18424-138]. Hypertension is already a very common ADR for PV.<br>The effects observed in female, but not male rats on derived minute volume are not deemed to be clinically relevant. |
| **Source:** Non clinical overview, INCB 18424-138, Adachi and Alam 1998, van der Bruggen et al 1995, Pazdrak et al 1995, [Ruxolitinib SmPC 2025]. | |

No additional non-clinical data is considered as required.

# 4 Part II Safety specification Module SIII Clinical trial exposure

## 4.1 Part II Module SIII Clinical trial exposure

Clinical trial exposure and safety information included in this RMP are based on MF, PV and GvHD patient populations.

- MF and PV studies include 3222 patients treated with ruxolitinib comprising 2848 patients with MF and 374 patients with PV.
- GvHD studies in adults and adolescents include 201 patients exposed to ruxolitinib in Study CINC424C2301, 71 patients exposed to ruxolitinib in Study INCB018424-271 and 235 patients exposed to ruxolitinib in Study CINC424D2301.
- Pooled pediatric GvHD studies include 45 patients exposed to ruxolitinib in Study INC424F12201 and six adolescent patients from CINC424C2301 study with acute GvHD, 45 patients exposed to ruxolitinib in Study CINC424G12201 and 10 adolescent patients in CINC424D2301 study with chronic GvHD patients.

**Myelofibrosis:**

- Randomized phase MF patient population consists of all MF patients from the Phase III studies, INCB 18424-351, CINC424A2352, considering only the randomized phase data of ruxolitinib treated patients, as well as the Placebo/Best available therapy (BAT) patients.
- Overall MF patients population consists of all MF patients treated with ruxolitinib, including data from the extension period of patients in Study INCB 18424351 and Study CINC424A2352 originally randomized to ruxolitinib continuing treatment in the extension, plus patients who crossed over to ruxolitinib in Study INCB 18424351 and Study CINC424A2352 and all patients in the Phase II MF study, INCB 18424-251 and Expanded-Access Study, CINC424A2401.

**Polycythemia vera:**

- Randomized phase PV patients population: includes data collected during the comparative treatment period, up to Week 32 for Study CINC424B2301 and up to Week 28 for CINC424B2401.
- Overall PV patients population: consists of all PV patients treated with ruxolitinib (i.e. all patients treated with ruxolitinib in Study CINC424B2301 and Study CINC424B2401, including those patients from the BAT who crossed over to ruxolitinib, as well as all PV patients treated with ruxolitinib in the Phase II study, Study INCB 18424256).

**Graft versus host disease:**

The analysis of ruxolitinib safety in patients with GvHD is primarily based on the randomized Phase III studies CINC424C2301 and CINC424D2301. The safety data from the single arm Phase II study, Study INCB018424-271 serves as supportive data.

The analysis of ruxolitinib safety in pediatric patients with treatment of corticosteroid-refractory or treatment-naive acute or chronic GvHD after allogenic stem cell transplantation is based on Phase II studies INC424F12201 (REACH 4), and CINC424G12201 (REACH 5) studies and adolescent patients from INC424C2301 (REACH 2) and INC424D2301 (REACH 3) studies.

The adolescent patients from C2301 and D2301 respectively are considered in the adult/adolescent population as well as in the pooled pediatric population.

**Acute Graft versus host disease:**

Safety data presented in this report for adult and adolescent patients with aGvHD:

- Data for ruxolitinib and BAT for the randomized phase in Study CINC424C2301 up to Day 28
- Data for entire treatment period up to data cut-off of secondary CSR (Date 06-Jan-2020) of ruxolitinib -treated and BAT patients in Study CINC424C2301
- Overall aGvHD population consists of all data from all ruxolitinib treated patients up to LPLV, including crossover patients in Study CINC424C2301
- Supportive data from Study INCB018424-271 entire treatment period

The safety data from Study CINC424C2301 and Study INCB018424-271 were not pooled as there were differences in the study design and frequency, severity and seriousness of AEs observed across the 2 studies during the entire treatment period.

**Acute Graft versus host disease in pediatric patients:**

The assessment of ruxolitinib safety in pediatric patients is based on the data from Study INC424F12201 and data from all ruxolitinib-treated adolescent patients (12-17 years of age) from study CINC424C2301 including those who crossed over from BAT arm. All available data up to LPLV are considered.

**Chronic Graft versus host disease**

The safety data presented for adult and adolescent patients with cGvHD:

- Randomized phase data for ruxolitinib and BAT for the randomized treatment period in Study CINC424D2301 up to Cycle 7 Day 1 (C7D1)
- Data for entire treatment period up to data cut-off of primary CSR (Date: 8-May-2020) of ruxolitinib and BAT treated patients in Study CINC424D2301
- Overall cGvHD population consists of all data from all ruxolitinib treated patients up to LPLV, including crossover patients in Study CINC424D2301

**Chronic Graft versus host disease in pediatric patients**

The assessment of ruxolitinib safety in pediatric patients with moderate and severe chronic GvHD after allogeneic stem cell transplantation is based on data from Study CINC424G12201 and from all ruxolitinib-treated adolescent patients (12-17 years of age) from study CINC424D2301 including those who crossed over from BAT arm. All available data up to data cut-off are considered.

The table below depicts the studies that are pooled in this RMP with the data cut-off dates for MF, PV and GvHD populations.

**Table 4-1 Studies pooled in the RMP**

| Database /population | Studies | LPLV/Data cut-off dates |
|---|---|---|
| Myelofibrosis | INCB 18424-251 | 01-Oct-2012 |
| | CINC424A2352 | 20-Apr-2015 |
| | INCB 18424-351 | 08-Jan-2016 |
| | CINC424A2401 | 26-Jan-2017 |
| Polycythemia vera | INCB 18424-256 | 20-Jun-2018 |
| | CINC424B2401 | 06-Apr-2018 |
| | CINC424B2301 | 09-Feb-2018 |
| Acute GvHD in adult and adolescent patients | CINC424C2301 | 23-Apr-2021 (Final CSR) |
| Acute GvHD in adult patients | INCB018424-271 | 05-Jun-2019 Final CSR) |
| Acute GvHD in pediatric patients | INC424F12201 | 02-Feb-2023 (Final CSR) |
| | Adolescent patients from CINC424C2301 study | 23-Apr-2021 (Final CSR) |
| Chronic GvHD in adult and adolescent patients | CINC424D2301 | 15-Dec-2022 (Final CSR) |
| Chronic GvHD in pediatric patients | CINC424G12201 | 26-Aug-2024 (Final CSR) |
| | Adolescent patients from CINC424D2301 study | 15-Dec-2022 (Final CSR) |

The safety data from Study CINC424C2301 and Study INCB018424-271 were not pooled as there were differences in the study design and frequency, severity and seriousness of AEs observed across the 2 studies during the entire treatment period.

Referencing nomenclature:

- Clinical studies in MF patients: INCB 18424-351, CINC424A2352, INCB 18424-251 and CINC424A2401 are referred to as Study 351, Study 352, Study 251 and Study A2401, respectively.
- Clinical studies in PV patients: CINC424B2301, CINC424B2401 and INCB 18424-256 are referred to as Study B2301, Study B2401 and Study 256, respectively.
- Clinical studies in GvHD patients: Study CINC424C2301, Study INCB018424-271, Study CINC424F12201, Study CINC424D2301, and Study CINC424G12201 are referred to as Study C2301, Study 271, Study F12201, Study D2301, and Study G12201, respectively.

## Exposure by duration

Clinical trial exposure in the overall MF and PV populations, overall aGvHD and cGvHD population, and aGvHD/cGvHD pediatric population by duration are provided in Table 4-2, Table 4-3 and Table 4-4 respectively.

**Table 4-2 Duration of exposure to ruxolitinib in MF and PV in adult patients-Safety set**

| | MF Patients (N=2848) | PV Patients (N=374) | Total (N=3222) |
|---|---|---|---|
| Exposure categories - n (%) | | | |
| 0 - <6 months | 656 (23.0) | 23 (6.1) | 679 (21.1) |
| 6 - <12 months | 615 (21.6) | 14 (3.7) | 629 (19.5) |
| 12 - <18 months | 323 (11.3) | 15 (4.0) | 338 (10.5) |
| 18 - <24 months | 230 (8.1) | 9 (2.4) | 239 (7.4) |
| 24 - <30 months | 228 (8.0) | 16 (4.3) | 244 (7.6) |
| 30 - <36 months | 251 (8.8) | 38 (10.2) | 289 (9.0) |
| 36 - <42 months | 176 (6.2) | 64 (17.1) | 240 (7.4) |
| 42 - <48 months | 100 (3.5) | 30 (8.0) | 130 (4.0) |
| >=48 months | 269 (9.4) | 165 (44.1) | 434 (13.5) |
| Duration of exposure (months) | | | |
| N | 2848 | 374 | 3222 |
| Mean | 20.420 | 43.829 | 23.138 |
| SD | 16.8420 | 23.5298 | 19.2633 |
| Median | 14.242 | 43.811 | 16.887 |
| Minimum | 0.03 | 0.03 | 0.03 |
| Maximum | 68.07 | 115.91 | 115.91 |
| Patient-years | 4846.41 | 1366.01 | 6212.42 |

**Source:** Annex 7b - Table 4.2-24

**Table 4-3 Duration of exposure to ruxolitinib in acute and chronic GvHD in adolescents and adult patients-Safety Set**

| | Acute GvHD | | Chronic GvHD |
|---|---|---|---|
| | Study C2301 Rux Overall N=201 | Study 271 Rux N=71 | Study D2301 Rux Overall N=235 |
| Total number of patients receiving the drug -n (%) | 201 (100) | 71 (100) | 235 (100) |
| Duration of exposure (weeks) | | | |
| Mean (SD) | 13.9 (14.73) | 18.8 (26.24) | 78.9 (58.05) |
| Median | 8.9 | 6.6 | 69.1 |
| Q1-Q3 | 3.3-23.9 | 2.1-33.9 | 21.0-133.6 |
| Min - Max | 0.3-96.9 | 0.6-115.9 | 0.7-164.7 |
| Duration of exposure categories -n (%) | | | |
| <= 4 weeks | 57 (28.4) | 29 (40.8) | 10 (4.3) |
| > 4 - 8 weeks | 38 (18.9) | 14 (19.7) | 13 (5.5) |
| > 8 - 12 weeks | 27 (13.4) | 2 (2.8) | 15 (6.4) |
| > 12 - 16 weeks | 10 (5.0) | 4 (5.6) | 12 (5.1) |
| > 16 - 20 weeks | 7 (3.5) | 2 (2.8) | 6 (2.6) |
| > 20 - 24 weeks | 23 (11.4) | 2 (2.8) | 11 (4.7) |

| | Acute GvHD | | Chronic GvHD |
|---|---|---|---|
| | Study C2301 Rux Overall N=201 | Study 271 Rux N=71 | Study D2301 Rux Overall N=235 |
| > 24 - 36 weeks | 27 (13.4) | 2 (2.8) | 15 (6.4) |
| > 36 - 48 weeks | 7 (3.5) | 8 (11.3) | 16 (6.8) |
| > 48 - 60 weeks | 2 (1.0) | 2 (2.8) | 11 (4.7) |
| > 60 - 72 weeks | 1 (0.5) | 2 (2.8) | 10 (4.3) |
| > 72 - 84 weeks | 0 | 1 (1.4) | 6 (2.6) |
| > 84 - 96 weeks | 0 | 1 (1.4) | 7 (3.0) |
| > 96 - 120 weeks | 2 (1.0) | 2 (2.8) | 18 (7.7) |
| > 120 - 144 weeks | 0 | 0 | 38 (16.2) |
| > 144 weeks | 0 | 0 | 47 (20.0) |
| Patient-Treatment-Years | 53.7 | 25.6 | 355.5 |

Patient-Treatment-Years is the sum of each patient's treatment exposure in years.
Source: (Annex 7c - Table 4.2-1)

**Table 4-4 Duration of exposure to ruxolitinib in acute and chronic GvHD in pediatric patients-Safety set**

| | **Acute GvHD (F12201+C2301) Total pediatric patients N=51** | **Chronic GvHD (G12201+D2301) Total pediatric patients N=55** |
|---|---|---|
| Total number of patients receiving the drug -n (%) | 51 (100) | 55 (100) |
| **Duration of exposure (weeks)** | | |
| Mean (SD) | 17.4 (12.51) | 65.5 (52.65) |
| Median | 16.7 | 57.1 |
| Q1-Q3 | 6.0-23.9 | 13.1-105.6 |
| Min - Max | 1.1-48.9 | 2.1-163.3 |
| **Duration of exposure categories -n (%)** | | |
| <= 4 weeks | 8 (15.7) | 4 (7.3) |
| > 4 - 8 weeks | 9 (17.6) | 4 (7.3) |
| > 8 - 12 weeks | 3 (5.9) | 2 (3.6) |
| > 12 - 16 weeks | 2 (3.9) | 4 (7.3) |
| > 16 - 20 weeks | 8 (15.7) | 4 (7.3) |
| > 20 - 24 weeks | 10 (19.6) | 0 |
| > 24 - 36 weeks | 6 (11.8) | 2 (3.6) |
| > 36 - 48 weeks | 4 (7.8) | 4 (7.3) |
| > 48 - 60 weeks | 1 (2.0) | 4 (7.3) |
| > 60 - 72 weeks | 0 | 6 (10.9) |
| > 72 - 84 weeks | 0 | 3 (5.5) |
| > 84 - 96 weeks | 0 | 3 (5.5) |
| > 96 - 120 weeks | 0 | 5 (9.1) |

| | Acute GvHD (F12201+C2301) Total pediatric patients N=51 | Chronic GvHD (G12201+D2301) Total pediatric patients N=55 |
|---|---|---|
| > 120 - 144 weeks | 0 | 2 (3.6) |
| > 144 weeks | 0 | 8 (14.5) |
| **Patient-Treatment-Years** | 17.0 | 69.0 |

Patient-Treatment-Years is the sum of each patient's treatment exposure in years.
Source: (Annex 7c Table 4.1.1)

## Exposure by age, gender and race

Clinical trial exposure in the overall MF and PV populations by age, gender and race is provided in Table 4-5.

Clinical trial exposure in the overall aGvHD and cGvHD adult and adolescent population by age and gender is provided in Table 4-6 and by race, is provided in Table 4-8.

Clinical trial exposure in pediatric aGvHD and cGvHD patients by age and gender is provided in Table 4-7 and by race is provided in Table 4-9.

**Table 4-5 Clinical trial exposure by age, gender, and race in MF and PV adult patients**

| Duration of Exposure (years) | MF patients N = 2848 n (Patient-Years) | PV patients N=374 n (Patient-Years) | Total (MF & PV) N = 3222 n (Patient-Years) |
|---|---|---|---|
| **Age group** | | | |
| ≤65 years | 1271 (2474.43) | 245 (922.58) | 1516 (3397.01) |
| >65 years | 1577 (2371.98) | 129 (443.43) | 1706 (2815.41) |
| **Gender** | | | |
| Male | 1566 (2584.44) | 229 (829.11) | 1795 (3413.55) |
| Female | 1282 (2261.97) | 145 (536.90) | 1427 (2798.87) |
| **Race** | | | |
| Caucasian | 2635 (4450.67) | 334 (1234.98) | 2969 (5685.65) |
| Non-Caucasian | 181 (316.73) | 40 (131.03) | 221 (447.76) |
| Unknown | 32 (79.0) | 0 | 32 (79.0) |

**Source:** Annex 7a - Table 4.2-9, Table 4.2-10, Table 4.2-11. Annex 7b – Table 4.2-17, Table 4.2-18, Table 4.2-19.

**Table 4-6 Clinical trial exposure by age, gender in acute and chronic GvHD in adolescent and adult patients-Safety set**

| | | Acute GvHD | | | | Chronic GvHD | |
|---|---|---|---|---|---|---|---|
| | | Study C2301 Rux overall N=201 | | Study 271 Rux N=71 | | Study D2301 Rux overall N=235 | |
| Gender | Age (years) | Patients n (%) | PTY | Patients n (%) | PTY | Patients n(%) | Patient-years |
| Total | Total | 201 (100.0) | 53.7 | 71 (100.0) | 25.6 | 235 (100.0) | 355.5 |
| | 12 - <18 | 6 (3.0) | 1.7 | 0 | N/A | 10 (4.3) | 14.9 |
| | 18 - 65 | 166 (82.6) | 47.9 | 62 (87.3) | 23.5 | 198 (84.3) | 305.3 |
| | >65 | 29 (14.4) | 4.0 | 9 (12.7) | 2.1 | 27 (11.5) | 35.3 |
| Female | Total | 85 (42.3) | 21.1 | 36 (50.7) | 9.9 | 83 (35.3) | 131.8 |
| | 12 - <18 | 4 (2.0) | 0.6 | 0 | N/A | 3 (1.3) | 4.1 |
| | 18 - 65 | 67 (33.3) | 18.7 | 33 (46.5) | 9.2 | 70 (29.8) | 108.6 |
| | >65 | 14 (7.0) | 1.8 | 3 (4.2) | 0.7 | 10 (4.3) | 19.1 |
| Male | Total | 116 (57.7) | 32.6 | 35 (49.3) | 15.7 | 152 (64.7) | 223.7 |
| | 12 - <18 | 2 (1.0) | 1.1 | 0 | N/A | 7 (3.0) | 10.8 |
| | 18 - 65 | 99 (49.3) | 29.2 | 29 (40.8) | 14.3 | 128 (54.5) | 196.7 |
| | >65 | 15 (7.5) | 2.3 | 6 (8.5) | 1.4 | 17 (7.2) | 16.2 |

Patient-Treatment-Years (PTY) is the sum of each patient's treatment exposure in years. PTY is based on the number of patients in each category.
**Source:** (Annex 7c – Table 4.2-2).

