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A Non-Interventional Long-term Safety Study of Ruxolitinib in Myelofibrosis

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Research question and objectives	A Post Authorization Safety Study (PASS) according to the EU Volume 9a of the Rules Governing Medicinal Products in the EU. This non-interventional, observational study intended to provide real-world safety data on patients with myelofibrosis (MF) who were exposed and non-exposed to ruxolitinib and thereby provide insights into disease management and the safety profile of ruxolitinib. **Primary objective**: • To document long-term safety in patients with MF prescribed ruxolitinib according to the prescribing information **Secondary objectives:** • To document the treatment of patients with MF including pharmacological and non-pharmacological management • To document the incidence and outcome of events of special interests

[redacted]

Countries of study	Austria, France, Germany, Italy, Netherlands, Switzerland, and United Kingdom

Marketing authorization holder

Marketing authorization holder(s)	Novartis Pharma A.G. Lichtstrasse 35, 4056 Basel, Switzerland

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1 Abstract

Title

A non-interventional long-term safety study of ruxolitinib in myelofibrosis

Version and date

Version 01

19-Mar-2019

Keywords

Ruxolitinib, myelofibrosis, disease management, incidence, long-term safety, events of special interest

Rationale and background

Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by progressive anemia, leucopenia or leucocytosis, thrombocytopenia or thrombocythemia, profound remodeling of bone marrow architecture with fibrosis, and multi-organ extramedullary hematopoiesis, which primarily involves the liver and spleen.

Ruxolitinib is a first-in-class oral Janus kinase 1/ Janus kinase 2 (JAK 1/JAK 2) inhibitor studied for the treatment of MF. Two Phase III registrational studies viz., INCB18424-351, (COMFORT-I) and INCB18424-352 (COMFORT II) demonstrated the safety and efficacy of ruxolitinib in the treatment of MF. Study INCB18424-351, a randomized, double-blind, placebo-controlled, multicenter study compared the efficacy and safety of ruxolitinib tablets to a matched placebo in 309 patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF). Study INCB18424-352 was an open-label, randomized, active-comparator, multicenter study compared the efficacy and safety of ruxolitinib tablets versus best available therapy as selected by the Investigator in 219 patients with PMF, PPV MF, or PET-MF. The primary endpoint of both these studies was the proportion of patients achieving ≥ 35% reduction in spleen volume from Baseline at week 24 in COMFORT I, and at week 48 in COMFORT II. Both studies met their primary endpoint with 41.9%% and 28% of responders (≥ 35% reduction in spleen volume). Bleeding has been identified as a risk associated with ruxolitinib treatment, mainly in the context of thrombocytopenia. Other identified risks were infections, although confounded by the immunocompromization due to the underlying condition.

Data from the 2 Phase III studies led to the subsequent approval of ruxolitinib for the treatment of patients with MF, including PMF, PPV-MF or PET-MF. Although the number of patients exposed in clinical studies is significant considering orphan status of MF, the experience was limited by the absence of post-marketing exposure including data on long-term use, and the typical restrictions imposed by inclusion and exclusion criteria in clinical studies. Therefore, it was agreed with European Medicines Agency (EMA) to collect data from patients with MF treated with ruxolitinib or with other treatments outside of clinical trial in normal clinical practice as a post- authorization safety study (PASS).

Research question and objectives

This was a PASS (post authorization safety study) according to the EU Volume 9a of the Rules Governing Medicinal Products in the EU. This non-interventional, observational study intended to provide real-world safety data on patients with MF exposed and non-exposed to ruxolitinib and thereby provide insights into disease management and the safety profile of ruxolitinib.

Primary objective

- To document long-term safety in patients with MF prescribed ruxolitinib according to the prescribing information.

Secondary objectives

- To document the treatment of patients with MF including pharmacological and non-pharmacological management

[redacted]

- To document the incidence and outcome of events of special interest including the following:
  - Bleeding events
  - Serious & opportunistic infections
  - Secondary malignancies
  - Deaths of any cause

Study design

This PASS was a prospective, multi-center, multinational non-interventional study for patients diagnosed with MF

Setting

Adult patients with a diagnosis of primary or secondary myelofibrosis were considered for this study.

Inclusion criteria

- Patients diagnosed with PMF according to WHO criteria and secondary myelofibrosis (Post-PV MF and Post –ET MF) according to International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria.

Exclusion criteria

- Patients who had not provided informed consent
- Patients who participated concurrently in an investigational study involving ruxolitinib or another JAK inhibitor

Note: patients previously treated with ruxolitinib through the Individual Patient Supply Program or enrolled in the Expanded Access Study CINC424A2401 (JUMP) and switched to commercial drug supply were eligible.

Patients and study size, including dropouts

The study planned to recruit patients diagnosed with MF exposed (at least 300 patients) and non-exposed (150 patients) to ruxolitinib with the objective of enrolling ruxolitinib exposed patients within 2 years. A minimum follow-up of at least 3 years was allowed for all patients to be enrolled. In the EU, a total of 100 sites, with 3-5 patients per site were planned.

Variables and data sources

This study was observational in nature and did not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. Available data were collected at patients' visits to their site. To maintain adequate data collection, the sites were encouraged to provide any updated patient data at 3-monthly intervals.

The data for this study were retrieved from Oracle Clinical/Remote Data Capture 4.6.2. A designated Contract Research Organization (CRO) performed the analysis following their own internal Standard Operating Procedures (SOPs) that have had been reviewed and approved by Novartis.