**Table 4-7 Clinical trial exposure by age, gender in acute and chronic GvHD pediatric patients-Safety set**

| | | Acute GvHD (F12201+C2301) Total pediatric patients N=51 | | Chronic GvHD (G12201+D2301) Total pediatric patients N=55 | |
|---|---|---|---|---|---|
| Gender | Age (years) | Patients n (%) | PTY | Patients n (%) | PTY |
| Total | Total | 51 (100.0) | 17.0 | 55 (100.0) | 69.0 |
| | >=2y - <6y | 15 (29.4) | 6.1 | 7 (12.7) | 9.5 |
| | >=6y - <12y | 12 (23.5) | 3.3 | 16 (29.1) | 19.3 |
| | >=12y - <18y | 24 (47.1) | 7.6 | 32 (58.2) | 40.2 |
| Female | Total | 21 (41.2) | 6.2 | 19 (34.5) | 24.3 |
| | >=2y - <6y | 5 (9.8) | 2.2 | 2 (3.6) | 1.9 |
| | >=6y - <12y | 7 (13.7) | 2.2 | 7 (12.7) | 9.9 |

| | | | | | |
|---|---|---|---|---|---|
| | >=12y - <18y | 9 (17.6) | 1.8 | 10 (18.2) | 12.4 |
| Male | Total | 30 (58.8) | 10.7 | 36 (65.5) | 44.8 |
| | >=2y - <6y | 10 (19.6) | 3.9 | 5 (9.1) | 7.6 |
| | >=6y - <12y | 5 (9.8) | 1.1 | 9 (16.4) | 9.4 |
| | >=12y - <18y | 15 (29.4) | 5.8 | 22 (40.0) | 27.8 |

Patient-Treatment-Years (PTY) is the sum of each patient's treatment exposure in years. PTY is based on the number of patients in each category.

Source: (Annex 7c - Table 4.1-2)-

**Table 4-8 Clinical trial exposure by race in acute and chronic GvHD adolescent and adult patients (Safety set)**

| | Acute GvHD | | | | Chronic GvHD | |
|---|---|---|---|---|---|---|
| | Study C2301 Rux overall N=201 | | Study 271 Rux N=71 | | Study D2301 Rux overall N=235 | |
| Race | Patients n (%) | PTY | Patients n (%) | PTY | Patients n (%) | PTY |
| White | 141 (70.1) | 36.2 | 66 (93.0) | 24.1 | 177 (75.3) | 250.5 |
| Asian | 26 (12.9) | 9.8 | 2 (2.8) | 0.1 | 38 (16.2) | 64.9 |
| Other | 8 (4.0) | 1.4 | 3 (4.2) | 1.4 | 15 (6.4) | 29.0 |
| Missing* | 26 (12.9) | 6.4 | 0 | N/A | 5 (2.1) | 11.1 |

*Race is not collected in France.

Patient-Treatment-Years (PTY) is the sum of each patient's treatment exposure in years. PTY is based on the number of patients in each category.

**Source:** (Annex 7c – Table 4.2-3).

**Table 4-9 Clinical trial exposure by race in acute and chronic GvHD pediatric patients-Safety set**

| | Acute GvHD (F12201+C2301) Total pediatric patients N=51 | | Chronic GvHD (G12201+D2301) Total pediatric patients N=55 | |
|---|---|---|---|---|
| Race | Patients n (%) | PTY | Patients n (%) | PTY |
| White | 25 (49.0) | 7.3 | 27 (49.1) | 24.3 |
| Asian | 11 (21.6) | 3.9 | 26 (47.3) | 40.7 |
| Other | 0 | NA | 2 (3.6) | 4.0 |
| Missing* | 15 (29.4) | 5.7 | 0 | NA |

*Race is not collected in France.

Patient-Treatment-Years (PTY) is the sum of each patient's treatment exposure in years. PTY is based on the number of patients in each category.

Source: (Annex 7c - Table 4.1-3)

# 5 Part II Safety specification Module SIV: Populations not studied in clinical trials

## 5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

**Table 5-1 Important exclusion criteria in pivotal studies in the development program**

| Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale for not including as missing information |
|---|---|---|---|
| Females who were pregnant or breastfeeding | Ruxolitinib was not teratogenic but was associated with increased late resorptions and fetotoxicity and was present in high concentration in the milk of lactating rats. | No | Ruxolitinib is contraindicated in pregnant and breast-feeding women. This is included in sections 4.3 and 4.6 of the SmPC. |
| Life expectancy of less than 6 months (For MF only) | Phase III clinical protocols enrolled patients with advanced MF. For this population, the median life expectancy is reported as 2-4 years. To adequately assess safety and efficacy of ruxolitinib in MF patients, Phase III studies were planned to manage patients for more than 6 months within the study protocols. | No | These criteria and management of hematological parameters are reflected in sections 4.2, 4.4 and 4.8 of SmPC. Routine pharmacovigilance (PhV) and risk minimization are well understood. |
| Treatment with hematopoietic growth factor receptor agonists (For MF only) | The hematopoietic growth factors granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), thrombopoietin and erythropoietin all require JAKs/STATs for transmembrane signal transduction (Vainchenker et al 2008). Thus, based on JAK/STAT signaling biology, concomitant treatment with hematopoietic growth factors may limit the effect of a JAK inhibitor. This notion is supported by preclinical studies showing a decrease | No | Based on the evaluation of data from Study CINC424AIC01T (Post authorization safety study [PASS]) and available information from literature, concurrent use of ruxolitinib and hematopoietic growth factor receptor agonists did not decrease the efficacy of ruxolitinib, and no significant toxicities were observed. |

| Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale for not including as missing information |
|---|---|---|---|
| | in JAK2 inhibitor efficacy by addition of increasing concentrations of erythropoietin to cell lines or patient cells (Jedidi et al 2009). Conversely, JAK inhibition suppresses the effect of the hematopoietic growth factors on hematopoietic cells and hematopoiesis; thus, ruxolitinib could reduce the efficacy of these hematopoietic growth factors. Despite the in vitro evidence of growth factor receptors on leukemic cells, (Begley et al 1987, Park et al 1989), studies of patients with acute leukemia have not suggested an adverse effect of drugs such as G-CSF or GM-CSF when used as priming during chemotherapy or after chemotherapy to accelerate neutrophil recovery (Wheatley 2009). Granulocytic growth factors would not be expected to be of any greater risk in patients with MF than in patients with AML. Some growth factor receptor agonists, however, such as thrombopoietin, are known to increase the clinical risk for development or progression of reticulin fiber deposition within the bone marrow, supported by preclinical studies in mice exposed to high and sustained levels of the factor (Yan et al 1996, Villeval et al 1997). Therefore, the use of thrombopoietin could exacerbate bone marrow fibrosis. | | |

| Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale for not including as missing information |
|---|---|---|---|
| | A possible pharmacodynamic (PD) interaction between ruxolitinib and hematopoietic growth factors has not been formally studied in MF patients. In the Phase III clinical protocols, the concurrent use of hematopoietic growth factors was discouraged, but not prohibited. In Study 352, 9 patients received concurrent treatment with ESAs for the management of anemia. Although the sample size is small, ESA's did not decrease the efficacy of ruxolitinib in terms of spleen size reduction and the adverse event (AE) profile was similar to patients who did not receive concurrent ESA's (McMullin et al 2011). Hematopoietic growth factors as well as ruxolitinib treatment require hematopoietic monitoring and the ruxolitinib dose is adjusted to clinical efficacy and hematopoietic parameters. Potential PD interactions are therefore detectable with established routine monitoring. | | |
| Subjects in whom MF disease is well controlled with current therapy and those with less severe MF | At the time of the initiation of the 2 pivotal studies, ruxolitinib was an experimental drug with data on safety and efficacy in MF limited to Phase II studies. In this indication, it would not have been justified to enroll patients to an experimental treatment whose disease was under control with available treatments. | No | Based on the data available from the publication, Palandri et al 2018, the safety profile on the patients with different severity from those in CTs (in Intermediate-1 risk MF patients) was comparable. |
| MF: Subjects with inadequate bone | In repeated dose toxicity studies, reversible lymphoid | No | This safety topic was studied in the additional |

| Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale for not including as missing information |
|---|---|---|---|
| marrow reserve: Subjects with any history of platelet counts <50000/µL or ANC <500/µL except during either treatment for a myeloproliferative disorder or treatment with cytotoxic therapy for any other reason.<br>PV: Inadequate bone marrow reserve demonstrated by platelet count that was <100000/µL or ANC that was ≤1000/µL | depletion in bone marrow and lymphoid organs in rats and dogs were noted. Reversible hematological effects included decreases in RBCs, reticulocytes, eosinophils and lymphocytes. The effects were those expected based on the pharmacology of JAK inhibition.<br>Of note, in patients with PV, low platelet counts and low ANC is unlikely due to the nature of disease characteristics and therefore, the exclusion criteria in PV trials were different than in MF trials. | | PhV activity, CINC424A2201. Based on the analysis in this study the safety profile in patient population with low platelet count is similar to the known safety profile of ruxolitinib in MF patients. Overall, the review of data on safety in MF patients with a platelet count below 100000/mm$^3$ did not reveal any new safety concerns.<br>The recommendation to minimize any safety concerns related to this is communicated in SmPC sections 4.2, 4.4 and 4.8. |
| Subjects with inadequate liver or renal function | The exclusion criteria were established as a precautionary measure, as at initiation of Phase III clinical studies, pharmacokinetic (PK) studies in special populations (hepatic insufficiency, renal insufficiency) were not completed. | No | The SmPC sections 4.2, 4.4 and 5.2, provides detailed guidance on the management of patients with hepatic or renal impairment, considering the results of special population studies. |
| Subjects with clinically significant bacterial, fungal, parasitic or viral infection which require therapy:<br>• Subjects with acute bacterial infections requiring antibiotic use should delay screening/enrollment until the course of antibiotic therapy has been completed<br>• Subjects with known active hepatitis A, B or C at Screening or with | Ruxolitinib is known to have an adverse effect on neutrophils which could render patients more vulnerable to infections. Lymphopenia was identified in animal studies; in human studies there was no notable imbalance between treatment and control arms. Janus kinase inhibition is associated with suppression of IFN gamma signaling lymphocytes and IFN gamma are involved in immune defense against mycobacterial infections. In addition, “infections” has been identified as an | No | “Serious infections” is, captured in the RMP as important identified risk and is an important safety topic to be monitored for all indications, MF, PV and GvHD. This item is appropriately communicated through current labeling in SmPC Section 4.4: 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 |

| Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale for not including as missing information |
|---|---|---|---|
| known human immunodeficiency virus positivity | identified risk of JAK inhibition. | | 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.<br>Tuberculosis (TB) has been reported in patients receiving ruxolitinib. Before starting treatment, patients should be evaluated for active and inactive ("latent") TB, as per local recommendations. This can include medical history, possible previous contact with TB and/or appropriate screening such as lung x-ray, tuberculin test and/or IFN-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.<br>Hepatitis B viral load (HBV-DNA titer) increases, with and without associated elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), have been reported in patients with chronic HBV infections taking ruxolitinib. The effect of ruxolitinib on viral replication in patients with |

| Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale for not including as missing information |
|---|---|---|---|
| | | | chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. |
| Subjects with an active malignancy over the previous 5 years except treated early stage SCC of the skin or treated BCC of the skin | Enrolling patients with an active malignancy or a recent history of an active malignancy who may require treatment including chemotherapy or irradiation could have led to an interaction with the safety and efficacy objectives of the protocols. | No | Analysis of pivotal trial data in MF and PV patients, showed no signal of subsequent malignancies.<br>The overall incidence from the long-term follow-up data (MF: 9.4%; PV: 17.4%) were assessed to be in line with that expected in the general MF and PV patient population, with considerations given to previous exposure to HU and/or history of prior malignancy.<br>This safety topic is appropriately communicated through labeling in Section 4.4 of the SmPC. |
| Subjects with cardiac disease which in the Investigator's opinion may jeopardize the safety of the subject or the compliance with the protocol<br>Subjects with currently uncontrolled or unstable angina<br>Subjects with currently rapid or paroxysmal atrial fibrillation<br>Subjects with recent (approximately 6 months) MI or | The safety profile of ruxolitinib has not demonstrated a risk for cardiovascular disease. However, the mean age of patients recruited was approximately 65 years and cardiovascular conditions are not uncommon in this population. The exclusion criteria aimed to identify patients with poorly controlled cardiac disease which could have led to a need for emergency medical interventions and poor adherence with the study protocol requirements. | No | Analysis of pivotal trial data for MF, PV and GvHD indications, showed no signal of cardiac events. A thorough QT study was conducted in 50 healthy subjects. There was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up to a supra-therapeutic dose of 200 mg indicating that ruxolitinib has no effect on cardiac repolarization. |

| Criteria | Reason for exclusion | Is it considered to be included as missing information? | Rationale for not including as missing information |
|---|---|---|---|
| acute coronary syndrome | | | |
| Subjects who have had splenic irradiation within 12 months prior to randomization | This exclusion criterion was added due to the potential interference with the efficacy end point of spleen size reduction. | No | Risk of cytopenias is appropriately communicated through the current labeling. |
| Women of child-bearing potential unless they are using 2 birth control methods | Animal studies have shown that ruxolitinib is embryolethal and fetotoxic. 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. | No | Developmental toxicity is captured as an important potential risk in the RMP. This item is appropriately communicated through current labeling in SmPC Section 4.6: Women of child-bearing potential should use effective contraception during the treatment with ruxolitinib. |
| **Source:** Yan et al 1996, Villeval et al 1997, McMullin et al 2011, Vainchenker et al 2008, Jedidi et al 2009, Begley et al 1987, Park et al 1989, Wheatley et al 2009, Palandri et al 2018, [Ruxolitinib SmPC 2025.] | | | |

## 5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency or those caused by prolonged exposure.

## 5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

**Table 5-2 Exposure of special populations included or not in clinical trial development programs**

| Type of special population | Exposure |
|---|---|
| Pregnant women and breastfeeding women | Not included in the clinical development program. |
| Children (≤18 years of age) | For MF and PV indications: Not included in the clinical development program.<br>For GvHD indication: 2 to <18 -year-old patients were included in the clinical development program (Annex 7c - Table 4-1.2). |
| Patients with hepatic impairment | Patients with hepatic impairment were included in the clinical development program (Annex 7a - Table 4.2-12, Annex 7b - Table 4.2-20 and (Annex 7c - Table 4.2-4) for |

| Type of special population | Exposure |
|---|---|
| | adults/adolescents patients and (Annex 7c - Table 4.1-4) for pediatric patients. |
| Patients with renal impairment | Patients with renal impairment were included in the clinical development program (Annex 7a - Table 4.2-13, Annex 7b -Table 4.2-21 and (Annex 7c – Table 4.2-5) for adults/adolescents patients and (Annex 7c - Table 4.1-5) for pediatric patients. |
| Patients with cardiovascular impairment | Patients with severe cardiovascular impairment were excluded from the clinical development program (Annex 7a - Table 4.2-14 and Annex 7b - Table 4.2-22). |
| Elderly patients (≥75 years) | Elderly patients (≥75 years) were included in the clinical development program.<br>The median duration of exposure of elderly patients with MF aged ≥75 years at study entry was 22.6 months and nearly 50% of these patients had exposure ≥24 months. Further details are presented in (Annex 7a - Table 4.2-15). The median duration of exposure of elderly patients with PV aged ≥75 years was 20.0 months and about 35% of these patients had exposure ≥24 months (Annex 7b - Table 4.2-23). |
| Patients with a disease severity different from inclusion criteria in CTs | Not included in the clinical development program. |
| Sub-populations carrying known and relevant polymorphisms | Not included in the clinical development program. |
| Population with relevant different ethnic origin | For MF and PV indications, patients of different racial and/or ethnic origin were included in the clinical development program (Ethnic Insensitivity Report, Study CINC424A2202, Modeling report-Ethnicity effect on Ruxolitinib PK, Summary of Clinical Pharmacology).<br>For GvHD indication, patients from different race were included in the clinical development program (Annex 7c – Table 4.2-3 for adults/adolescents patients and (Annex 7c - Table 4.1-3) for pediatric patients. |

# 6 Part II Safety specification Module SV: Post-authorization experience

Ruxolitinib is currently indicated for the treatment of patients with MF, including PMF, PPV-MF or PET-MF and for the treatment of adult patients with PV who are resistant to or intolerant of HU, and for the treatment of adults and paediatric patients aged 28 days and older with acute GvHD or for the treatment of adults and paediatric patients aged 6 months and older with chronic GvHDwho have inadequate response to corticosteroids or other systemic therapies. An analysis of the safety profile of ruxolitinib in patients treated for unapproved indications, which includes both adult and pediatric patients, reveals that the current safety profile of ruxolitinib is aligned with that of patients being treated for approved indications.