Sites which enrolled patients in this study recorded data on electronic CRF provided by Novartis (or designee) which captured, checked, stored, and analyzed the data. CRO followed their own internal SOPs that had been reviewed and approved by Novartis.

Concomitant medications entered into the database were coded using the WHO Drug Reference List, which employed the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions were coded using the Medical dictionary for regulatory activities (MedDRA) version 21.0 terminology.

Statistical methods

Demographic and other Baseline characteristics including medical history and prior treatment were summarized descriptively. The incidence of on-treatment adverse events (AEs) were summarized by

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system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Similar summaries were also produced for treatment-related AEs.

All adverse drug reactions (ADR) and serious AEs (SAE) data were analyzed for identified and potential risks as presented in the Risk Management Plan (RMP).

With 300 patients, there was 95% probability that at least 1 patient would experience an AE that has a true probability of occurrence of 1%. Furthermore, 300 patients provide enough precision ensuring the margin of error on a 95% confidence interval for estimating the rate of specific AEs of interest (herpes zoster, urinary tract infections [UTI], tuberculosis, bleeding, and intracranial hemorrhage) is less than 5%, assuming the observed rate was similar to what was observed in the prior Phase III studies.

Results

Two hundred and sixty patients in the prevalent users cohort (181 long-term users and 79 short term users), 32 in the new users cohort, 170 in the non-exposed to ruxolitinib cohort, and 57 in the switched to ruxolitinib cohort were included in the study. Patient demographics and Baseline disease characteristics were representative of a population of patients with MF, the majority of them with primary MF. The median age ranged between 68 and 72.5 among all the cohorts (range: 21 to 92 years). The risk stratification of MF in most of the patients in all the cohorts was intermediate -1 or -2 risk. Deaths and administrative problems were the primary reasons for a majority of the patients to discontinue from the study. The common reasons that led to death included the progression of the underlying MF disease, sepsis, AML, pneumonia, and general disorder death.

The frequently reported ADRs across all types of cohorts included: anemia, thrombocytopenia, herpes zoster, epistaxis, and UTIs. As expected, anemia was reported in a higher frequency in the new users cohort and in the switch to ruxolitinib cohort compared to the prevalent users cohort. The incidence rate of ADRs was similar across all cohorts except in the switch to ruxolitinib cohort, who had slightly higher incidence rate. The incidence rates of thrombocytopenia and anemia were higher in the patients who switched to ruxolitinib cohort. The incidence rate of anemia was higher in the new users cohort compared to the prevalent users cohort. The primary reasons for dose reductions and dose interruptions were medical decisions, followed by ADRs across all the cohorts. The dose of ruxolitinib was reduced in 51.4% of the patients in the prevalent users cohort, 53.1% of the patients in the new users cohort, and 45.6% of the patients in the switch to ruxolitinib cohort.

The incidence of treatment-emergent SAEs was reported at a higher frequency in the prevalent users cohort compared to all the other cohorts (61.4% vs < 54% in all the other cohorts). The most frequently reported (at least 3%) treatment-emergent SAEs in the prevalent users cohort included anemia, pneumonia, general physical health deterioration, sepsis, death, MF, dyspnoea, abdominal pain, UTI, cardiac failure, pyrexia, renal failure, fall, basal cell carcinoma, and squamous cell carcinoma. A higher incidence rate of treatment-emergent SAEs (≥ 1.5) in the prevalent users cohort included anemia, pneumonia, general physical health deterioration, sepsis, death, MF, UTI, abdominal pain, and dyspnea. The incidence rate of anemia was higher in the new users cohort compared to the prevalent users cohort.

A higher proportion of patients in the non-exposed to ruxolitinib cohort and patients in the switched to ruxolitinib cohort received concomitant medications to treat and manage MF compared to the other cohorts. Non-pharmacological treatment for MF in the majority of patients included splenectomy, allograft, venesection, bloodletting, and allogenic stem cell transplantation. Constitutional symptoms were reported in at least 50% of the patients in the prevalent users cohorts and in the patients switch to ruxolitinib cohort and in a lower percentage of patients in the new users cohort and the non-exposed to ruxolitinib cohort. Night sweats were the most frequently reported symptom in all cohorts.

Prior malignant tumors were reported in higher percentage of patients in the new users cohort (21.9%) and prevalent users cohort (18.9%). During the study, secondary malignancies were reported in higher proportion of the patients in the prevalent users cohort followed by the new users cohort, switch to ruxolitinib cohort, and non-exposed to ruxolitinib cohort (24.7% vs 15.6% vs 14% vs 6.6%, respectively). In order to evaluate the role of ruxolitinib and other factors in these events, an exploratory analyses were carried out using multivariate cox-regression models.

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Patients treated with ruxolitinib were at a lower risk for AML (HR: 0.36; 95% CI: 0.22 to 0.58; p < 0.001) and tended to be at a higher risk for non-melanoma skin cancers (NMSCs) (HR: 1.19 (95% CI: 0.87 to 1.61; p = 0.273). Ruxolitinib did not appear to have an impact on other malignancies such as other solid tumors, or other hematological tumors. Based on the Cox regression model analyses, apart from age and gender, type of MF (increased risk for post PV-MF), prior history of malignancy especially prior NMSC were important risk factors for secondary malignancy of NMSC.

The interpretation of the exploratory cox-regression models should be performed with caution as the number of patients and events are very few and the collection of the data is different in non-interventional studies (NIS) than in Phase 3 trials. There may be also a selection bias in regards to risk for AML, since in the prevalent users cohort only those patients were enrolled who were on ruxolitinib treatment for a while without developing an AML.

Bleeding events were reported in a higher percentage of patients in the prevalent users cohort followed by patients in the switch to ruxolitinib cohort and new users cohort. With regards to bleeding events, bruising and other haemorrhage events were most frequently reported in the majority of patients across all cohorts. Serious and opportunistic infections were reported in a higher percentage of patients in the new users cohort followed by the prevalent users cohort and the switch to ruxolitinib cohort.

Decreased hemoglobin was the most frequently observed haematology abnormality with at least 15% of patients in all cohorts having a shift from grade 1 to grade 3. For majority of the biochemistry parameters, no patient had a shift from grade 0 to grade 4 with few exceptions.

Discussion

The long-term safety of ruxolitinib as assessed in this real world PASS study was consistent with the previous findings (COMFORT I/II). Of note, the study comprised of a broader population including patients at lower risk and elderly patients. No new or unexpected safety signals were identified with long-term treatment. Overall, the safety profile was supportive of long-term treatment with ruxolitinib in patients with MF.

The common AEs that led to death included the progression of the underlying MF disease, sepsis, AML, pneumonia, and general disorder death. Most of these are similar to the findings in the COMFORT-I study. The incidence rates of treatment-emergent ADRs did not show any major differences between the prevalent users cohort and the new users cohort. Most of the treatment-emergent ADRs were reported in less than 1 per 100 PY. Hematological abnormalities such as decreased hemoglobin, decreased lymphocyte count, decreased neutrophil count were reported in patients who had long-term exposure to ruxolitinib as expected. The most common hematological AEs included anemia and thrombocytopenia; but these AEs rarely led to treatment discontinuation.

Secondary malignancies were reported in higher percentage of patients in the prevalent users cohort, followed by the new users cohort, switch to ruxolitinib cohort, and non-exposed to ruxolitinib cohort. An exploratory multivariate cox regression models of time to first secondary malignancy event was carried out including variables to adjust for differences in duration of ruxolitinib treatment and imbalances in the Baseline characteristics or other risk factors (e.g. prior malignant tumors) that might impact secondary malignancies. Ruxolitinib did not appear to have an impact on other malignancies such as other solid tumors, or other hematological tumors. Based on the cox regression model, apart from age and gender, type of MF (increased risk for post PV-MF), prior history of malignancy especially prior NMSC were important risk factors for secondary malignancy of NMSC. The previous history of malignancies and prior exposure to HU were observed to be the most relevant risk factors associated with the probability of developing secondary malignancies. However, it should be noted that the interpretation of cox-regression models should be performed with caution as the number of patients and events are very few and the collection of the data is different in the NIS than in Phase 3 trials.

Overall, the safety profile was supportive of long-term treatment with ruxolitinib, with no unexpected safety signals.

Conclusion

[redacted]

The safety profile of ruxolitinib is consistent with previous studies, although a broader population including patients at lower risk and elderly patients were included. There were no new or unexpected ADRs identified with long-term treatment.

Marketing Authorization Holder(s)

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Name(s) and Affiliation(s) of Principal Investigator(s)

[redacted]

2 List of abbreviations

AE	adverse event
ADR	adverse drug reaction
AML	acute myeloid leukemia
COMFORT	Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DBL	data base lock
DIPSS	Dynamic International Prognostic Scoring System
ELN	European Leukemia Network
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EoSI	event of special interest
ET	essential thrombocythemia
EU	European Union
FAS	full analysis set
GI	gastrointestinal
HU	hydroxyurea
IPSS	International Prognostic Scoring System
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK	Janus Kinase
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MPN	myeloproliferative neoplasm
NIS	non-interventional study
NMSC	non-melanoma skin cancer
PASS	Post-Authorization Safety Study
PET-MF	post essential thrombocythemia-myelofibrosis
PMF	primary myelofibrosis
PPV-MF	post polycythemia vera-myelofibrosis
PRBC	packed red blood cells
PV	polycythemia vera
PY	patient years
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
UTI	urinary tract infection
WHO	World Health Organization

3 Investigators

A list of all Investigators, their affiliations, plus that of other important staff is provided in Appendix 16.1.4.

4 Other responsible parties

Not applicable

5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date	Comments
First patient first visit	31-Dec-2012	03-Jun-2013	
Start of data collection	31-Dec-2012	03-Jun-2013	
Last patient last visit	30-Mar-2018	10-Apr-2018	
End of data collection (DBL)	02-Jul-2018	05-Jul-2018	
Registration in the EU PAS register	07-Jan-2013	07-Jan-2013	ENCePP number 3296
Final report of study results	30-Jun-2019	19-Mar-2019	
Any other important milestone applicable to the study	--	--	Not applicable

EU PAS: European Union post-authorisation studies

6 Rationale and background

Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) that can present as an apparently de novo disorder (primary myelofibrosis (PMF)) or evolve from other MPNs and can be termed as secondary MF, post polycythemia vera-MF (PPV-MF) or post essential thrombocythemia MF (PET-MF). The hallmark feature of MF is massive splenomegaly. MF is characterized by progressive anemia, leucopenia or leucocytosis, thrombocytopenia or thrombocythemia, profound remodeling of bone marrow architecture with fibrosis, and multiorgan extramedullary hematopoiesis, which primarily involves the liver and spleen (Barbui et al 2011). Patients may experience severe constitutional symptoms, sequelae of massive splenomegaly, dyspnea, pain, limited mobility, early satiety, a catabolic state with cachexia, ineffective hematopoiesis and hematopoietic failure, risk of vascular events, progression to leukemia, and premature death (Barbui et al 2011 and Mesa et al 2007).