## 6.1 Part II Module SV.1. Post-authorization exposure

The cumulative postmarketing exposure since the first launch of the product up to the data cutoff date of PSUR (reporting period: 23-Feb-2024 – 22-Feb-2025) is estimated to be approximately 469,548 PTY.

### 6.1.1 Part II Module SV.1.1 Method used to calculate exposure

The postmarketing exposure is estimated based on worldwide sales volume in kilogram (kg) of active substance through PSUR with DLP of 22Feb2025 and the Defined Daily Dose (DDD). The DDD for ruxolitinib is 30 mg. The sales volume of ruxolitinib cumulatively since the IBD of the product was estimated to be approximately 5141.55 kg active substance [redacted]). The estimated cumulative exposure was approximately 469,548 PTY.

The cumulative exposure broken down by geographical region and reporting interval is presented in Table 6-1.

### 6.1.2 Part II Module SV.1.2. Exposure

**Table 6-1 Cumulative exposure from marketing experience (Patient-treatment years)**

| PSUR reporting interval | [redacted] | [redacted] | [redacted] | [redacted] | Total |
|---|---|---|---|---|---|
| 16-Nov-2011 to 22-Feb-2013 | [redacted] | [redacted] | [redacted] | [redacted] | 2726 |
| 23-Feb-2013 to 22-Aug-2013 | [redacted] | [redacted] | [redacted] | [redacted] | 2429 |
| 23-Aug-2013 to 22-Feb-2014 | [redacted] | [redacted] | [redacted] | [redacted] | 2998 |
| 23-Feb-2014 to 22-Aug-2014 | [redacted] | [redacted] | [redacted] | [redacted] | 3765 |
| 23-Aug-2014 to 22-Feb-2015 | [redacted] | [redacted] | [redacted] | [redacted] | 4998 |
| 23-Feb-2015 to 22-Feb-2016 | [redacted] | [redacted] | [redacted] | [redacted] | 14394 |
| 23-Feb-2016 to 22-Feb-2017 | [redacted] | [redacted] | [redacted] | [redacted] | 20671 |
| 23-Feb-2017 to 22-Feb-2018 | [redacted] | [redacted] | [redacted] | [redacted] | 27169 |
| 23-Feb-2018 to 22-Feb-2019 | [redacted] | [redacted] | [redacted] | [redacted] | 33398 |
| 23-Feb-2019 to 22-Feb-2020 | [redacted] | [redacted] | [redacted] | [redacted] | 39591 |
| 23-Feb-2020 to 22-Feb-2021 | [redacted] | [redacted] | [redacted] | [redacted] | 47650 |
| 23-Feb-2021 to 22-Feb-2022 | [redacted] | [redacted] | [redacted] | [redacted] | 55984 |
| 23-Feb-2022 to 22-Feb-2023 | [redacted] | [redacted] | [redacted] | [redacted] | 64678 |
| 23-Feb-2024 to 22-Feb-2025 | [redacted] | [redacted] | [redacted] | [redacted] | 81276 |
| **Cumulative (PTY)#** | [redacted] | [redacted] | [redacted] | [redacted] | **469548** |

EU: European Union; EEA: European Economic Area; PSUR= Periodic Update Safety Report; PTY= Patient Treatment Year; ROW=Rest of the World; US: United States

[redacted]

**Sales originating from the United Kingdom, which were presented under the EU/EEA region in previous PSURs, are now presented under ROW.

# The sales for each PSUR period provided in the above table were provided based upon the sales at the DLP for each PSUR period. The cumulative sales total is provided based upon total sales to date. Hence, the sum of individual period sales may not match the total cumulative sales.

# 7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

## 7.1 Potential for misuse for illegal purposes

A possible risk of misuse or dependence on ruxolitinib is not anticipated on the basis of its mechanism of action and lack of psychopharmacologic effects. While no clinical studies have been carried out to specifically investigate abuse potential, no evidence has emerged from CTs which would suggest a potential for abuse or dependence with ruxolitinib.

# 8 Part II Safety specification Module SVII: Identified and potential risks

## 8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

### 8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

This section in not applicable as the RMP was already approved.

### 8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

This section in not applicable as the RMP was already approved.

## 8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

Long-term safety in pediatric patients (GvHD only) classified as missing information remains unchanged. The safety concern will continue to be monitored in the PSURs.

## 8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

The Medical Dictionary for Regulatory Activities (MedDRA) search terms included in Annex 1 will be used for PhV of AE and Serious Adverse Event (SAE) data collection originating from solicited and unsolicited reports and for the EudraVigilance interface. MedDRA version 21.1 has been used for signal detection in the pooled analysis for MF and PV, for clinical database and for the analysis of Novartis global safety database.

For GvHD patient population, AEs were coded using the different MedDRA versions as specified in the analysis outputs footnotes.

For all important identified risks, important potential risk and missing information, relevant cases from cumulative reviews in PSURs (DLP: 22-Feb-2025) were retrieved by searching Novartis safety database using MedDRA version 27.1.

### Common Terminology Criteria for Adverse Events

Events of grade ≥3 severity listed below were determined using Common Terminology Criteria for Adverse Events (CTCAE) grading Version 3.0 (Study B2301, PV study) or 4.03 (Study A2401, MF study and Study B2401, PV study, and all GvHD studies), which was used in the clinical database to provide information about the severity of AEs, laboratory and vital sign data (CTCAE). CTCAE grade 1 = mild, grade 2 = moderate, grade 3 = severe and grade 4 = life-threatening abnormalities, grade 5 = death. In analyses for MF or PV indication, any reports of CTCAE grade 5 were categorized as grade 4 with a fatal outcome, whereas for GvHD grade 5 events are reported separately.

### Data Presentation

**MF and PV in adult patients:**
The data included in the following tabulations are AE, laboratory and vital sign data reported in patients receiving ruxolitinib or comparator treatment in MF and PV patients including CT data from MF studies (Study 251, Study 352, Study 351 and Study A2401) and PV studies (Study 256, Study B2401 and Study B2301). Where possible, data were pooled; however, laboratory data from Study 251 was not pooled due to the differences in the database structure between the Incyte database holding the data for Study 251 and the Novartis database holding data for Study 351, Study 352 and Study A2401.

The "Overall MF population" column depicts data from all patients (n=2848) treated with ruxolitinib in Phase III Study 351 and Study 352 (including patients who crossed over to ruxolitinib), patients from Study 251 and Expanded-Access Study, A2401. Laboratory data are based on 2690 patients from Study 351, Study 352 and Study A2401.

The "Overall PV population" column depicts data from all patients (n=374) treated with ruxolitinib in Study B2301 and Study B2401 (including patients who crossed over to ruxolitinib) and patients with PV treated with ruxolitinib in Study 256.

**GvHD in adult/adolescent patients:**

The data from GvHD adult/adolescent patients included in the following tabulations were from CT data from aGvHD (Study C2301 [N=201], Study 271 [N=71]) and cGvHD (Study D2301 [N=235]) studies.

**GvHD in pediatric patients:**

The data from GvHD pediatric patients included in the following tabulations were pooled from aGvHD [Study F12201 (N=45), and adolescents from Study C2301 (N=6) and cGvHD Study G12201 (N=45), and adolescents from Study D2301 (N=10)] studies.

The term "Rux overall" in Table 8-2 depicts data from all ruxolitinib treated patients including those randomized to ruxolitinib and those who crossed over to ruxolitinib from BAT arm.

Note: Adolescent patients from C2301 and D2301 respectively are considered in the adult/adolescent population as well as in the pooled pediatric population.

## 8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

### 8.3.1.1 Important Identified Risk: Serious infections

**Table 8-1 Clinical trial data of Serious infections**

| Infections and infestations | Overall MF population N=2848 n (%) 95% CI | Overall PV population N=374 n (%) 95% CI |
|---|---|---|
| Any AE | 1405 (49.3) (47.5 - 51.2) | 241 (64.4) (59.4 - 69.3) |
| AE related to study drug | 220 (7.7) (6.8 - 8.8) | 69 (18.4) (14.6 - 22.8) |
| Serious AE | 487 (17.1) (15.7 - 18.5) | 49 (13.1) (9.9 - 16.9) |

| | | |
|---|---|---|
| Grade 3 or 4 AE | 458 (16.1) (14.8 - 17.5) | 50 (13.4) (10.1 - 17.2) |
| AE leading to dose reduction | 11 (1.8) (0.9 – 3.2) | 1 (0.3) (0.0 - 1.5) |
| AE leading to dose adjustment or interruption* | 111 (5.0) (4.1 - 6.0) | - |
| AE leading to study drug discontinuation | 219 (7.7) (6.7 - 8.7) | 3 (0.8) (0.2 - 2.3) |
| **Opportunistic infections** | **Overall MF population N=2848 n (%) 95% CI** | **Overall PV population N=374 n (%) 95% CI** |
| Any AE | 21 (0.7) (0.5 - 1.1) | 0 |
| AE related to study drug | 7 (0.2) (0.1 - 0.5) | 0 |
| Serious AE | 13 (0.5) (0.2 - 0.8) | 0 |
| Grade 3 or 4 AE | 12 (0.4) (0.2 - 0.7) | 0 |
| AE leading to dose reduction | 0 | 0 |
| AE leading to dose adjustment or interruption* | 2 (0.1) (0.0 - 0.3) | - |
| AE leading to study drug discontinuation | 11 (0.4) (0.2 - 0.7) | 0 |
| **Pneumonia** | **Overall MF population N=2848 n (%) 95% CI** | **Overall PV population N=374 n (%) 95% CI** |
| Any AE | 341 (12.0) (10.8 - 13.2) | 28 (7.5) (5.0 - 10.6) |
| AE related to study drug | 53 (1.9) (1.4 - 2.4) | 6 (1.6) (0.6 – 3.5) |
| Serious AE | 234 (8.2) (7.2 - 9.3) | 18 (4.8) (2.9 - 7.5) |
| Grade 3 or 4 AE | 208 (7.3) (6.4 - 8.3) | 17 (4.5) (2.7 - 7.2) |
| AE leading to dose reduction | 2 (0.3) (0.0 - 1.2) | 1 (0.3) (0.0 – 1.5) |
| AE leading to dose adjustment or interruption* | 37 (1.7) (1.2 - 2.3) | - |
| AE leading to study drug discontinuation | 78 (2.7) (2.2 - 3.4) | 1 (0.3) (0.0 – 1.5) |
| **Sepsis and Septic Shock** | **Overall MF population N=2848 n (%) 95% CI** | **Overall PV population N=374 n (%) 95% CI** |
| Any AE | 122 (4.3) (3.6 - 5.1) | 3 (0.8) (0.2 - 2.3) |
| AE related to study drug | 15 (0.5) (0.3 - 0.9) | 1 (0.3) (0.0 - 1.5) |
| Serious AE | 110 (3.9) (3.2 - 4.6) | 3 (0.8) (0.2 - 2.3) |
| Grade 3 or 4 AE | 116 (4.1) (3.4 - 4.9) | 2 (0.5) (0.1 - 1.9) |
| AE leading to dose reduction | 3 (0.5) (0.1 – 1.4) | 0 |
| AE leading to dose adjustment or interruption* | 11 (0.5) (0.2 - 0.9) | - |
| AE leading to study drug discontinuation | 42 (1.5) (1.1 - 2.0) | 0 |
| **Other infections** | **Overall MF population N=2848 n (%) 95% CI** | **Overall PV population N=374 n (%) 95% CI** |
| Any AE | 1092 (38.3) (36.6 - 40.2) | 207 (55.3) (50.2 - 60.5) |
| AE related to study drug | 103 (3.6) (3.0 - 4.4) | 40 (10.7) (7.8 - 14.3) |
| Serious AE | 212 (7.4) (6.5 - 8.5) | 27 (7.2) (4.8 - 10.3) |
| Grade 3 or 4 AE | 193 (6.8) (5.9 - 7.8) | 25 (6.7) (4.4 - 9.7) |

| | | |
|---|---|---|
| AE leading to dose reduction | 7 (1.1) (0.5 - 2.3) | 0 |
| AE leading to dose adjustment or interruption* | 50 (2.2) (1.7 - 2.9) | - |
| AE leading to study drug discontinuation | 133 (4.7) 3.9 - 5.5 | 2 (0.5) (0.1 - 1.9) |

* For Study A2401, dose reduction was not collected separately, but only together with interruption in "AE leading to dose adjustment or interruption".
Numbers (n) represent counts of patients.
MedDRA version 21.1
**Source:** Annex 7a - Table 8.3-12.9, Table 8.3-9.3, Table 8.3-10.3, Table 8.3-11.3, Table 8.3-12.3; Annex 7b - Table 8.3-12.11, Table 8.3-9.5, Table 8.3-10.5, Table 8.3-11.5, Table 8.3-12.5.

**Table 8-2 Clinical trial data of serious infections in adult and adolescent patients with acute or chronic GvHD**

| Infections and infestations* in acute and chronic GvHD | Acute GvHD | | Chronic GvHD |
|---|---|---|---|
| | Study C2301 Rux overall N=201 n (%) | Study 271 Rux N=71 n (%) | Study D2301 Rux overall N=235 n (%) |
| Number of patients with at least one event, n (%) | 159 (79.1) | 58 (81.7) | 178 (75.7) |
| 95% CI | (72.8,84.5) | (70.7,89.9) | (69.7,81.1) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 159 (655.1) | 58 (652.6) | 178 (113.5) |
| Maximum grade, n (%) | | | |
| Grade 3 AEs | 55 (27.4) | 26 (36.6) | 51 (21.7) |
| Grade 4 AEs | 23 (11.4) | 20 (28.2) | 6 (2.6) |
| Grade 5 AEs | 26 (12.9) | 0 | 15 (6.4) |
| Treatment-related AEs, n (%) | 51 (25.4) | 21 (29.6) | 71 (30.2) |
| SAEs, n (%) | 80 (39.8) | 36 (50.7) | 72 (30.6) |
| Action taken, n (%) | | | |
| Drug Withdrawn | 18 (9.0) | 9 (12.7) | 23 (9.8) |
| Dose Reduced | 3 (1.5) | 2 (2.8) | 15 (6.4) |
| Dose Increased | 0 | 0 | 0 |
| Drug Interrupted | 20 (10.0) | 8 (11.3) | 21 (8.9) |
| Dose Not Changed/NA/Unknown | 153 (76.1) | 46 (64.8) | 169 (71.9) |
| Missing | 0 | 0 | 1 (0.4) |
| Medication or therapy taken, n (%) | 150 (74.6) | 56 (78.9) | 158 (67.2) |
| AE outcome, n (%) | | | |
| Recovered/Resolved | 116 (57.7) | 42 (59.2) | 154 (65.5) |
| Recovering/Resolving | 9 (4.5) | 5 (7.0) | 19 (8.1) |
| Not Recovered/Not Resolved | 70 (34.8) | 29 (40.8) | 36 (15.3) |
| Recovered/Resolved With Sequelae | 5 (2.5) | 1 (1.4) | 2 (0.9) |
| Fatal | 26 (12.9) | 10 (14.1) | 15 (6.4) |
| Unknown | 3 (1.5) | 0 | 0 |
| Missing | 0 | 0 | 1 (0.4) |

| **Herpes zoster in acute and chronic GvHD** | **Acute GvHD** | | **Chronic GvHD** |
|---|---|---|---|
| | **Study C2301 Rux overall N=201 n (%)** | **Study 271 Rux N=71 n (%)** | **Study D2301 Rux overall N=235 n (%)** |
| Number of patients with at least one event, n (%) | 4 (2.0) | 0 | 8 (3.4) |
| 95% CI | (0.5,5.0) | (NE,NE) | (1.5,6.6) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 4 (6.2) | 0 | 8 (2.0) |
| Maximum grade, n (%) | | | |
| Grade 3 AEs | 2 (1.0) | 0 | 5 (2.1) |
| Grade 4 AEs | 0 | 0 | 0 |
| Grade 5 AEs | 0 | 0 | 0 |
| Treatment-related AEs, n (%) | 0 | 0 | 5 (2.1) |
| SAEs, n (%) | 1 (0.5) | 0 | 5 (2.1) |
| Action taken, n (%) | | | |
| Drug Withdrawn | 0 | 0 | 1 (0.4) |
| Dose Reduced | 0 | 0 | 0 |
| Dose Increased | 0 | 0 | 0 |
| Drug Interrupted | 1 (0.5) | 0 | 3 (1.3) |
| Dose Not Changed/NA/Unknown | 3 (1.5) | 0 | 5 (2.1) |
| Missing | 0 | 0 | 0 |
| Medication or therapy taken, n (%) | 4 (2.0) | 0 | 8 (3.4) |
| AE outcome, n (%) | | | |
| Recovered/Resolved | 4 (2.0) | 0 | 7 (3.0) |
| Recovering/Resolving | 0 | 0 | 0 |
| Not Recovered/Not Resolved | 0 | 0 | 2 (0.9) |
| Recovered/Resolved With Sequelae | 0 | 0 | 0 |
| Fatal | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 |
| Missing | 0 | 0 | 0 |

| **Urinary tract infections (UTI) in acute and chronic GvHD** | **Acute GvHD** | | **Chronic GvHD** |
|---|---|---|---|
| | **Study C2301 Rux overall N=201 n (%)** | **Study 271 Rux N=71 n (%)** | **Study D2301 Rux overall N=235 n (%)** |
| Number of patients with at least one event, n (%) | 36 (17.9) | 10 (14.1) | 23 (9.8) |
| 95% CI | (12.9,23.9) | (7.0,24.4) | (6.3,14.3) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 36 (62.7) | 10 (38.2) | 23 (6.4) |
| Maximum grade, n (%) | | | |
| Grade 3 AEs | 12 (6.0) | 6 (8.5) | 3 (1.3) |

| | | | |
|---|---|---|---|
| Grade 4 AEs | 1 (0.5) | 0 | 0 |
| Grade 5 AEs | 0 | 0 | 0 |
| Treatment-related AEs, n (%) | 9 (4.5) | 3 (4.2) | 10 (4.3) |
| SAEs, n (%) | 4 (2.0) | 3 (4.2) | 2 (0.9) |
| Action taken, n (%) | | | |
| Drug Withdrawn | 1 (0.5) | 0 | 0 |
| Dose Reduced | 0 | 0 | 2 (0.9) |
| Dose Increased | 0 | 0 | 0 |
| Drug Interrupted | 1 (0.5) | 0 | 0 |
| Dose Not Changed/NA/Unknown | 34 (16.9) | 10 (14.1) | 23 (9.8) |
| Missing | 0 | 0 | 0 |
| Medication or therapy taken, n (%) | 27 (13.4) | 10 (14.1) | 20 (8.5) |
| AE outcome, n (%) | | | |
| Recovered/Resolved | 25 (12.4) | 9 (12.7) | 20 (8.5) |
| Recovering/Resolving | 0 | 1 (1.4) | 0 |
| Not Recovered/Not Resolved | 11 (5.5) | 1 (1.4) | 3 (1.3) |
| Recovered/Resolved With Sequelae | 0 | 0 | 0 |
| Fatal | 0 | 0 | 0 |
| Unknown | 1 (0.5) | 0 | 0 |
| Missing | 0 | 0 | 0 |

| **Opportunistic infections in acute and chronic GvHD** | **Acute GvHD** | | **Chronic GvHD** |
|---|---|---|---|
| | **Study C2301 Rux overall N=201 n (%)** | **Study 271 Rux N=71 n (%)** | **Study D2301 Rux overall N=235 n (%)** |
| Number of patients with at least one event, n (%) | 68 (33.8) | 15 (21.1) | 31 (13.2) |
| 95% CI | (27.3,40.8) | (12.3,32.4) | (9.1,18.2) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 68 (144.5) | 15 (58.2) | 31 (8.0) |
| Maximum grade, n (%) | | | |
| Grade 3 AEs | 26 (12.9) | 5 (7.0) | 7 (3.0) |
| Grade 4 AEs | 1 (0.5) | 2 (2.8) | 0 |
| Grade 5 AEs | 0 | 0 | 2 (0.9) |
| Treatment-related AEs, n (%) | 17 (8.5) | 4 (5.6) | 11 (4.7) |
| SAEs, n (%) | 15 (7.5) | 3 (4.2) | 10 (4.3) |
| Action taken, n (%) | | | |
| Drug Withdrawn | 3 (1.5) | 0 | 1 (0.4) |
| Dose Reduced | 0 | 1 (1.4) | 2 (0.9) |
| Dose Increased | 0 | 0 | 0 |
| Drug Interrupted | 1 (0.5) | 1 (1.4) | 2 (0.9) |
| Dose Not Changed/NA/Unknown | 68 (33.8) | 13 (18.3) | 28 (11.9) |
| Missing | 0 | 0 | 0 |
| Medication or therapy taken, n (%) | 63 (31.3) | 15 (21.1) | 25 (10.6) |

| | | | |
|---|---|---|---|
| AE outcome, n (%) | | | |
| Recovered/Resolved | 42 (20.9) | 6 (8.5) | 23 (9.8) |
| Recovering/Resolving | 4 (2.0) | 1 (1.4) | 2 (0.9) |
| Not Recovered/Not Resolved | 26 (12.9) | 7 (9.9) | 5 (2.1) |
| Recovered/Resolved With Sequelae | 2 (1.0) | 1 (1.4) | 0 |
| Fatal | 0 | 0 | 2 (0.9) |
| Unknown | 0 | 0 | 0 |
| Missing | 0 | 0 | 0 |

| **Pneumonia in acute and chronic GvHD** | **Acute GvHD** | | **Chronic GvHD** |
|---|---|---|---|
| | **Study C2301 Rux overall N=201 n (%)** | **Study 271 Rux N=71 n (%)** | **Study D2301 Rux overall N=235 n (%)** |
| Number of patients with at least one event, n (%) | 38 (18.9) | 17 (23.9) | 54 (23.0) |
| 95% CI | (13.7,25.0) | (14.6,35.5) | (17.8,28.9) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 38 (62.9) | 17 (67.3) | 54 (15.2) |
| Maximum grade, n (%) | | | |
| Grade 3 AEs | 17 (8.5) | 10 (14.1) | 33 (14.0) |
| Grade 4 AEs | 7 (3.5) | 5 (7.0) | 3 (1.3) |
| Grade 5 AEs | 4 (2.0) | 0 | 7 (3.0) |
| Treatment-related AEs, n (%) | 14 (7.0) | 4 (5.6) | 26 (11.1) |
| SAEs, n (%) | 21 (10.4) | 11 (15.5) | 41 (17.4) |
| Action taken, n (%) | | | |
| Drug Withdrawn | 4 (2.0) | 1 (1.4) | 11 (4.7) |
| Dose Reduced | 0 | 1 (1.4) | 6 (2.6) |
| Dose Increased | 0 | 0 | 0 |
| Drug Interrupted | 6 (3.0) | 0 | 12 (5.1) |
| Dose Not Changed/NA/Unknown | 32 (15.9) | 16 (22.5) | 41 (17.4) |
| Missing | 0 | 0 | 0 |
| Medication or therapy taken, n (%) | 37 (18.4) | 16 (22.5) | 54 (23.0) |
| AE outcome, n (%) | | | |
| Recovered/Resolved | 23 (11.4) | 8 (11.3) | 35 (14.9) |
| Recovering/Resolving | 1 (0.5) | 1 (1.4) | 5 (2.1) |
| Not Recovered/Not Resolved | 14 (7.0) | 6 (8.5) | 10 (4.3) |
| Recovered/Resolved With Sequelae | 0 | 1 (1.4) | 1 (0.4) |
| Fatal | 4 (2.0) | 3 (4.2) | 7 (3.0) |
| Unknown | 0 | 0 | 0 |
| Missing | 0 | 0 | 0 |

| **Sepsis and septic shock in acute and chronic GvHD** | **Acute GvHD** | **Chronic GvHD** |
|---|---|---|

| | Study C2301 Rux overall N=201 n (%) | Study 271 Rux N=71 n (%) | Study D2301 Rux overall N=235 n (%) |
|---|---|---|---|
| Number of patients with at least one event, n (%) | 53 (26.4) | 16 (22.5) | 12 (5.1) |
| 95% CI | (20.4,33.0) | (13.5,34.0) | (2.7,8.7) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 53 (84.7) | 16 (60.2) | 12 (3.0) |
| Maximum grade, n (%) | | | |
| Grade 3 AEs | 10 (5.0) | 3 (4.2) | 5 (2.1) |
| Grade 4 AEs | 16 (8.0) | 12 (16.9) | 3 (1.3) |
| Grade 5 AEs | 20 (10.0) | 0 | 4 (1.7) |
| Treatment-related AEs, n (%) | 15 (7.5) | 4 (5.6) | 6 (2.6) |
| SAEs, n (%) | 40 (19.9) | 14 (19.7) | 10 (4.3) |
| Action taken, n (%) | | | |
| Drug Withdrawn | 8 (4.0) | 5 (7.0) | 5 (2.1) |
| Dose Reduced | 0 | 0 | 2 (0.9) |
| Dose Increased | 0 | 0 | 0 |
| Drug Interrupted | 10 (5.0) | 6 (8.5) | 1 (0.4) |
| Dose Not Changed/NA/Unknown | 41 (20.4) | 7 (9.9) | 6 (2.6) |
| Missing | 0 | 0 | 0 |
| Medication or therapy taken, n (%) | 47 (23.4) | 13 (18.3) | 11 (4.7) |
| AE outcome, n (%) | | | |
| Recovered/Resolved | 26 (12.9) | 8 (11.3) | 5 (2.1) |
| Recovering/Resolving | 1 (0.5) | 0 | 0 |
| Not Recovered/Not Resolved | 7 (3.5) | 4 (5.6) | 3 (1.3) |
| Recovered/Resolved With Sequelae | 1 (0.5) | 0 | 0 |
| Fatal | 20 (10.0) | 4 (5.6) | 4 (1.7) |
| Unknown | 1 (0.5) | 0 | 0 |
| Missing | 0 | 0 | 0 |

| **CMV infection/disease in acute and chronic GvHD** | **Acute GvHD** | | **Chronic GvHD** |
|---|---|---|---|
| | **Study C2301 Rux overall N=201** | **Study 271 Rux N=71** | **Study D2301 Rux overall N=235** |
| Number of patients with at least one event, n (%) | 66 (32.8) | 14 (19.7) | 24 (10.2) |
| 95% CI | (26.4,39.8) | (11.2,30.9) | (6.7,14.8) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 66 (140.9) | 14 (55.5) | 24 (6.2) |
| Maximum grade, n (%) | | | |
| Grade 3 AEs | 23 (11.4) | 6 (8.5) | 4 (1.7) |
| Grade 4 AEs | 1 (0.5) | 0 | 0 |
| Grade 5 AEs | 0 | 0 | 0 |
| Treatment-related AEs, n (%) | 16 (8.0) | 4 (5.6) | 10 (4.3) |

| | | | |
|---|---|---|---|
| SAEs, n (%) | 14 (7.0) | 1 (1.4) | 5 (2.1) |
| Action taken, n (%) | | | |
| Drug Withdrawn | 2 (1.0) | 1 (1.4) | 0 |
| Dose Reduced | 1 (0.5) | 0 | 0 |
| Dose Increased | 0 | 0 | 0 |
| Drug Interrupted | 2 (1.0) | 1 (1.4) | 1 (0.4) |
| Dose Not Changed/NA/Unknown | 65 (32.3) | 12 (16.9) | 24 (10.2) |
| Missing | 0 | 0 | 0 |
| Medication or therapy taken, n (%) | 65 (32.3) | 14 (19.7) | 21 (8.9) |
| AE outcome, n (%) | | | |
| Recovered/Resolved | 45 (22.4) | 9 (12.7) | 19 (8.1) |
| Recovering/Resolving | 5 (2.5) | 0 | 0 |
| Not Recovered/Not Resolved | 19 (9.5) | 5 (7.0) | 5 (2.1) |
| Recovered/Resolved With Sequelae | 1 (0.5) | 0 | 0 |
| Fatal | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 |
| Missing | 0 | 0 | 0 |

| **Other infections in acute and chronic GvHD** | **Acute GvHD** | | **Chronic GvHD** |
|---|---|---|---|
| | **Study C2301 Rux overall N=201** | **Study 271 Rux N=71** | **Study D2301 Rux overall N=235** |
| Number of patients with at least one event, n (%) | 109 (54.2) | 42 (59.2) | 143 (60.9) |
| 95% CI | (47.1,61.3) | (46.8,70.7) | (54.3,67.1) |
| Exposure-adjusted overall incidence,n (EAIR per 100 PTY) | 109 (288.4) | 42 (303.4) | 143 (69.5) |
| Maximum grade, n (%) | | | |
| Grade 3 AEs | 38 (18.9) | 22 (31.0) | 24 (10.2) |
| Grade 4 AEs | 8 (4.0) | 8 (11.3) | 1 (0.4) |
| Grade 5 AEs | 5 (2.5) | 0 | 2 (0.9) |
| Treatment-related AEs, n (%) | 21 (10.4) | 14 (19.7) | 46 (19.6) |
| SAEs, n (%) | 27 (13.4) | 19 (26.8) | 26 (11.1) |
| Action taken, n (%) | | | |
| Drug Withdrawn | 3 (1.5) | 3 (4.2) | 4 (1.7) |
| Dose Reduced | 2 (1.0) | 2 (2.8) | 6 (2.6) |
| Dose Increased | 0 | 0 | 0 |
| Drug Interrupted | 4 (2.0) | 3 (4.2) | 9 (3.8) |
| Dose Not Changed/NA/Unknown | 107 (53.2) | 37 (52.1) | 136 (57.9) |
| Missing | 0 | 0 | 1 (0.4) |
| Medication or therapy taken, n (%) | 96 (47.8) | 38 (53.5) | 116 (49.4) |
| AE outcome, n (%) | | | |
| Recovered/Resolved | 78 (38.8) | 30 (42.3) | 131 (55.7) |
| Recovering/Resolving | 1 (0.5) | 2 (2.8) | 13 (5.5) |
| Not Recovered/Not Resolved | 45 (22.4) | 18 (25.4) | 21 (8.9) |

| | | | |
|---|---|---|---|
| Recovered/Resolved With Sequelae | 2 (1.0) | 0 | 1 (0.4) |
| Fatal | 5 (2.5) | 5 (7.0) | 2 (0.9) |
| Unknown | 2 (1.0) | 0 | 0 |
| Missing | 0 | 0 | 1 (0.4) |

*Infections and infestations are grouped and presented under risk topic "Serious infections" in Annex 7c - Table 4.3-2.
In study 271 all fatal AEs are reported as grade 4.
Numbers (n) represent counts of patients.
For category "maximum grade" a patient with multiple severity grades (of the same PT or different PTs) for the risk is only counted once under the maximum grade.
A patient may be counted in several rows for action taken and outcome.
Action taken refers to ruxolitinib treatment.
MedDRA version 26.0, CTCAE version 4.03, Case Retrieval Strategy version released 2023-09-07.
Source: Annex 7c - Table 4.3-2

**Table 8-3 Clinical trial data of serious infections in pediatric patients with acute or chronic GvHD**

| | (Acute GvHD) F12201+C2301 Total pediatric patients N=51 n (%) | (Chronic GvHD) G12201+D2301 Total pediatric patients N=55 n (%) |
|---|---|---|
| **Infections and infestations*** | | |
| Number of patients with at least one event, n (%) | 36 (70.6) | 43 (78.2) |
| 95% CI | (56.2,82.5) | (65.0,88.2) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 36 (501.7) | 42 (172.0) |
| Maximum grade, n (%) | | |
| Grade 3 AEs | 13 (25.5) | 14 (25.5) |
| Grade 4 AEs | 3 (5.9) | 3 (5.5) |
| Grade 5 AEs | 0 | 2 (3.6) |
| Treatment-related AEs, n (%) | 5 (9.8) | 9 (16.4) |
| SAEs, n (%) | 14 (27.5) | 21 (38.2) |
| Action taken, n (%) | | |
| Drug Withdrawn | 1 (2.0) | 4 (7.3) |
| Dose Reduced | 2 (3.9) | 1 (1.8) |
| Dose Increased | 0 | 0 |
| Drug Interrupted | 2 (3.9) | 6 (10.9) |
| Dose Not Changed/NA/Unknown | 35 (68.6) | 40 (72.7) |
| Missing | 0 | 0 |
| Medication or therapy taken, n (%) | 36 (70.6) | 39 (70.9) |
| AE outcome, n (%) | | |
| Recovered/Resolved | 29 (56.9) | 36 (65.5) |
| Recovering/Resolving | 2 (3.9) | 2 (3.6) |

| | (Acute GvHD) F12201+C2301 Total pediatric patients N=51 n (%) | (Chronic GvHD) G12201+D2301 Total pediatric patients N=55 n (%) |
|---|---|---|
| Not Recovered/Not Resolved | 10 (19.6) | 11 (20.0) |
| Recovered/Resolved With Sequelae | 1 (2.0) | 2 (3.6) |
| Fatal | 0 | 2 (3.6) |
| Unknown | 1 (2.0) | 0 |
| Missing | 0 | 0 |
| **Herpes zoster** | | |
| Number of patients with at least one event, n (%) | 2 (3.9) | 3 (5.5) |
| 95% CI | (0.5,13.5) | (1.1,15.1) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 2 (9.6) | 3 (4.8) |
| Maximum grade, n (%) | | |
| Grade 3 AEs | 1 (2.0) | 3 (5.5) |
| Grade 4 AEs | 0 | 0 |
| Grade 5 AEs | 0 | 0 |
| Treatment-related AEs, n (%) | 0 | 2 (3.6) |
| SAEs, n (%) | 1 (2.0) | 3 (5.5) |
| Action taken, n (%) | | |
| Drug Withdrawn | 0 | 1 (1.8) |
| Dose Reduced | 0 | 0 |
| Dose Increased | 0 | 0 |
| Drug Interrupted | 0 | 0 |
| Dose Not Changed/NA/Unknown | 2 (3.9) | 2 (3.6) |
| Missing | 0 | 0 |
| Medication or therapy taken, n (%) | 2 (3.9) | 3 (5.5) |
| AE outcome, n (%) | | |
| Recovered/Resolved | 2 (3.9) | 3 (5.5) |
| Recovering/Resolving | 0 | 0 |
| Not Recovered/Not Resolved | 0 | 0 |
| Recovered/Resolved With Sequelae | 0 | 0 |
| Fatal | 0 | 0 |
| Unknown | 0 | 0 |
| Missing | 0 | 0 |
| **Urinary tract infections (UTI)** | | |
| Number of patients with at least one event, n (%) | 5 (9.8) | 3 (5.5) |
| 95% CI | (3.3,21.4) | (1.1,15.1) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 5 (25.8) | 3 (4.1) |