A retrospective, multicenter analysis reported on behalf of the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) identified 5 risk factors independently associated with shortened survival in PMF: age > 65 years, presence of constitutional symptoms, anemia, leukocytosis, and a circulating blast percentage of ≥ 1% (Cervantes et al 2009). A Study by International Prognostic Scoring System (IPSS) led to the development of 2 additional scoring systems to assess the prognostic value of risk factors in patients diagnosed with PMF: the Dynamic International Prognostic Scoring System (DIPSS) (Passamonti et al 2010) and the DIPSS Plus (Verstovsek et al 2010).

[redacted]

Until the approval of ruxolitinib in Nov-2011, patients with PMF, PPV-MF, or PET-MF had a critical unmet medical need.

Ruxolitinib is a first-in-class oral Janus kinase 1/ Janus kinase 2 (JAK 1/JAK 2) inhibitor studied for the treatment of MF. Two Phase III registration studies viz., INCB18424-351, (Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment-I (COMFORT-I)) and INCB18424-352 (COMFORT II) demonstrated the safety and efficacy of ruxolitinib in the treatment of MF. Study INCB18424-351, a randomized, double-blind, placebo-controlled, multicenter study compared the efficacy and safety of ruxolitinib tablets to a matched placebo in 309 patients with PMF, PPV-MF, or PET-MF (Verstovsek et al 2012). Study INCB18424-352 was an open-label, randomized, active-comparator, multicenter study compared the efficacy and safety of ruxolitinib tablets versus best available therapy as selected by the Investigator in 219 patients with PMF, PPV MF, or PET-MF (Harrison et al 2012). The primary endpoint of both these studies was the proportion of patients achieving ≥ 35% reduction in spleen volume from Baseline at week 24 in COMFORT I, and at week 48 in COMFORT II. Both studies met their primary endpoint with 41.9% and 28% of responders (≥ 35% reduction in spleen volume). Bleeding has been identified as a risk associated with ruxolitinib treatment, mainly in the context of thrombocytopenia. Other identified risks were infections, although confounded by the immunocompromization due to the underlying condition.

In the United States, ruxolitinib was first licensed and marketed in 2011 for the treatment of patients with intermediate or high-risk myelofibrosis, including PMF, PPV-MF and PET-MF. At the time point of submission to the Marketing Authorization Application in the EU, a total of 589 MF patients were exposed to ruxolitinib Phase III studies, which was equivalent to 622 patient years of exposure. Although the number of patients exposed in clinical studies is significant considering orphan status of MF, the experience was limited by the absence of post-marketing exposure including data on long-term use, and the typical restrictions imposed by inclusion and exclusion criteria in clinical studies. Therefore, it was agreed with EMA to collect data from patients with MF treated with ruxolitinib or with other treatments outside of clinical trial in normal clinical practice as a Post Authorization Safety Study (PASS).

7 Research question and objectives

This was a PASS according to the EU Volume 9a of the Rules Governing Medicinal Products in the EU. This non-interventional, observational study intended to provide real-world safety data on patients with MF exposed and non-exposed to ruxolitinib and thereby provide insights into the disease management and safety profile of ruxolitinib (Table 7-1).

Table 7-1 Objectives and related endpoints

Objective	Endpoint
Primary	
To document long-term safety in patients with MF prescribed ruxolitinib according to the prescribing information	Incidence of adverse drug reactions (ADRs) Incidence of serious adverse events (SAEs)
Secondary	
To document the treatment of patients with MF including pharmacological and non-pharmacological management	Management of MF and co-morbidities including: Medications for treatment and management of MF Non-pharmacological treatments for MF

[redacted]

Objective	Endpoint
	Use of blood or platelet transfusions
	Medications for the management of co-morbidities
	Subsequent bone marrow biopsies
	Spleen length
	Constitutional symptoms
	Body weight
	JAK2V617F allele burden measurements, chromosomal abnormalities
To document the incidence and outcome of events of special interests (EoSI)	Bleeding events
	Serious & opportunistic infections
	Secondary malignancies
	Deaths of any cause

8 Amendments and updates to the protocol

The study protocol was amended one time (12-Jun-2014) to adapt the original protocol to the new Novartis template for non-interventional studies. In addition to the alignment of protocol with the new template, the following changes were made:

- The protocol milestones were updated as per the study timelines
- Reference to IWG-MRT criteria for diagnosis of secondary MF has been included to clarify the diagnostic criteria used to enroll secondary MF patients
- ADRs/SAEs after discontinuation of ruxolitinib treatment and pregnancies were deleted from the secondary objectives as EoSI
- Clarified data transfer procedure

The amendment to the protocol did not impact the way the data were collected for this study. The original protocol and the details of the amendment can be referred from Appendix 16.1.1-Table 5-1.

9 Research methods

9.1 Study design

This was a prospective, multicenter, multi-national disease registry for patients diagnosed with MF. The study sites were identified in collaboration with European Leukemia Network (ELN). The study was planned to enroll at least 300 patients diagnosed with MF exposed and non-exposed to ruxolitinib within 2 years, with the expectation that approximately 150 patients not exposed to ruxolitinib will be enrolled during this period. The enrolled patients were planned to be followed up for at least 3 years.