| | (Acute GvHD) F12201+C2301 Total pediatric patients N=51 n (%) | (Chronic GvHD) G12201+D2301 Total pediatric patients N=55 n (%) |
|---|---|---|
| Maximum grade, n (%) | | |
| Grade 3 AEs | 1 (2.0) | 1 (1.8) |
| Grade 4 AEs | 0 | 0 |
| Grade 5 AEs | 0 | 0 |
| Treatment-related AEs, n (%) | 0 | 0 |
| SAEs, n (%) | 2 (3.9) | 1 (1.8) |
| Action taken, n (%) | | |
| Drug Withdrawn | 0 | 0 |
| Dose Reduced | 0 | 0 |
| Dose Increased | 0 | 0 |
| Drug Interrupted | 0 | 0 |
| Dose Not Changed/NA/Unknown | 5 (9.8) | 3 (5.5) |
| Missing | 0 | 0 |
| Medication or therapy taken, n (%) | 5 (9.8) | 3 (5.5) |
| AE outcome, n (%) | | |
| Recovered/Resolved | 5 (9.8) | 3 (5.5) |
| Recovering/Resolving | 0 | 0 |
| Not Recovered/Not Resolved | 0 | 0 |
| Recovered/Resolved With Sequelae | 0 | 0 |
| Fatal | 0 | 0 |
| Unknown | 0 | 0 |
| Missing | 0 | 0 |
| **Opportunistic infections** | | |
| Number of patients with at least one event, n (%) | 10 (19.6) | 7 (12.7) |
| 95% CI | (9.8,33.1) | (5.3,24,5) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 10 (57.4) | 7 (9.4) |
| Maximum grade, n (%) | | |
| Grade 3 AEs | 3 (5.9) | 1 (1.8) |
| Grade 4 AEs | 0 | 0 |
| Grade 5 AEs | 0 | 1 (1.8) |
| Treatment-related AEs, n (%) | 2 (3.9) | 1 (1.8) |
| SAEs, n (%) | 2 (3.9) | 3 (5.5) |
| Action taken, n (%) | | |
| Drug Withdrawn | 0 | 1 (1.8) |
| Dose Reduced | 1 (2.0) | 0 |
| Dose Increased | 0 | 0 |
| Drug Interrupted | 0 | 2 (3.6) |

| | (Acute GvHD) F12201+C2301 Total pediatric patients N=51 n (%) | (Chronic GvHD) G12201+D2301 Total pediatric patients N=55 n (%) |
|---|---|---|
| Dose Not Changed/NA/Unknown | 10 (19.6) | 7 (12.7) |
| Missing | 0 | 0 |
| Medication or therapy taken, n (%) | 10 (19.6) | 7 (12.7) |
| AE outcome, n (%) | | |
| Recovered/Resolved | 7 (13.7) | 6 (10.9) |
| Recovering/Resolving | 2 (3.9) | 0 |
| Not Recovered/Not Resolved | 3 (5.9) | 0 |
| Recovered/Resolved With Sequelae | 0 | 0 |
| Fatal | 0 | 1 (1.8) |
| Unknown | 0 | 0 |
| Missing | 0 | 0 |
| **Pneumonia** | | |
| Number of patients with at least one event, n (%) | 3 (5.9) | 10 (18.2) |
| 95% CI | (1.2,16.2) | (9.1,30.9) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 3 (14.8) | 10 (14.5) |
| Maximum grade, n (%) | | |
| Grade 3 AEs | 1 (2.0) | 6 (10.9) |
| Grade 4 AEs | 0 | 1 (1.8) |
| Grade 5 AEs | 0 | 0 |
| Treatment-related AEs, n (%) | 0 | 3 (5.5) |
| SAEs, n (%) | 1 (2.0) | 5 (9.1) |
| Action taken, n (%) | | |
| Drug Withdrawn | 0 | 0 |
| Dose Reduced | 0 | 0 |
| Dose Increased | 0 | 0 |
| Drug Interrupted | 1 (2.0) | 2 (3.6) |
| Dose Not Changed/NA/Unknown | 2 (3.9) | 9 (16.4) |
| Missing | 0 | 0 |
| Medication or therapy taken, n (%) | 3 (5.9) | 9 (16.4) |
| AE outcome, n (%) | | |
| Recovered/Resolved | 2 (3.9) | 8 (14.5) |
| Recovering/Resolving | 0 | 0 |
| Not Recovered/Not Resolved | 1 (2.0) | 2 (3.6) |
| Recovered/Resolved With Sequelae | 0 | 0 |
| Fatal | 0 | 0 |
| Unknown | 0 | 0 |
| Missing | 0 | 0 |

| | (Acute GvHD) F12201+C2301 Total pediatric patients N=51 n (%) | (Chronic GvHD) G12201+D2301 Total pediatric patients N=55 n (%) |
|---|---|---|
| **Sepsis and septic shock** | | |
| Number of patients with at least one event, n (%) | 5 (9.8) | 2 (3.6) |
| 95% CI | (3.3,21.4) | (0.4,12.5) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 5 (24.8) | 2 (3.0) |
| Maximum grade, n (%) | | |
| Grade 3 AEs | 1 (2.0) | 1 (1.8) |
| Grade 4 AEs | 3 (5.9) | 0 |
| Grade 5 AEs | 0 | 1 (1.8) |
| Treatment-related AEs, n (%) | 0 | 0 |
| SAEs, n (%) | 4 (7.8) | 2 (3.6) |
| Action taken, n (%) | | |
| Drug Withdrawn | 0 | 0 |
| Dose Reduced | 0 | 0 |
| Dose Increased | 0 | 0 |
| Drug Interrupted | 0 | 1 (1.8) |
| Dose Not Changed/NA/Unknown | 5 (9.8) | 1 (1.8) |
| Missing | 0 | 0 |
| Medication or therapy taken, n (%) | 5 (9.8) | 2 (3.6) |
| AE outcome, n (%) | | |
| Recovered/Resolved | 4 (7.8) | 0 |
| Recovering/Resolving | 0 | 1 (1.8) |
| Not Recovered/Not Resolved | 0 | 0 |
| Recovered/Resolved With Sequelae | 1 (2.0) | 0 |
| Fatal | 0 | 1 (1.8) |
| Unknown | 0 | 0 |
| Missing | 0 | 0 |
| **CMV infection/disease** | | |
| Number of patients with at least one event, n (%) | 16 (31.4) | 5(9.1) |
| 95% CI | (19.1,45.9) | (3.0,20.0) |
| Exposure-adjusted overall incidence, n (EAIR per 100 PTY) | 16 (105.5) | 5 (6.7) |
| Maximum grade, n (%) | | |
| Grade 3 AEs | 3 (5.9) | 0 |
| Grade 4 AEs | 0 | 0 |
| Grade 5 AEs | 0 | 0 |
| Treatment-related AEs, n (%) | 4 (7.8) | 1 (1.8) |

| | (Acute GvHD) F12201+C2301 Total pediatric patients N=51 n (%) | (Chronic GvHD) G12201+D2301 Total pediatric patients N=55 n (%) |
|---|---|---|
| SAEs, n (%) | 3 (5.9) | 1 (1.8) |
| Action taken, n (%) | | |
| Drug Withdrawn | 0 | 0 |
| Dose Reduced | 1 (2.0) | 0 |
| Dose Increased | 0 | 0 |
| Drug Interrupted | 0 | 0 |
| Dose Not Changed/NA/Unknown | 16 (31.4) | 5 (9.1) |
| Missing | 0 | 0 |
| Medication or therapy taken, n (%) | 16 (31.4) | 5 (9.1) |
| AE outcome, n (%) | | |
| Recovered/Resolved | 12 (23.5) | 5 (9.1) |
| Recovering/Resolving | 2 (3.9) | 0 |
| Not Recovered/Not Resolved | 3 (5.9) | 0 |
| Recovered/Resolved With Sequelae | 0 | 0 |
| Fatal | 0 | 0 |
| Unknown | 0 | 0 |
| Missing | 0 | 0 |
| **Other infections** | | |
| Number of patients with at least one event, n (%) | 29 (56.9) | 38 (69.1) |
| 95% CI | (42.2,70.7) | (55.2,80.9) |
| Exposure-adjusted overall incidence,n (EAIR per 100 PTY) | 29 (279.2) | 38 (129.6) |
| Maximum grade, n (%) | | |
| Grade 3 AEs | 10 (19.6) | 7 (12.7) |
| Grade 4 AEs | 0 | 2 (3.6) |
| Grade 5 AEs | 0 | 0 |
| Treatment-related AEs, n (%) | 3 (5.9) | 4 (7.3) |
| SAEs, n (%) | 6 (11.8) | 11 (20.0) |
| Action taken, n (%) | | |
| Drug Withdrawn | 1 (2.0) | 1 (1.8) |
| Dose Reduced | 1 (2.0) | 1 (1.8) |
| Dose Increased | 0 | 0 |
| Drug Interrupted | 1 (2.0) | 3 (5.5) |
| Dose Not Changed/NA/Unknown | 28 (54.9) | 37 (67.3) |
| Missing | 0 | 0 |
| Medication or therapy taken, n (%) | 26 (51.0) | 32 (58.2) |
| AE outcome, n (%) | | |
| Recovered/Resolved | 23 (45.1) | 35 (63.6) |

| | (Acute GvHD) F12201+C2301 Total pediatric patients N=51 n (%) | (Chronic GvHD) G12201+D2301 Total pediatric patients N=55 n (%) |
|---|---|---|
| Recovering/Resolving | 0 | 1 (1.8) |
| Not Recovered/Not Resolved | 7 (13.7) | 8 (14.5) |
| Recovered/Resolved With Sequelae | 0 | 2 (3.6) |
| Fatal | 0 | 0 |
| Unknown | 1 (2.0) | 0 |
| Missing | 0 | 0 |

*Infections and infestations are grouped and presented under risk topic "Infections excluding Tuberculosis",

Numbers (n) represent counts of patients.

For category "maximum grade" a patient with multiple severity grades (of the same PT or different PTs) for the AESI/risk is only counted once under the maximum grade.

A patient may be counted in several rows for action taken and outcome.

Action taken refers to ruxolitinib treatment.

MedDRA version 26.0 and version 27.1, CTCAE version 4.03, Case Retrieval Strategy version released 2023-07-12 and 2025-02-05.

Source: (Annex7c- Table 2.6-3.1c, Table 2.6-3.2)

**Table 8-4 Important Identified Risk – Serious infections: Other details**

| Serious infections (MedDRA Terms - Provided at the end of this table) | Details |
|---|---|
| Potential mechanisms | Possibly a consequence of JAK inhibition. |
| Evidence source(s) and strength of evidence | The frequently reported infections in MF include viral reactivation of herpes zoster (HZ) (shingles), urinary tract infections (UTI) Infections were frequently reported cause of death due to AEs in patients with MF. The frequency and severity of infections appear to be higher in MF patients than in PV patients.<br>In GvHD indication, as expected in this patient population, the proportion of patients with serious infections AEs reported was similar in the adult and adolescent group and in the pooled pediatric patients. The most common PTs included CMV infections including reactivation, sepsis, pneumonia and upper respiratory tract infections (Table 8-2 and Table 8-3 ). |
| Characterization of the risk: | Data from interventional trials:<br>Myelofibrosis<br>In the randomized period of 2 pivotal studies, 53.8% of ruxolitinib-randomized patients had a minimum of 1 infection compared with 42.4% and 45.2% of patients randomized to placebo and BAT in Study 351 and Study 352, respectively (Annex 7a-Table 2.1-1.4).<br>The majority of infections were balanced between ruxolitinib-randomized patients and comparator arms except UTIs (12.6% on ruxolitinib vs. 4.6% on placebo and 6.8% on BAT), HZ infections (4.0% on ruxolitinib vs. 0.7% on placebo and 0 on BAT) and TB (0.3% on ruxolitinib vs. 0 in control arms) (Annex 7a-Table 2.1-5.14.1, Table 2.1-5.16.1, 2.1-5.22.1). |

| Serious infections (MedDRA Terms - Provided at the end of this table) | Details |
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| | In the overall MF population, 49.3% of patients had at a minimum of 1 infection other than TB. Serious and grade ≥3 severity infections were reported in 17.1% and 16.1% of patients, respectively. Infections led to dose reductions and study drug discontinuation in 1.8% and 7.7% of patients, respectively.<br>The most commonly reported MedDRA preferred term (PTs) included Pneumonia (9.3%), UTI (8.0%), Nasopharyngitis (6.9%), Bronchitis (6.7%) and HZ (6.5%) (Annex 7a-Table 8.3-12.9).<br>This topic is further discussed in the following categories (some of which overlap): Opportunistic infections, Pneumonia, Sepsis and septic shock and Other infections.<br>Opportunistic infections:<br>No opportunistic infections were reported in randomized period of pivotal studies in MF. Opportunistic infections were reported in 21 patients (0.7%) of the overall MF population with the exposure-adjusted incidence of 0.42/100 PTY (Annex 7a-Table 8.3-9.3).<br>Thirteen patients (0.5%) reported SAEs and 12 patients (0.4%) had events of grade ≥3 severity. No AEs required dose reduction. Eleven patients (0.4%) required study drug discontinuation. Oesophageal candidiasis was reported in 4 patients (0.1%). The other reported MedDRA PTs included Aspergillus infection, Bronchopulmonary aspergillosis, Pneumocystis jirovecii infection and Pneumocystis jirovecii pneumonia (Annex 7a-Table 8.3-9.3).<br>Pneumonia:<br>In the randomized period of 2 pivotal phase III studies in MF, pneumonia was reported in 8.3% of patients randomized to ruxolitinib compared to 7.9% of patients randomized to placebo in Study 351 and 9.6% of patients randomized to BAT in Study 352 (PSUR 07, Appendix 10-Table 8.3-10.7). The corresponding exposure-adjusted incidence per 100 PTY in ruxolitinib-treated patients, placebo arm in Study 351 and BAT arm in Study 352 were 8.5, 12.2 and 10.4, respectively. In the overall MF patient population, pneumonia (group of PTs) was reported in 12.0% of patients. The exposure-adjusted incidence was 7.21/100 PTY. Serious events and events of grade ≥3 severity were reported in 8.2% and 7.3% of patients, respectively. In 2 patients (0.3%), AEs required a dose reduction and 2.7% of patients had study drug discontinued due to AEs. The most frequently reported MedDRA PTs included Pneumonia (9.3%) and Lung infection (0.9%) (Annex 7a-Table 8.3-10.3).<br>Sepsis and septic shock:<br>In the randomized period of 2 pivotal studies in MF, sepsis/septic shock events were reported in 3% patients randomized to ruxolitinib compared to 2% and 0% of patients randomized to placebo in Study 351 and BAT in Study 352, respectively. The exposure adjusted incidence per 100 PTY in ruxolitinib and placebo patients was 3.1 and 3.0, respectively (Annex 7a-Table 8.3-11.7).<br>In the overall MF population, sepsis and septic shock (group of PTs) were reported in 4.3% of patients. The exposure-adjusted incidence was 2.44/100 PTY. Serious events and events of grade ≥3 severity were reported in 3.9% and 4.1% of patients, respectively. In 3 patients (0.5%), AEs |

| Serious infections (MedDRA Terms - Provided at the end of this table) | Details |
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| | required dose reduction and 1.5% of patients had study drug discontinued due to AEs (Annex 7a-Table 8.3-11.3).<br>Other infections:<br>In the overall MF patient population, other infections (group of PTs) were reported in 38.3% of patients. Serious events and events of grade ≥3 severity were reported in 7.4% and 6.8% of patients, respectively. In 1.1% of patients, the AEs required dose reduction and 4.7% of patients had the study drug discontinued due to AEs. The most frequently reported PTs included Nasopharyngitis (6.9%), Bronchitis (6.7%) and Upper respiratory tract infection (6.2%) (Annex 7a-Table 8.3-12.3).<br>Polycythemia vera<br>In general, the frequency, severity and seriousness of infections in ruxolitinib-treated patients with PV appeared to be lower compared to patients with MF. This should be interpreted in the content of difference in the overall duration of exposure between the 2 populations.<br>In the overall PV population, more than half of the patients had infection AEs excluding TB (64.4%). Rarely patients required dose reduction (1 patient) or study drug discontinuation (3 patients) due to these events. The most frequently reported MedDRA PT included Herpes zoster (15.2%), Nasopharyngitis (14.4%), Bronchitis (12.6%), Influenza (11.5%) and Upper respiratory tract infection (9.1%) (Annex 7b-Table 8.3-12.11).<br>Infections are further discussed in following categories (some of which overlap): Opportunistic infections, Pneumonia, Sepsis and septic shock and Other infections.<br>Opportunistic infections:<br>No opportunistic infections were reported in the overall PV population (Annex 7b-Table 8.3-9.5).<br>Pneumonia:<br>In the overall PV patient population, pneumonia (group of PTs) was reported in 7.5 % of patients. Grade ≥3 severity events were reported in 4.5% of patients and 4.8% of patients had SAEs. The event resulted in dose reduction and study drug discontinuation due to AEs in 1 patient each, respectively (0.3%) (Annex 7b-Table 8.3-10.5).<br>Sepsis and septic shock:<br>In the overall PV patient population, sepsis or septic shock events were reported in 3 patients (0.8 %). Of these, Sepsis and urosepsis were reported in 2 patients (0.5) and 1 patient (0.3%), respectively. No dose reduction or study drug discontinuation was required (Annex 7b-Table 8.3-11.5).<br>Other infections:<br>In the overall PV population, other infections (group of PTs) were reported in 55.3% of patients. Both serious events and events of grade ≥3 severity were reported in 7.2% and 6.7%, respectively. In 2 patients (0.5%), infection(s) resulted in study discontinuation and none of the events required dose reduction. The most frequently reported PTs included Nasopharyngitis (14.4%), Bronchitis (12.6%), Influenza (11.5%) and Upper respiratory tract infection (9.1%) (Annex 7b-Table 8.3-12.5).<br>Phase III comparative period: |

| Serious infections (MedDRA Terms - Provided at the end of this table) | Details |
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| | Infections were reported in 35.9% of ruxolitinib-randomized patients compared with 37.8% and 22.7% of BAT-randomized patients in Study B2301 and Study B2401, respectively. Serious and severe events were balanced across the studies' arms (RMP v 8.0, Annex 12-Table 8.3-12.13).<br>Herpes zoster was reported in 4.3% of ruxolitinib-randomized patients and no patients randomized to BAT (RMP v 8.0, Annex 12-Table 8.3-6.1).<br>Urinary tract infections were reported in 6.0% of ruxolitinib-randomized patients compared with 2.7% and 0 patients randomized to BAT in Study B2301 and Study B2401, respectively (RMP v 8.0, Annex 12-Table 8.3-7.1).<br>Data from Study CINC424AIC01T (PASS):<br>Study CINC424AIC01T was a non-Interventional long-term safety study of ruxolitinib in MF patients in a real-world setting.<br>Pneumonia:<br>Pneumonia-related events were reported in 17% of the patients in the prevalent users cohort (17.8% long-term users and 15.2% short-term users), 9.4% in the new users cohort, 9.6% in the non-exposed to ruxolitinib cohort, and 21.1% in the switch to ruxolitinib cohort. The most frequently reported pneumonia-related events in the prevalent users cohort, new users cohort, non-exposed to ruxolitinib cohort, and switch to ruxolitinib cohort included 'pneumonia' (10.8% vs 3.1% vs 8.4% vs 7%), lung infection (3.5% vs 6.3% vs 0% vs 3.5%) and lower respiratory tract infection (2.3% vs 0% vs 0.6% vs 7%) (Study CINC424AIC01T Clinical study report [CSR] Table 10-15 and Table 14.3.1-2.1.3).<br>Sepsis and septic shock:<br>Sepsis and septic shock-related events were reported in a higher proportion of patients in the prevalent users cohort (10.8%), and in a comparable proportion of the patients in the new users cohort and in the non-exposed to ruxolitinib cohort (6.3% vs 6.6%). The most frequently reported events in the prevalent users cohort, the new users cohort, the non-exposed to ruxolitinib cohort and the switch to ruxolitinib cohort were sepsis (5.4% vs 0% vs 1.8% vs 1.8%) and septic shock (1.5% vs 3.1% vs 1.8% vs 0%) (Study CINC424AIC01T CSR- Table 10-15 and Table 14.3.1-2.1.3).<br>Opportunistic infections:<br>Opportunistic infections-related events were reported in 2.7% of the patients in the prevalent users cohort (3.9% long-term users and none in the short-term users), and 1 patient (1.8%) in the switch to ruxolitinib cohort. None of the patients in the other cohorts had any opportunistic infections (Study CINC424AIC01T CSR-Table 10-15).<br>Other infections:<br>Other infections-related events were reported in 44.8% of the patients in the prevalent users cohort, 40.6% in the new users cohort, 36.8% in the switch to ruxolitinib cohort, and 17.4% in the non-exposed to ruxolitinib cohort.<br>The most frequently reported (at least in 5% in any cohort) other infections-related events in the prevalent users cohort, the new users cohort, the non-exposed to ruxolitinib cohort, and the switch to ruxolitinib cohort included bronchitis (10.8% vs 9.4% vs 2.4% vs 5.3%), nasopharyngitis (9.3% |

| Serious infections (MedDRA Terms - Provided at the end of this table) | Details |
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| | vs 6.3% vs 2.4% vs 8.8%), respiratory tract infection (2.7% vs 9.4% vs 0% vs 1.8%), infection (4.6% vs 6.3% vs 0.6% vs 1.8%), gastroenteritis (1.5% vs 3.1% vs 1.2% vs 7%), and influenza (0.4% vs 0% vs 1.2% vs 8.8%). Febrile infection was reported in 6.3% of the patients in the new users cohort (Study CINC424AIC01T CSR -Table 10-15 and Table 14.3.1-2.1.3).<br>Data from Study CINC424A2201:<br>Study CINC424A2201 is to evaluate the safety of ruxolitinib in MF patients with a baseline platelet count <100000/mm$^3$ (Stratum 1: ≥75000/mm$^3$ to <100000/mm$^3$, and Stratum 2: ≥50000/mm$^3$ to <75000/mm$^3$).<br>Overall, the incidence of infections excluding TB was 59.1% in Stratum 1 and 68% in Stratum 2. Treatment-related events were reported in 27.3% and 28% patients of Stratum 1 and 2, respectively. The frequent PTs (>10%) in Stratum 1 were nasopharyngitis (15.9%) and upper respiratory tract infection (11.4%) while in Stratum 2 were nasopharyngitis (24%), upper respiratory tract infection (12%), bronchitis (16%), and influenza (12%). Overall, infection events were mostly non-serious and grade 1 or 2 in severity in both the strata. Serious infection events were reported in 13.6% patients of Stratum 1 and 20% patients of Stratum 2. Grade 4 and grade 3 events were reported in 4 patients each of Stratum 1, and in 3 patients and 1 patient, respectively in Stratum 2. In Group 2 (10 mg b.i.d., MSSD), 4 patients in Stratum 1 and 3 patients in Stratum 2 reported serious infections excluding TB (Study CINC424A2201 CSR - Table 12-16 and Table 14.3.1-5.1).<br>Graft versus Host Disease:<br>Serious infections are presented in the Table 8-2 for analysis in Study 271, Study C2301 and Study D2301 (adult and adolescent patients) and in Table 8-3 Clinical trial data of serious infections in pediatric patients with acute or chronic GvHD for pediatric data in acute GvHD (Study C2301 + F12201) and chronic GvHD (Study D2301 + G12201).<br>Acute GvHD:<br>Adults /adolescents<br>Infections:<br>In Study C2301, up to Day 28 (randomized period), overall infections were reported in 61.2% of ruxolitinib-randomized patients compared to 58.7% of patients randomized to BAT. The risk difference between the 2 arms was not significant (2.5%; 95% CI: -8.5, 13.6). A positive risk difference means higher frequency in the ruxolitinib arm compared to the BAT arm, but since the CI includes zero, this difference between the 2 treatment arms is not significant ([SCS] – Appendix 1 - Table 2.1-11.10). Frequently (>5%) reported PTs in ruxolitinib and BAT arms included CMV infection reactivation (21.7% vs. 16.7%), sepsis (7.2% vs. 4%), CMV infection (5.3% vs. 4%), UTI (5.3% vs. 4.7%) and pneumonia (3.9% vs. 5.3)<br>([SCS] – Appendix 1 - Table 2.1-11.10). Up to data cut-off of secondary CSR, the exposure-adjusted overall incidence of infections in the ruxolitinib arm was 681.9/100 PTY and 787.0/100 PTY in the BAT arm<br>([SCS] Appendix 1-Table 2.1-12.10). Majority of the patients had the first infection within the first 2 months of treatment ([SCS] – Appendix 1 Figure 2.1-7.1). |

| Serious infections (MedDRA Terms - Provided at the end of this table) | Details |
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| | In the ruxolitinib overall population in Study C2301 up to LPLV, 79.1% of patients had infections with exposure-adjusted incidence of 655.1/ 100 PTY (Annex 7c-Table 4.3-2).<br>In Study 271, the exposure-adjusted overall incidence rate was 652.6/100 PTY. The AE profile for infections was similar to Study C2301 treatment (Annex 7c-Table 4.3-2).<br>Infections above include all the other infections categories and are further discussed in the following categories:<br>Herpes zoster:<br>In Study C2301, up to Day 28, no patients reported HZ in ruxolitinib arm compared with 1 patient in BAT arm ([SCS] – Appendix 1 – Table 2.1-11.11). Up to data cut-off of secondary CSR, the exposure-adjusted incidence was 6.2/100 PTY in ruxolitinib arm compared to 10.1/100 PTY in BAT arm ([SCS] – Appendix 1 – Table 2.1-12.11).<br>In the ruxolitinib overall population in Study C2301 up to LPLV, exposure-adjusted incidence of HZ was 6.2/100 PTY. Treatment-related AEs and SAEs were noted in 0% and 0.5% respectively. All patients recovered from events after treatment (Annex 7c-Table 4.3-2).<br>In Study 271, no patients reported HZ (Annex 7c-Table 4.3-2).<br>Urinary tract infection:<br>In Study C2301, up to Day 28, UTIs were reported in 9.9% of patients in ruxolitinib arm compared with 10.7 % in BAT arm ([SCS] - Appendix 1 – Table 2.1-11.12). Up to data cut-off of secondary CSR, the exposure-adjusted incidence was 69.3/100 PTY and 78.2/10 PTY in ruxolitinib and BAT arms, respectively ([SCS] – Appendix 1 - Table 2.1-12.12).<br>In the ruxolitinib overall population up to LPLV, the exposure-adjusted overall incidence rate was 62.7/100 PTY. Treatment-related AEs and SAEs were noted in 4.5% and 2.0%, respectively; 12.4% AEs were recovered or resolved. With the exception of UTI (8.5%) and cystitis (4.5%), all other PTs were in less than 2% (Annex 7c-Table 4.3-2).<br>In Study 271, UTI were reported in 10 patients (14.1%) with the exposure adjusted incidence of 38.2/100 PTY. Three patients (4.2%) reported SAEs and 6 patients (8.5%) had events of grade ≥3 severity. No patient required dose reduction or study drug discontinuation Annex 7c-Table 4.3-2).<br>Opportunistic infections:<br>In Study C2301, up to Day 28, Opportunistic infections were reported in 27.0% in ruxolitinib arm compared with 22.0% in BAT arm. Frequently (≥2%) reported PTs in ruxolitinib and BAT arms included CMV infection reactivation (21.7% vs. 16.7%), Epstein-Barr virus infection reactivation (2.6% vs. 2.7%) and bronchopulmonary aspergillosis (2% vs. 0%) ([SCS] - Appendix 1 - Table 2.1-11.14). Up to data cut-off of secondary CSR, the exposure-adjusted incidence rates was 148.9/100 PTY in the ruxolitinib arm and 166.8/100 PTY in the BAT arm ([SCS] - Appendix 1 - Table 2.1-12.14).<br>In ruxolitinib overall population in Study C2301, opportunistic infections were reported in 68 patients (33.8%) with the exposure-adjusted incidence of 144.5/100 PTY. Treatment-related AEs and SAEs were noted in 8.5% and |

| Serious infections (MedDRA Terms - Provided at the end of this table) | Details |
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| | 7.5% respectively. In 20.9% AEs were recovered or resolved. There were no fatal AEs (Annex 7c-Table 4.3-2).<br>In Study 271, opportunistic infections were reported in 15 patients (21.1%) with the exposure-adjusted incidence of 58.2/100 PTY. Three patients (4.2%) reported SAEs and 7 patients (9.9%) had events of grade ≥3 severity. Dose reduction was required in 1 patient (1.4%). No patient required study drug discontinuation (Annex 7c-Table 4.3-2).<br>Pneumonia:<br>In the Study C2301, up to Day 28, pneumonia were reported in 7.2% of ruxolitinib-randomized patients compared with 10.0% of patients randomized to BAT ([SCS] – Appendix 1 - Table 2.1-11.15). Up to data cut-off of secondary CSR, the exposure-adjusted overall incidence was 60.4/100 PTY in the ruxolitinib arm and 92.4/100 PTY in the BAT arm ([SCS] – Appendix 1 – Table 2.1-12.15).<br>In ruxolitinib overall population in Study C2301, pneumonia were reported in 38 patients (18.9%) with the exposure adjusted incidence of 62.9/100 PTY. Treatment-related AEs and SAEs were noted in 7.0% and 10.4%, respectively; 11.4% AEs were recovered or resolved. Fatal outcome was reported in four patients. (Annex 7c-Table 4.3-2).<br>In Study 271, pneumonia were reported in 17 patients (23.9%) with the exposure-adjusted incidence of 67.3/100 PTY. Eleven patients (15.5%) reported SAEs and 15 patients (21.1%) had events of grade ≥3 severity. Dose reduction and study drug discontinuation required in 1 patient (1.4%) each (Annex 7c-Table 4.3-2).<br>Sepsis and septic shock:<br>In Study C2301, up to Day 28, sepsis and septic shock were reported in 12.5% of ruxolitinib-randomized patients compared with 8.7% of patients randomized to BAT. Frequently (>2%) reported PTs included sepsis (7.2% vs. 4%), septic shock (2.6% vs. 2.7%) ([SCS] – Appendix 1 - Table 2.1-11.16).<br>Up to data cut-off of secondary CSR, the exposure-adjusted incidence rates was 79.4/100 PTY in the ruxolitinib arm and 111.3/100 PTY in the BAT arm ([SCS] – Appendix 1 - Table 2.1-12.16).<br>In ruxolitinib overall population in Study C2301, sepsis and septic shock were reported in 53 patients (26.4%) with the exposure-adjusted incidence of 84.7/100 PTY. Treatment-related AEs and SAEs were noted in 7.5% and 19.9%, respectively; 12.9% AEs were recovered or resolved; 10% resulted in fatal outcome (Annex 7c-Table 4.3-2).<br>In Study 271, sepsis and septic shock were reported in 16 patients (22.5%) with the exposure-adjusted incidence of 60.2/100 PTY. Fourteen patients (19.7%) reported SAEs and 15 patients (21.1%) had events of grade ≥3 severity. No patient required dose reduction. Study drug discontinuation required in 5 patients (7.0%) (Annex 7c-Table 4.3-2).<br>Cytomegalovirus infection/disease:<br>In Study C2301, up to Day 28, CMV infection/disease were reported in 28.3% of ruxolitinib-randomized patients compared with 24.0% of patients randomized to BAT. Frequently (>1%) reported PTs in ruxolitinib and BAT arms included CMV infection reactivation (21.7% vs. 16.7%), CMV infection |

| Serious infections (MedDRA Terms - Provided at the end of this table) | Details |
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| | (5.3% vs. 4%), CMV colitis (1.3% vs. 1.3%), CMV viremia (0.7% vs. 1.3%), CMV test positive (1.3% vs.0.7%) ([SCS] - Appendix 1 - Table 2.1-11.20). Up to data cut-off of secondary CSR, the exposure-adjusted incidence rates was 154.0/100 PTY in the ruxolitinib arm and 214.5/100 PTY in the BAT arm ([SCS] – Appendix 1 – Table 2.1-12.20).<br>In ruxolitinib overall population of Study C2301, CMV infection/disease were reported in 66 patients (32.8%) with the exposure-adjusted incidence of 140.9/100 PTY. Treatment-related AEs and SAEs were noted in 8.0% and 7.0% respectively. In 22.4% patients, AEs were recovered or resolved (Annex 7c-Table 4.3-2).<br>In Study 271, the exposure adjusted overall incidence rate was 55.5/100 PTY (Annex 7c-Table 4.3-2).<br>Pooled pediatric population<br>Infections: (Annex 7c-Table 2.6-3.1c)<br>In the pooled pediatric population, 36 patients (70.6%) reported infection-related terms. The most frequent PTs (≥ 5%) were CMV infection reactivation (11.8%), bronchitis (9.8%), EBV infection reactivation (7.8%), and COVID-19, CMV infection, device-related infection, and rhinitis (5.9% each) (). The majority of patients (20 of 36) experienced events of grade ≤ 2. No fatal AEs were reported.<br>A similar frequency of infections was observed across the age groups.<br>Infections above include all the other infections categories discussed in the following categories:<br>Herpes zoster:Two pediatric patients (3.9%) reported HZ, including one grade 3 event. No action was taken with ruxolitinib. The outcome was complete recovery in both cases.<br>Urinary tract infections (UTI): Five pediatric patients (9.8%) developed UTI, including one grade 3 event. There were no grade 4 events.No action was taken with ruxolitinib. The outcome was complete recovery in all cases.<br>Opportunistic infections:Ten pediatric patients (19.6%) developed opportunistic infections, including 3 grade 3 events. There were no grade 4 events. The PTs reported in >5% of patients were cytomegalovirus infection reactivation (11.8%) and Epstein-Barr virus infection reactivation (7.8%), Ruxolitinib dose was reduced in one patient. The outcome was complete recovery in 7 patients (13.7%), recovering in two patients (3.9%) and not recovered in 3 patients (5.9%).<br>Pneumonia:Three pediatric patients (5.9%) developed pneumonia, including one grade 3 event. There were no grade 4 events. For 2 patients (3.9%), no action was taken with respect to ruxolitinib, while 1 patient (2.0%) had drug interruption. The outcome was complete recovery in two patients, while one patient had not recovered<br>Sepsis and septic shock:Five patients (9.8%) reported events of sepsis and septic shock, including one grade 3 (2.0%) and 3 grade 4 (5.9%) events. For all patients, no action was taken with respect to ruxolitinib. The outcome was complete recovery in 4 patients (7.8%), while one patient (2.0%) had recovered with sequelae.<br>CMV infection/disease: |