9.2 Setting

This study aimed to collect comprehensive data on the evolution and management of the condition in a real-world setting to evaluate the long-term safety data of ruxolitinib. Hence, the selection of the participating sites reviewed the following aspects:

Participating centers with required infrastructure for adequate data management and trained personnel for the treatment and management of patients with hematological malignancies were identified by requesting the data from ELN. One hundred suitable centers were identified in collaboration with the ELN in EU countries (Austria, France, Germany, Italy, Netherlands, Switzerland, and United Kingdom).

The recruitment of patients was monitored on a continuous basis by Novartis. If the recruitment rate fell below projections, Novartis was to make any effort to identify and qualify additional sites. The identification of additional sites was performed with involvement of the ELN, for which the European Registry for MPN towards a better understanding of Epidemiology, Survival and Treatment (ERNEST) registry provided information on potential candidates.

9.3 Patients

9.3.1 Patient population

Adult patients with a diagnosis of primary or secondary MF.

9.3.2 Inclusion and exclusion criteria

Inclusion criteria

- Patients diagnosed with PMF according to WHO criteria and secondary MF (Post- PV MF and Post –essential thrombocytopenia (ET) MF) according to IWG-MRT criteria.

Exclusion criteria

- Patients who did not provide informed consent
- Patients who were participated concurrently in an investigational study involving ruxolitinib or another JAK inhibitor

Note: patients previously treated with ruxolitinib through the Individual Patient Supply Program or enrolled in the Expanded Access Study CINC424A2401 and switched to commercial drug supply were eligible.

9.4 Variables

As this was a non-interventional study, only examinations that were part of the routine assessment of the patients were considered for recording all available data on the safety, treatment and treatment outcome. For further details on variables, please refer to Appendix 16.1.1-Section 9.3.

9.4.1 Patient demographics and other Baseline characteristics

Unless otherwise stated, Baseline was defined as the first observation at the time the patient was included in the registry. The following information was collected at Baseline:

1. Patient age, gender and race
2. MF diagnosis (major and minor criteria which qualified the patient for diagnosis of MF)
3. Date of first diagnosis of MF

[redacted]

4. MF current risk group (DIPSS risk category for patients previously diagnosed and IPSS risk category for newly-diagnosed)
5. JAK2V617F mutation status
6. Spleen length
7. Constitutional symptoms
8. Body weight
9. Prior transfusional history (packed red blood cells (PRBC's) and platelets)
10. Date and results of bone-marrow biopsies (including fibrosis score and staining methodology)
11. Prior treatments of MF, including dose, dates and duration (whichever data were available), including interventions such as splenectomy or irradiation therapy
12. Co-morbidities, including organ impairments and previous infections
13. Prior history of malignancies with date of first diagnosis, pathology, treatments and current state

9.4.2 Management of myelofibrosis and co-morbidities

During the observation period, the following information on the management of MF was collected:

1. Medications for treatment and management of MF with start date, stop date, dose and dose change, and reason for dose change or discontinuation, as appropriate
2. Non-pharmacologic treatments for MF including dates, morbidities, duration of response and outcome
3. Medications for MF symptoms, with start and stop date, dose and indication
4. Use of blood or platelet transfusions
5. Medications for the management of co-morbidities, with start and stop date, dose and indication
6. Subsequent bone marrow biopsies as clinically indicated during standard clinical care, reporting fibrosis scores and blast percentage
7. Spleen length
8. Constitutional symptoms
9. Body weight
10. JAK2V617F allele burden measurements, chromosomal abnormalities

9.4.3 Laboratory evaluations

At Baseline and during the observation period, hematology, clinical chemistry data were collected and recorded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Other relevant laboratory abnormalities that represented an adverse EoSI or SAE were collected.

9.4.4 Treatment discontinuation

Reason(s) for discontinuation from this study was collected:

- Patient withdrew consent

[redacted]

- Lost to follow-up
- Administrative problems
- Death

9.5 Data sources and measurement

The data for this study were retrieved from the Oracle Clinical/Remote Data Capture 4.6.2 provided by [redacted]. [redacted], a designated contract research organization (CRO), performed the analysis following their own internal standard operating procedures that were reviewed and approved by Novartis.

Initiation of the participating sites was performed by Novartis. Before study initiation, a Novartis representative reviewed the protocol and case report form (CRF) with the physicians and their staff.

Sites enrolling patients in this study recorded data on electronic CRF provided by Novartis which captured, checked, stored and analyzed the data.

Concomitant or prior medications entered into the database were coded using the WHO Drug Reference List. Medical history/current medical conditions and adverse events (AEs) were coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Safety data were transferred to Novartis at a frequency as defined in the protocol. Clinical data were transferred to Novartis after closure of the study.

9.6 Bias

The study design included strategies to minimize bias, which is inherent in non-interventional studies.

In order to minimize selection bias of participating sites, centers were identified through the ELN. Although not all consecutively screened patients were included in the study, the method of site selection and the limited inclusion and exclusion criteria may have minimized a potential selection bias reflecting the safety of ruxolitinib in the real world.

Selection bias due to the inclusion of prevalent users of ruxolitinib was a potential bias for the study. Patients with MF were included regardless of the time since diagnosis or treatment duration, which resulted in a wide range of different exposure durations to ruxolitinib at Baseline. The inclusion of prevalent users could have introduced a selection bias as the frequency of AEs might vary over time since treatment initiation. To prevent this potential bias, analyses were stratified according to previous exposure to ruxolitinib (Vandenbroucke and Pearce 2015).