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| | Sixteen patients (31.4%) reported CMV infection/disease, including 3 grade 3 events. There were no grade 4 events. Ruxolitinib dose was reduced in one patient, while no action was taken for all the other patients. The outcome was complete recovery in 12 patients (23.5%), recovering in two patients (3.9%) and not recovered in 3 patients (5.9%).<br>Chronic GvHD:<br>Adults/adolescents<br>Infections:<br>In Study D2301, up to C7D1 (randomized period), the incidence of Infections was similar between the ruxolitinib (62.4%) and the BAT arms (58.2%) The risk difference between the 2 arms was not significant (4.2%; 95% CI: -6.5, 14.9). Frequently (>5%) reported PTs in ruxolitinib and BAT arms included pneumonia (10.9% vs. 12.7%), upper respiratory tract infection (8.5% vs. 8.2%), UTI (6.7% vs. 3.2%), nasopharyngitis (6.1% vs. 3.8%), Betapolyomavirus (BK virus) infection (5.5% vs. 1.3%) and CMV infection reactivation (5.5% vs. 8.2%) ([SCS] Appendix 1 - Table 2.1-11.10).<br>Up to the data cut-off of the primary CSR, the exposure-adjusted overall incidence rates was 169.0/100 PTY in the ruxolitinib arm and 185.0/100 PTY in the BAT arm ([SCS] – Appendix 1 - Table 2.1-12.10).<br>In the ruxolitinib overall population up to LPLV, the exposure-adjusted overall incidence rate was 113.5/100 PTY. Treatment-related AEs and SAEs were noted in 30.2% and 30.6%, respectively. At the time of LPLV, 65.5% of patients had AEs that were recovered or resolved (Annex 7c-Table 4.3-2).<br>Infections above include all the types of infections discussed in the following categories:<br>Herpes zoster:<br>In Study D2301, up to C7D1, 1.2% patients reported HZ in ruxolitinib arm compared with 0% in BAT arm ([SCS] - Appendix 1 – Table 2.1-11.11). Up to data cut-off of the primary CSR, the exposure-adjusted incidence of 1.9/100 PTY in ruxolitinib arm compared to 0 in BAT arm (Annex 7c-Table 4.3-2).<br>In the ruxolitinib overall population in Study D2301 up to LPLV, exposure-adjusted incidence was 2.0/100 PTY. Treatment-related AEs and SAEs were noted in 2.1% each (Annex 7c-Table 4.3-2).<br>Urinary tract infection:<br>In Study D2301, up to C7D1, UTIs were reported in 8.5% of patients in ruxolitinib arm compared with 6.3 % in BAT arm ([SCS] – Appendix 1 – Table 2.1-11.12). Up to data cut-off of the primary CSR, the exposure-adjusted incidence was 12.6/100 PTY and 15.3/100 PTY in ruxolitinib and BAT arms ([SCS] – Appendix 1 – Table 2.1-12.12).<br>In the ruxolitinib overall population, the exposure-adjusted overall incidence rate was 6.4/100 PTY. Treatment-related AEs and SAEs were noted in 4.3% and 0.9%, respectively. In 8.5%, AEs were recovered or resolved (Annex 7c-Table 4.3-2).<br>Opportunistic infections:<br>In Study D2301, up to C7D1, opportunistic infections was similar between the ruxolitinib (11.5%) and the BAT arms (12%). Frequently (≥2%) reported |

| Serious infections (MedDRA Terms - Provided at the end of this table) | Details |
|---|---|
| | PTs in ruxolitinib and BAT arms included CMV infection reactivation (5.5% vs. 8.2%), bronchopulmonary aspergillosis (1.2% vs. 2.5%) and respiratory syncytial virus infection (2.4% vs. 1.3%) ([SCS] - Appendix 1 - Table 2.1-11.14). Up to data cut-off of the primary CSR, the exposure- -adjusted incidence rates was 14.1/100 PTY in the ruxolitinib arm and 22.2/100 PTY in the BAT arm ([SCS] – Appendix 1 - Table 2.1-12.14).<br>In ruxolitinib overall population, opportunistic infection was reported in 31 (13.2%) patients with the exposure adjusted overall incidence rate was 8.0/100 PTY. Treatment-related AEs and SAEs were noted in 4.7% and 4.3%, respectively. Adverse events were recovered or resolved in 9.8% of patients. Fatal AEs were reported in 2 patients (Annex 7c-Table 4.3-2).<br>Pneumonia:<br>In Study D2301, up to C7D1, the incidence of pneumonia was similar between the ruxolitinib (19.4%) and the BAT arms (17.1%) ([SCS] – Appendix 1 – Table 2.1-11.15). Up to data cut-off of the primary CSR, the exposure-adjusted overall incidence was 27.5/100 PTY in the ruxolitinib arm and 29.0/100 PTY in the BAT arm ([SCS] – Appendix 1 - Table 2.1-12.15).<br>In ruxolitinib overall population, the exposure-adjusted overall incidence rate was 15.2/100 PTY. Treatment-related AEs and SAEs were noted in 11.1% and 17.4% patients, respectively. In 14.9%, AEs were recovered or resolved. Fatal outcomes were reported in 7 patients. (Annex 7c-Table 4.3-2).<br>Sepsis and septic shock:<br>In Study D2301, up to C7D1, sepsis and septic shock were reported in 2.4% in ruxolitinib arm and 6.3% in BAT arm. Frequently (>1%) reported PTs included sepsis (1.2% vs. 1.9%), septic shock (0.6% vs. 1.9%) ([SCS] – Appendix 1 - Table 2.1-11.16). Up to data cut-off of the primary CSR, the exposure-adjusted incidence rates was 4.5/100 PTY in the ruxolitinib arm and 10.9/100 PTY in the BAT arm ([SCS] – Appendix 1 - Table 2.1-12.16).<br>In ruxolitinib overall population in Study D2301, the exposure-adjusted overall incidence rate was 3.0/100 PTY. Treatment-related AEs and SAEs were noted in 2.6% and 4.3%, respectively. Adverse events were recovered or resolved in 2.1% of patients and in1.7% events resulted in fatal outcome (Annex 7c-Table 4.3-2).<br>CMV infection/disease:<br>In Study D2301, up to C7D1, CMV infection/disease was similar between the ruxolitinib (9.1%) and the BAT arms (10.8). Frequently (>1%) reported PTs included CMV infection reactivation (5.5% vs. 8.2%), CMV infection, CMV test positive (1.2% vs. 1.3% each), CMV viremia and pneumonia cytomegaloviral (0.6% vs. 1.3% each) ([SCS] – Appendix 1 - Table 2.1-11.20). Up to data cut-off of the primary CSR, the exposure-adjusted incidence rates was 10.7/100 PTY in the ruxolitinib arm and 18.4/100 PTY in the BAT arm ([SCS] – Appendix 1 - Table 2.1-12.20).<br>In ruxolitinib overall population, the exposure adjusted overall incidence rate was 6.2/100 PTY. Treatment related AEs and SAEs were noted in 4.3% and 2.1%, respectively. In 8.15% of patients, AEs were recovered or resolved (Annex 7c-Table 4.3-2). |

| Serious infections (MedDRA Terms - Provided at the end of this table) | Details |
|---|---|
| | Pooled Pediatric population<br>Infections: In the pooled pediatric population, 43 patients (78.2%) reported infections. The Proportion of infections were higher in the ≥ 2 to < 6y age group (85.7%) compared to the ≥ 6 to < 12 y and ≥ 12 to 18 y which were respectively 81.3% and 68.2% .The most frequently reported AEs by PTs (≥ 10%) were COVID-19 (23.6%), upper respiratory tract infection (20%), influenza and pneumonia (12.7% each) and conjunctivitis (10.9%) (Appendix 7c-Table 2.6-3.2). Two fatal SAEs (aspergillus infection and septic shock) were reported.<br>The median exposure of ruxolitinib upon which the adverse drug reaction frequency categories for chronic GvHD pediatric patients are based was 57.1 weeks (range: 2.1 to 163.3 weeks) (Appendix 7c-Table 4.1-1).<br>Safety database:<br>Cumulatively till PSUR DLP of 22-Feb-2025, the reporting rate (RR) of pneumonia, other opportunistic infections, and sepsis/septic shock are 2.9, 0.8, and 0.9 per 1000 PTY. The findings from the PSUR analysis were comparable with the results seen so far in the CTs. The review of the data received during the current reporting interval, compared to the cumulative data showed no significant change in frequency, severity or pattern of this safety concern. |
| Risk factors and risk groups | Low neutrophil count, pre-existing comorbidities (chronic obstructive pulmonary disease [COPD], asthma, diabetes), co-medication [corticosteroids], higher dose, lack of dose adjustment if strong cytochrome P450 (CYP)3A4 inhibitors or fluconazole are used or the patient develops hepatic impairment, moderate or severe renal impairment (creatinine clearance [CrCl] <30mL/min) or has end stage renal failure requiring hemodialysis. |
| Preventability | Preventable by monitoring clinical signs and symptoms of infection, their prompt recognition and treatment. Before starting ruxolitinib, patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral and opportunistic infections. Ruxolitinib therapy should not be started until active serious infections have resolved. Physicians should carefully observe patients receiving ruxolitinib for signs and symptoms of infections and initiate appropriate treatment promptly. Dose discontinuation is recommended, if the ANC falls below 500/µL as indicated in the SmPC. |
| Impact on the benefit-risk balance of the product | The benefit-risk balance of ruxolitinib is not impacted by this risk considering the nature of the treatment indication(s) and if any, it is of low impact. The SmPC provides adequate information on timely identification and management of this risk. Data review for this risk in the latest PSUR for ruxolitinib also confirms no impact on the benefit-risk of ruxolitinib treatment with regards to the risk. |
| Public health impact | The public health impact depends on the prompt recognition, treatment and their clinical consequences. Preventable as described above. With prompt treatment the public health concern is low. |
| MedDRA terms | The risk is defined using the System Organ Class of Infections and infestations with the monitoring focused on serious infections. Infections are further categorized based on grouping of PTs: UTI, HZ, Opportunistic |

| Serious infections (MedDRA Terms - Provided at the end of this table) | Details |
|---|---|
| | infections, Pneumonia, Sepsis and septic shock, CMV infection and Other infections.<br>For GvHD indication: (Annex 7c- Listing 2-1). |

### 8.3.1.2 Important Potential Risk: Developmental toxicity

**Table 8-5 Important Potential Risk - Developmental toxicity**

| **Developmental toxicity** (MedDRA Terms - Provided at the end of this table) | **Details** |
|---|---|
| Potential mechanisms | Unknown |
| Evidence source(s) and strength of evidence | Myelofibrosis or PV is mainly a condition of the adult population; the median age of patients recruited in Phase III studies was about 66 years. Cases of childhood age are very rare. The number of female patients of child-bearing potential receiving ruxolitinib is therefore, expected to be limited. In the pivotal studies, 6 female patients, ≤45 years representing 1.1% of the total population were enrolled. Due to the severity of the oncological condition the fertility rate of these elderly female patients is expected to be low. There are no data from the use of ruxolitinib in pregnant women with PV. Animal studies have shown that ruxolitinib is embryotoxic (causing harm to the embryo) and fetotoxic (causing harm to the fetus). 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 counseling regarding potential risks to the fetus. |
| Characterization of the risk: | In non-clinical studies, ruxolitinib decreased fetal 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. The potential risk for humans is unknown.<br>In lactating rats, ruxolitinib and/or its metabolites were excreted into the milk with a concentration that was 13-fold higher than the maternal plasma concentration. It is unknown whether ruxolitinib and/or its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded.<br>No pregnancies were reported in CTs of MF or PV patients. Myelofibrosis or PV are mainly a condition of the adult population and cases of childhood age are very rare.<br>Myelofibrosis is a rare condition and the median age of patients recruited in Phase III studies was about 66 years. The number of female patients of child-bearing potential receiving ruxolitinib is therefore, expected to be limited. |

| **Developmental toxicity** (MedDRA Terms - Provided at the end of this table) | **Details** |
|---|---|
| | In the pivotal studies, 6 female patients, ≤45 years representing 1.1% of the total population, were enrolled. The proposed product label lists pregnancy under "Contraindications" and specifies recommendations in case pregnancy occurs during treatment. Due to the severity of the oncological condition, the fertility rate of these elderly female patients is expected to be low.<br>Long-term survivors of HCT are increasing in number because of improved transplant outcomes and better supportive care. In addition, the expanding indications for transplantation have led to an increase in the number of patients receiving HCT. The HCT recipients may already be at high risk for gonadal damage and infertility from previous exposure to chemotherapy and irradiation during pre-transplant therapies. These risks are further increased by most transplant conditioning regimens. However, a large case series of pregnancies after autologous and allo-HCT, provides evidence of preserved fertility, most frequently in young adult age group (15-30 years) and who received non-total body irradiation based conditioning regimen. Pregnancies have been reported despite the presence of cGvHD indicating that the cGvHD and its therapies may not always impair fertility. The majority of reported pregnancies occurred within 5 to 10 years after transplantation; but some occurred within the first year post-transplant (Loren et al 2011).<br>**Data from interventional trials:**<br>**Myelofibrosis and Polycythemia vera**<br>As of yet, current clinical data did not have any reports or evidence suggesting developmental toxicity in either patient population.<br>**Data from Study CINC424AIC01T (PASS):**<br>No pregnancy was reported in Study CINC424AIC01T.<br>**Graft versus Host Disease:**<br>Clinical data did not include any pregnancy reports or evidence suggesting developmental toxicity in GvHD population.<br>**Safety database:**<br>Cumulatively, till PSUR DLP of 22-Feb-2025 135 cases reported fetal exposure. This includes fetal exposure via mother (pregnancies of female patients who have taken ruxolitinib) and fetal exposure via father (pregnancies of the partners of males who have taken ruxolitinib).<br>The pregnancy with maternal exposure and congenital anomaly in the newborn is discussed below:<br>[redacted] patient was treated with ruxolitinib during the first trimester of pregnancy and with oxymetholone during the second and third trimesters of pregnancy. The neonate [redacted] was found to have ambiguous genitalia 1 week after birth. At the time of birth no malformations were noted. No information was reported in regard to the karyotype of the child. None of the cases received during the reporting interval and cumulatively were noteworthy. Thus, causality of ruxolitinib with regard to developmental toxicity was not established. |
| Risk factors and risk groups | Women of child-bearing potential not using effective contraception, breast feeding women. |

| **Developmental toxicity** (MedDRA Terms - Provided at the end of this table) | **Details** |
|---|---|
| Preventability | Exposure during pregnancy can be prevented by ensuring women of child-bearing potential take effective contraception and that ruxolitinib is not used during pregnancy.<br>Exposure through breast milk can be prevented by ensuring women do not breast feed whilst taking ruxolitinib. |
| Impact on the benefit-risk balance of the product | The benefit-risk balance of ruxolitinib is not impacted by this risk considering the nature of the treatment indication(s) and if any, it is of low impact. The SmPC provides adequate information on timely identification and management of this risk. Data review for this risk in the latest PSUR (reporting period: 23-Feb-2024 to 22-Feb-2025) for ruxolitinib also confirms no impact on the benefit-risk of ruxolitinib treatment with regards to the risk. |
| Public health impact | The public health impact is considered low if ruxolitinib is used as indicated in the label. |
| MedDRA terms | Populations at risk of developmental toxicity will be identified by SMQ Pregnancy and Neonatal Topics (broad). The MedDRA terms to be used for PhV are any PTs reported for in utero exposure (ICH E11 criteria will be used for analysis). |