Patients with MF managed in the real-world were followed-up to assess the long-term safety of ruxolitinib. The non-randomized, observational and unblinded nature of this study may be possible sources of bias in data collection, and should be considered when evaluating the results. For example, there could be information bias if patients treated with ruxolitinib were more carefully assessed for AEs. Hence, direct comparison between patients exposed to ruxolitinib and patients not exposed to ruxolitinib is challenging. In addition, those MF patients who an investigator decides to treat with ruxolitinib might be those with more serious clinical

[redacted]

manifestations such as splenomegaly and pronounced disease symptoms. This might have resulted in a different frequency of AEs reported because of differences in the seriousness of underlying disease; resulting in a potential indication bias. Nevertheless, data received on non-exposed patients provides valuable context information that supports the interpretation of safety observations.

9.7 Study size

The study planned to recruit patients diagnosed with MF exposed and non-exposed to ruxolitinib with the objective of enrolling at least 300 patients exposed to ruxolitinib within 2 years. It was expected that about 150 patients not exposed to ruxolitinib would be recruited during the enrolment period.

9.8 Data transformation

For the analyses, the patients were grouped into the following cohorts, by status of exposure to ruxolitinib at the time of study enrollment (the first informed consent form signed date):

- Prevalent users cohort: exposed patients who were previously treated with ruxolitinib (patients who were previously taking ruxolitinib and continue to take ruxolitinib on or after the time of study enrollment).

  By duration of exposure to ruxolitinib prior to study enrollment, sub-groups are applied to prevalent users:
  - Short term users: exposed to ruxolitinib < 6 months before study enrollment
  - Long term users: exposed to ruxolitinib ≥ 6 months before study enrollment
- New users cohort: exposed patients who were newly treated with ruxolitinib (patients who have not previously taken ruxolitinib and start ruxolitinib at time of study enrollment)
- Non-exposed cohort: patients who were not treated with ruxolitinib at the time of study enrollment. However, these patients might have received treatment with ruxolitinib prior entering the study.
- Switch to ruxolitinib cohort: A subset of non-exposed cohort, who become exposed to ruxolitinib during the study as per Investigator's decision. Since, patients in this cohort were part of the non-exposed cohort, these patients might also have received treatment with ruxolitinib prior entering the study.

The details of transformation to compute other derived variables are presented in the Statistical Analysis Plan (Appendix 16.1.9) and includes information on how the following were derived:

- Study day of events or assessments
- Baseline assessments for each cohort
- Last contact date
- Duration of pervious exposure to ruxolitinib before enrollment
- Duration of exposure to ruxolitinib from enrollment
- Duration of on study from enrollment date
- Cumulative dose and dose intensity
- Change and percentage change from Baseline for bone marrow biopsies

[redacted]

9.9 Statistical methods

Data analysis for the clinical study report was performed by [redacted], a designated CRO, after the last patient had completed 3 years in the study or discontinued early. The data base lock (DBL) for the final analysis was 05-Jul-2018.

Unless otherwise specified, qualitative data was described using frequency and percentages, a missing category was included as applicable; while quantitative data was described using descriptive statistics such as n, mean, standard deviation, median, minimum, and maximum.

9.9.1 Analysis sets

Full analysis set (FAS): consisted of all patients who enrolled into this non-interventional study.

Safety set (SS): consisted of all patients who had at least one post-baseline safety assessment and were exposed to at least one non-zero dose of ruxolitinib.

Safety set modified (SS-Mod): consisted of all patients who had at least one post-baseline safety assessment.

9.9.2 Main summary measures

The main summary measures of interest for this report were the incidence of ADRs and SAEs. The long-term safety of ruxolitinib was the primary objective of this study.

The primary and secondary endpoints of the study are presented in Table 7-1.

9.9.2.1 Patient demographics and Baseline characteristics

Demographic and other Baseline characteristics including medical history and prior treatment were summarized descriptively. Categorical data were summarized by frequency and percentages. Quantitative data were summarized by the number of patients (n), mean, standard deviation, median, minimum, and maximum. Data were summarized descriptively and separately for patients exposed to ruxolitinib and non-exposed to ruxolitinib. The FAS was used for all Baseline and demographic summaries and listings unless otherwise specified.

9.9.2.2 Treatments

Information about ruxolitinib treatment including daily dose, interruptions, and duration of exposure was summarized by descriptive statistics and corresponding listing were presented. Treatment with ruxolitinib was at the discretion of the investigator in accordance with the prescribing information. Other medications administered for MF were captured and summarized.

9.9.2.3 Primary analysis

The primary objective of this non-interventional study was to document long-term safety in patients with MF prescribed ruxolitinib according to the prescribing information.

Data were summarized descriptively and separately for patients exposed to ruxolitinib and non-exposed to ruxolitinib.

Safety analyses were performed in two different ways:

[redacted]

1. Safety summaries based on assessments prior to the switch to ruxolitinib
    - For the prevalent users cohort or the new users cohort: assessments collected no later than 28 days after ruxolitinib discontinuation.
    - For the non-exposed cohort that remained non-exposed throughout the study: assessments collected up to end of study.
    - For the switch to ruxolitinib cohort: assessments collected before the switch to ruxolitinib.

All safety assessments collected later than 28 days after ruxolitinib discontinuation for exposed patients are listed and flagged.

2. Safety summaries based on assessments collected after the switch to ruxolitinib
    - For the switch to ruxolitinib cohort: assessments collected from the date of first exposure to ruxolitinib up to 28 days after discontinuation of ruxolitinib.

Any events occurring more than 28 days after discontinuation of the ruxolitinib are listed and flagged.

For exposed patients, the incidence of on-treatment ADRs and SAEs were summarized by system organ class (SOC) and preferred term using MedDRA. Similar summaries were also produced for treatment-related SAEs. The listings covered events that occurred during the on-treatment and post-treatment period. Events that occurred during the post-treatment period were flagged. All ADR and SAE data were analyzed according to the specifications of the ruxolitinib risk management plan.

For the purpose of this study, an ADR was defined as a response to ruxolitinib treatment (medical condition, clinical sign, and symptom or laboratory value) which is noxious and unintended. Response in this context means that:

- A causal relationship between ruxolitinib treatment and the event is at least possible as determined by the reporter
- The event occurred after first exposure to ruxolitinib (treatment emergent)

9.9.2.4 Secondary analysis

Concomitant medications for MF, concomitant PRBC/Platelet transfusion and other concomitant medications were summarized by the WHO drug class and drug team for both the exposed and non-exposed cohorts by SS-Mod. The number and percentage of patients who received any blood component transfusion were summarized. All data collected for the pharmacological and non-pharmacological management of patients with MF were listed by cohort. Medications for MF symptoms, with start and stop date, dose and indication were not analyzed as the data was not available in the clinical database.

The incidence and outcomes of EoSI were also documented.

Incidence of AEs related to EoSI were presented for all patients by cohort (using SS -Mod) based on the specific grouping of AEs.

Summary statistics for time to first event were summarized individually for the following EoSI events: bleeding events, serious and opportunistic infections and secondary malignancies.

[redacted]

Deaths: Separate summaries for on-treatment and all deaths were produced by SOC, preferred term and cohort. All deaths were listed, post-treatment deaths were flagged.

Spleen length: A listing of spleen length and change from Baseline of patients with palpable spleen is provided.

Constitutional symptoms and symptoms related to MF: Number and percentage of patients who had constitutional symptoms and symptoms related to MF are summarized by cohort and associated listings are provided.

Bone marrow biopsies: The reporting fibrosis score was to be tabulated in shift table from Baseline to worst post-baseline.

Analysis of blast percentage using descriptive summary statistics for Baseline is performed. Change and percent change from Baseline is also summarized for patients with both Baseline and post-baseline values.

JAK2V617F mutation: number of percentage of JAK2v617F mutation category results were summarized by cohort and visit. Data collected on MF and co-morbidities management were listed.

9.9.2.5 Other safety analyses

Laboratory data: The following summaries of laboratory evaluations for hematology and biochemistry parameters were provided

- Worst post-baseline CTCAE grade (regardless of the Baseline status). Each patient was counted only for the worst grade observed post-baseline
- Shift tables using CTCAE grades to compare Baseline to the worst post-baseline value
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/ (low and high) classification to compare Baseline to the worst post-baseline value.

A listing of laboratory values was provided by laboratory parameter. A separate listing displaying notable laboratory abnormalities is also provided.

Vital signs: A listing of body weight, change from Baseline and abnormality was provided.

9.9.2.6 Interim analyses

No interim analyses were performed.

9.9.3 Main statistical methods

Study data were summarized descriptively and separately by cohort. Categorical data were summarized by frequency and percentages. Quantitative data were summarized by the number of patients (n), mean, standard deviation, median, minimum, maximum.

9.9.4 Missing values

Imputation rules for partially missing dates are described in the Appendix of Statistical Analysis Plan (SAP). Unless otherwise specified, no imputation for missing data was conducted.

[redacted]

9.9.5 Sensitivity analyses

Not applicable

9.9.6 Amendments to the statistical analysis plan

All statistical analyses were provided as foreseen in the latest version of the statistical plan ready before DBL.

The SAP was amended once before DBL.

Exploratory multivariate analyses on secondary malignancies were included in the SAP after the DBL.

These amendments did not contain any other major changes.

9.10 Quality control

Data quality assurance

Novartis data management or designated CRO reviewed the data entered into the CRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

Data recording and document retention

This study being non-interventional/observational in nature did not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. The available data from routine clinical management of the patients were collected at the patients' visits to their site. To maintain adequate data collection, the sites were encouraged to provide any updated patient data at 3-monthly intervals.

The data was collected on all patients with a confirmed diagnosis of MF, irrespective of treatment modalities employed, disease severity, age, concurrent conditions or other factors that were typically controlled in interventional settings by inclusion or exclusion criteria. This study design allowed a follow-up of "real-world" patients for at least 3 years; which was significantly longer than exposure experience from ruxolitinib clinical studies in MF patients. Furthermore, the disease registry allowed continued follow-up of patients independent of exposure to certain drugs. The study collected data from several European countries that had balanced for local treatment patterns.

In all scenarios, the physician maintained source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the CRF was traceable to these source documents in the patient's file. The physician also kept the original informed consent form signed by the patient (a signed copy was given to the patient). The physician gave Novartis (or designee) access to all relevant source documents to confirm their consistency with the CRF entries. No information in source documents about the identity of the patients was disclosed.