### 8.3.2 Part II Module SVII.3.2. Presentation of the missing information

**Table 8-6 Missing information: Long-term safety in pediatric patients (GvHD only)**

| **Long-term safety in pediatric patients (GvHD only)** | **Details** |
|---|---|
| Evidence source | As a result of the findings from juvenile toxicity studies in rats (See Table 3-1), safety analysis in pediatric patients receiving ruxolitinib is being performed including a focused review of cases of reduced bone growth and fractures in pediatric patients in the PSUR. Based on the cumulative review of limited data on pediatric patients available from published literature and safety database, no new safety issues including reduced bone growth and fractures in pediatric patients receiving ruxolitinib (for various indications) were identified.<br>Standard treatment does not differ between adolescents and adults. Mortality risks for all adults and adolescents with SR aGvHD are a continuum, with no age breakpoint, with only approximately 49% of all patients surviving beyond 6 months after allo-SCT (Martin et al 2012). The long-term prognosis of cGvHD appears to be slightly better in children when compared to adults; however, they suffer from similar complications and also have poor long-term outcomes (Dhir et al 2014). In addition, the standard treatment of SR-GvHD does not differ between adolescents and adults (Dignan et al 2012, Jacobsohn 2010).<br>Khandelwal et al (2017) described a retrospective clinical experience of 13 pediatric patients of median age 8.5 years (range, 1.6 to 16.5) who received ruxolitinib for steroid refractory aGvHD, administered orally at 5 mg b.i.d. for children ≥25 kg or 2.5 mg b.i.d. if <25 kg. Adverse effects in |

| Long-term safety in pediatric patients (GvHD only) | Details |
|---|---|
| | 13 patients included grade 3 to 4 elevated ALT (n=7), grade 3 to 4 neutropenia (n=5) and grade 4 thrombocytopenia (n=3). No patients experienced life-threatening bleeding. All observed adverse effects resolved after discontinuation of ruxolitinib.<br>Another recent analysis in 22 SR-GvHD (acute and chronic) pediatric patients aged 5 months to 18 years treated with ruxolitinib dosing planned as noted in Khandelwal et al (2017), showed high overall response rate (ORR) in aGvHD (n=13) and cGvHD (n=9), of 77% and 89%, respectively (Vicent et al 2019). There were 54%, 18% and 13% infections caused by virus, bacteria and fungi, respectively.<br>Schoettler et al (2019), described a single center experience of treating patients aged 7 to 21 years (n=5) with bronchiolitis obliterans syndrome, cGvHD of the lungs with ruxolitinib. Of 5 patients, ruxolitinib was steroid sparing in 4 patients with an evaluable response; 3 were able to stop steroids, and 1 weaned significantly. Four patients tolerated ruxolitinib with no adverse effects and 1 patient (treated for 4 months with ruxolitinib) had a grade 3 fungal infection (occurred after months of steroid treatment, not directly attributed to ruxolitinib) and had to discontinue ruxolitinib due to infection.<br>In Study C2301, the median duration of exposure to ruxolitinib of the 6 patients (including 1 cross-over patients), up to data cut-off was 14.2 weeks (range: 1.6 to 34.6) ([SCS] - Appendix 1 - Table 5.1-1.1.2). In Study D2301, the median duration of exposure to ruxolitinib, up to data cut-off for these 8 patients was 40.3 weeks (range: 2.6 to 112.1) ([SCS] - Appendix 1 - Table 5.1-1.1.2). The AE profile of adolescent patients in both the studies were similar to overall population with no new safety concern ([SCS] – Section 5.1.1).<br>In the acute GvHD and chronic GvHD pediatric population studies, the median durations of exposure were respectively 16.7 weeks (range: 1.1 to 48.9 weeks) and 57.1 weeks (range: 2.1 to 163.3 weeks) (See table 4-4).<br><br>In the Study CINC424G12201 the most common AEs by PT (>10%) were anemia, COVID-19, pyrexia. neutrophil count decreased, upper respiratory tract infection, neutropenia, headache, hypertension, platelet count decreased, Cough, Pneumonia, Alanine aminotransferase increased, cytomegalovirus infection reactivation, Diarrhoea, Nasopharyngitis, thrombocytopenia, vomiting and White blood cell count decreased.<br>The most common AEs of ≥ grade 3 were anemia, neutrophil count decreased, neutropenia and platelet count decreased. The most frequently reported AEs suspected related to study treatment were anemia (15.6%) and neutropenia (13.3%). No growth retardation AEs were reported. SAEs were observed in 57.8% of all subjects [Study G12201 Final CSR-Table 12-3].<br>The SAEs reported in multiple subjects were pyrexia (6.7%, n=3) and COVID-19, herpes zoster, hyponatremia, muscular weakness, and pneumonia (each 4.4%, n=2) [Study G12201 Final CSR-Table12-8].AEs suspected to be related to study treatment occurred in 60.0% of all subjects of which 20% were SAEs [Study G12201 Final CSR-Section 12.1.2.2 and Section 12.2.2.1].. The median exposure time to ruxolitinib was 12.7 months (range: 0.5 to 37.6) [Study G12201 Final CSR-Section 10.6.1]. |

| Long-term safety in pediatric patients (GvHD only) | Details |
|---|---|
| | No new safety concerns were identified in the F12201 and G12201 pediatric studies [Study INC424F12201 Final CSR], [Study G12201Final CSR] |
| Anticipated risk/consequence of the missing information | Based on the overall data collected in Study F12201 and G12201 (as well as in adolescents enrolled in Study C2301 and D2301), the safety profile of ruxolitinib in pediatric patients with acute and chronic GvHD remains consistent with the known mechanism of action and the previous clinical experience. No new safety concerns have been identified. However, considering the median exposure of 12.7 months accumulated in Study G12201, there is limited information about the long-term safety (≥12 months) of ruxolitinib in pediatric patients.<br>The safety concern will continue to be monitored via routine pharmacovigilance activities and presented in PSURs. |

# 9 Part II Safety specification Module SVIII: Summary of the safety concerns

**Table 9-1 Table Part II SVIII.1: Summary of safety concerns**

| | |
|---|---|
| Important identified risk | Serious infections |
| Important potential risk | Developmental toxicity |
| Missing information | Long-term safety in pediatric patients (GvHD only) |

# 10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

## 10.1 Part III.1. Routine pharmacovigilance activities

### 10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

**Specific adverse reaction follow-up questionnaires for risks:**

No specific adverse reaction follow-up questionnaires were proposed for the risks in the program.

**Other forms of routine pharmacovigilance activities for risks**

No other forms of routine PhV activities for risks were proposed.

## 10.2 Part III.2. Additional pharmacovigilance activities

None.

## 10.3 Part III.3. Summary Table of additional pharmacovigilance activities

**Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities**

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization | | | | |
| None | | | | |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances | | | | |
| None | | | | |
| **Category 3** - Required additional pharmacovigilance activities | | | | |
| None | | | | |

# 11 Part IV: Plans for post-authorization efficacy studies

There are no post-authorization efficacy studies.

# 12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

**Risk Minimization Plan**

## 12.1 Part V.1. Routine risk minimization measures

**Table 12-1 Part V.1: Description of routine risk minimization measures by safety concern**

| Safety concern | Routine risk minimization activities |
|---|---|
| **Important identified risk** | |
| Serious infections | **Routine risk communication**<br>SmPC Section 4.4<br>SmPC Section 4.8<br>**Routine risk minimization activities recommending specific clinical measures:**<br>Patients should be assessed for the risk of developing serious infections. Treatment with ruxolitinib should not be started until active serious infections have resolved.<br>**Other routine risk minimization measures beyond the Product Information:**<br>None |
| **Important potential risk** | |
| Developmental toxicity | **Routine risk communication**<br>SmPC Section 4.1<br>SmPC Section 4.2<br>SmPC Section 4.3<br>SmPC Section 4.6<br>SmPC Section 5.3<br>**Routine risk minimization activities recommending specific clinical measures:**<br>Women of childbearing potential should use effective contraception during the treatment. Should pregnancy 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 fetus. Breastfeeding should be discontinued when treatment with ruxolitinib is started.<br>**Other routine risk minimization measures beyond the Product Information:**<br>None |
| **Missing information** | |
| Long-term safety in pediatric patients (GvHD only) | **Routine risk communication**<br>SmPC Section 4.2<br>**Routine risk minimization activities recommending specific clinical measures:**<br>None<br>**Other routine risk minimization measures beyond the Product Information:** |

| Safety concern | Routine risk minimization activities |
|---|---|
| | None |

## 12.2 Part V.2. Additional Risk minimization measures

No additional risk minimization measures are proposed.

## 12.3 Part V.3. Summary of risk minimization measures

**Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns**

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| **Important identified risk** | | |
| Serious infections | Routine risk minimization measures:<br>SmPC Section 4.4: Precaution for monitoring, treatment and description of risk factors and nature of risk.<br>Section 4.8: The ADRs of UTI, HZ, pneumonia and sepsis are listed.<br>Additional risk minimization measures:<br>None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None<br>Additional PhV activities:<br>None |
| **Important potential risk** | | |
| Developmental toxicity | Routine risk minimization measures:<br>SmPC Section 4.1<br>SmPC Section 4.2<br>SmPC Section 4.3<br>SmPC Section 4.6<br>SmPC Section 5.3<br>Additional risk minimization measures:<br>None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None<br>Additional PhV activities:<br>None |
| **Missing information** | | |
| Long-term safety in pediatric patients (GvHD only) | Routine risk minimization measures:<br>SmPC Section 4.2<br>Additional risk minimization measures:<br>None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional PhV activities: None |

# 13 Part VI: Summary of the risk management plan Jakavi® (ruxolitinib)

This is a summary of the RMP for Jakavi. The RMP details important risks of Jakavi, how these risks can be minimized and how more information will be obtained about Jakavi's risks and uncertainties (missing information).

Jakavi's SmPC and its package leaflet give essential information to health care professionals (HCPs) and patients on how Jakavi should be used.

This summary of the RMP for Jakavi should be read in the context of all this information including the AR of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Jakavi's RMP.

## 13.1 Part VI: I. The medicine and what it is used for

Jakavi is a selective inhibitor of the JAKs. Jakavi is authorized for the treatment of disease related splenomegaly or symptoms in adult patients with PMF (also known as chronic IMF), PPVMF or PETMF. Jakavi is indicated for the treatment of adult patients with PV who are resistant to or intolerant of HU. Currently, ruxolitinib is also indicated for the treatment of patients with GvHD aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies. Jakavi is also indicated for the treatment of adults and pediatric patients aged 28 days and olderwith acute graft versus host disease who have inadequate response to corticosteroids or other systemic therapies and 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. Jakavi contains "ruxolitinib" as the active ingredient and it is given by oral route.

The recommended starting dose of Jakavi in MF is 15 mg given orally b.i.d. for patients with a platelet count between 100000/$mm^3$ and 200000/$mm^3$ and 20 mg b.i.d. for patients with a platelet count of >200000/$mm^3$. The recommended starting dose in patients with platelet counts between 75000/$mm^3$ and <100000/$mm^3$ and between 50000/$mm^3$ and <75000/$mm^3$ is 10 mg b.i.d. and 5 mg b.i.d., respectively. The patients should be titrated cautiously.

The recommended starting dose of Jakavi in PV is 10 mg given orally b.i.d.

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

| Age Group | Starting dose |
|---|---|
| 12 years old and above | 10 mg orally twice daily |
| 6 years to less than 12 years old | 5 mg orally twice daily |
| 28 days to less than 6 years old | 8 mg/$m^2$ orally twice daily |

The recommended starting dose of Jakavi in patients with chronic graft versus host disease (GvHD) is based on age groups (see Table below):

| Age Group | Starting dose |
|---|---|
| 12 years old and above | 10 mg orally twice daily |

| | |
|---|---|
| 6 years to less than 12 years old | 5 mg orally twice daily |
| 6 months to less than 6 years old | 8 mg/m² orally twice daily |

These starting doses in GvHD can be administered using either the tablet for patients at or above 6 years old who can swallow tablets or the oral solution for patients under 12 years old.

Doses may be titrated based on safety and efficacy. Treatment should be discontinued for platelet counts less than 50000/mm$^3$ or ANC less than 500/mm$^3$. In PV, treatment should also be interrupted when hemoglobin is below 8 g/dl. After recovery of blood counts above these levels, dosing may be re-started at 5 mg b.i.d. and gradually increased based on careful monitoring of complete blood cell count, including a WBC count differential.

In MF, dose reductions should be considered if the platelet count decreases below 125000/mm$^3$, with the goal of avoiding dose interruptions for thrombocytopenia. In PV, dose reductions should also be considered if hemoglobin decreases below 12 g/dl and is recommended if it decreases below 10 g/dl.

Dose reductions and temporary interruptions may be needed in GvHD patients with thrombocytopenia, neutropenia, and elevated total bilirubin after standard supportive therapy including growth-factors, anti-infective therapies and transfusions.

One dose level reduction step is recommended (10 mg b.i.d. to 5 mg b.i.d. or 5 mg b.i.d. to 5 mg once daily). In patients who are unable to tolerate ruxolitinib at a dose of 5 mg once daily, treatment should be interrupted.

In GvHD, tapering of ruxolitinib may be considered in patients with a response and after having discontinued corticosteroids. A 50% dose reduction every 2 months is recommended. If signs or symptoms of GvHD reoccur during or after the taper of ruxolitinib, re-escalation of treatment should be considered.

Further information about the evaluation of Jakavi's benefits can be found in Jakavi's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to product's EPAR summary landing page on the EMA webpage: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002464/WC500133225.pdf.

## 13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Jakavi together with measures to minimize such risks and the proposed studies for learning more about Jakavi's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures. There are no additional risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine PhV activities.

If important information that may affect the safe use of Jakavi is not yet available, it is listed under 'missing information' below.

- Long-term safety in pediatric patients (GvHD only)

### 13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of Jakavi are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Jakavi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

**Table 13-1 List of important risks and missing information**

| | |
|---|---|
| Important identified risk | Serious infections |
| Important potential risk | Developmental toxicity |
| Missing information | Long-term safety in pediatric patients (GvHD only) |

### 13.2.2 Part VI - II B: Summary of important risks

**Table 13-2 Important identified risk: Serious infections**

| | |
|---|---|
| Evidence for linking the risk to the medicine | The frequently reported infections include: viral reactivation of HZ (shingles), UTI. Infections were frequently reported cause of death due to AEs in patients with MF. The frequency and severity of infections appear to be higher in MF patients than in PV patients.<br>In GvHD indication, as expected in this patient population, infections were frequently reported AEs; most common infections reported in adult as well as pediatric patients included CMV infections including reactivation, sepsis, pneumonia and upper respiratory tract infections. |
| Risk factors and risk groups | Low neutrophil count, pre-existing comorbidities COPD, asthma, diabetes, co-medication (corticosteroids), higher dose, lack of dose adjustment if strong CYP3A4 inhibitors or fluconazole are used or the patient develops hepatic impairment, moderate or severe renal impairment (CrCl <30 mL/min) or has end stage renal failure requiring hemodialysis. |
| Risk minimization measures | **Routine risk minimization measures:**<br>SmPC Section 4.4: Precaution for monitoring, treatment and description of risk factors and nature of risk.<br>Section 4.8: Undesirable effects.<br>**Additional risk minimization measures**<br>None |

**Table 13-3 Important potential risk: Developmental toxicity**

| | |
|---|---|
| Evidence for linking the risk to the medicine | Myelofibrosis or PV is mainly a condition of the adult population; the median age of patients recruited in Phase III studies was about 66 years. Cases of childhood age are very rare. The number of female patients of child-bearing potential receiving Jakavi is therefore expected to be limited. In the pivotal studies, 6 female patients, ≤45 years representing 1.1% of the total population were enrolled. Due to the severity of the oncological condition the fertility rate of these elderly female patients is expected to be low. There are no data from the use |

| | |
|---|---|
| | of Jakavi in pregnant women.. Animal studies have shown that Jakavi is embryotoxic (causing harm to the embryo) and fetotoxic (causing harm to the fetus). Women of child-bearing potential should use effective contraception during the treatment with Jakavi. In case pregnancy should occur during treatment with Jakavi, a risk-benefit evaluation must be carried out on an individual basis with careful counseling regarding potential risks to the fetus. |
| Risk factors and risk groups | Women of child-bearing potential not using effective contraception, breast feeding women. |
| Risk minimization measures | **Routine risk minimization measures**<br>SmPC Section 4.1<br>Section 4.2<br>Section 4.3<br>Section 4.6<br>Section 5.3<br>**Additional risk minimization measures**<br>None |

**Table 13-4 Long-term safety in pediatric patients (GvHD only)**

| | |
|---|---|
| Risk minimization measures | **Routine risk minimization measures**<br>SmPC Section 4.2<br>**Additional risk minimization measures**<br>None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None |

### 13.2.3 Part VI – II C: Post-authorization development plan

#### 13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Jakavi.

#### 13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no ongoing or planned additional pharmacovigilance activities.

# 14 Part VII: Annexes

## Annex 4 - Specific adverse drug reaction follow-up forms

Targeted follow-up forms have not been proposed.

## Annex 6 - Details of proposed additional risk minimization activities (if applicable)

No additional risk minimization activities have been proposed.