[redacted]

10 Results

10.1 Data sets analyzed

The definitions of the analysis sets are presented in Section 9.9.1. All 260 patients in the prevalent users cohort were included in the FAS while 259 were included in both the Safety set (all patients who were exposed to ruxolitinib and had at least one post-baseline safety assessment) and Safety set modified (patients with at least one post-baseline safety assessment, which also includes non-exposed patients). The number of patients in the new users cohort (N=32), and the switch to ruxolitinib cohort (N=57) were the same in all the analysis sets. The number of patients in the non-exposed to ruxolitinib cohort at the time of enrollment were 170 in the FAS and 167 in the SS-Mod and were not considered for Safety set as they have not received at least one dose of ruxolitinib (Table 10-1).

Table 10-1 Analysis population, by cohort (Full analysis set)

	Prevalent users					
Analysis set	Long Term N = 181 n (%)	Short Term N = 79 n (%)	Total N = 260 n (%)	New users N = 32 n (%)	Non-Exposed[1] N = 170 n (%)	Switch to Ruxo[2] N = 57 n (%)
Full analysis set (FAS)	181 (100)	79 (100)	260 (100)	32 (100)	170 (100)	57 (100)
Safety set (SS)[3]	180 (99.4)	79 (100)	259 (99.6)	32 (100)	NA	57 (100)
Safety set modified (SS-Mod)[4]	180 (99.4)	79 (100)	259 (99.6)	32 (100)	167 (98.2)	57 (100)

- [1] N is the number of patients non-exposed to study drug at the time of enrollment (including switchers).
- [2] N is the number of patients who switched to ruxolitinib during the study.
- [3] consisted of all patients who had at least one post-baseline safety assessment and were exposed to at least one non-zero dose of ruxolitinib
- [4] consisted of all patients who had at least one post-baseline safety assessment.

Source: Table 14.1-2.1

10.2 Participants

The number of patients enrolled included: two hundred and sixty patients in the prevalent users cohort (181 long-term users and 79 short-term users), 32 in the new users cohort, 170 in the non-exposed to ruxolitinib cohort, and 57 in the switched to ruxolitinib cohort. One hundred and four patients (57.5%) in the long-term users, 49 patients (62%) in the short-term users, 20 patients (62.5%) in the new users cohort, 95 patients (55.9%) in the non-exposed to ruxolitinib cohort, and 28 patients (49.1%) in the switched to ruxolitinib cohort discontinued from the study. The primary reasons for the majority of the discontinuations included death (33.7% of the patients in the long-term users and 39.2% of the patients in the short-term users, 28.1% each in the new users cohort and switch to ruxolitinib cohort; and 28.2% of the patients in the non-exposed to ruxolitinib cohort) and administrative problems (14.4% of the long-term users, 10.1% of the short-term users, 15.6% of the new users cohort, 11.2% of the non-exposed to ruxolitinib cohort, and 8.8% of the patients switched to ruxolitinib cohort) (Table 10-2).

The patients who discontinued the study after meeting the complete follow-up criteria, continued ruxolitinib treatment as usual.

Table 10-2 Patient disposition, by cohort (Full analysis set)

	Prevalent users					
Primary reason for study discontinuation	**Long Term N = 181 n (%)**	**Short Term N = 79 n (%)**	**Total N = 260 n (%)**	**New users N = 32 n (%)**	**Non-Exposed[1] N = 170 n (%)**	**Switch to Ruxo[2] N = 57 n (%)**
Total number of patients discontinued	**104 (57.5)**	**49 (62.0)**	**153 (58.8)**	**20 (62.5)**	**95 (55.9)**	**28 (49.1)**
Patient withdrew consent	6 (3.3)	5 (6.3)	11 (4.2)	5 (15.6)	8 (4.7)	2 (3.5)
Lost to follow-up	10 (5.5)	4 (5.1)	14 (5.4)	1 (3.1)	17 (10.0)	4 (7.0)
Administrative problems	26 (14.4)	8 (10.1)	34 (13.1)	5 (15.6)	19 (11.2)	5 (8.8)
Death	61 (33.7)	31 (39.2)	92 (35.4)	9 (28.1)	48 (28.2)	16 (28.1)
Disease progression [3]	1 (0.6)	1 (1.3)	2 (0.8)	0	3 (1.8)	1 (1.8)

- [1] N is the number of patients non-exposed to study drug at the time of enrollment (including switchers).
- [2] N is the number of patients who switched to ruxolitinib during the study.
- [3] A category applied prior to CRF amendment.

Source: Table 14.1-1.1

10.3 Descriptive data

Demographics

Patient demographic characteristics were well balanced across all types of users. The median age of the patients in the prevalent users cohort, non-exposed to ruxolitinib cohort, and switched to ruxolitinib cohort was 69 years while it was 72.50 years in the new users cohort. More than 50% of the patients were male in all cohorts except in the switched to ruxolitinib cohort (45.6%). The majority of patients were Caucasians (Table 10-3).

Table 10-3 Demographics by cohort (Full analysis set)

	Prevalent users					
	Long Term N = 181	**Short Term N = 79**	**Total N = 260**	**New users N = 32**	**Non-Exposed[1] N = 170**	**Switch to Ruxo[2] N = 57**
Age (years)						
n	181	79	260	32	170	57
Mean	67.20	68.40	67.60	70.80	67.40	68.50
SD	10.50	10.49	10.49	11.37	13.01	11.99
Median	69	68	69	72.50	69	69
Minimum	37	37	37	47	21	30
Maximum	92	92	92	90	92	9 1
Age category, n (%)						
< 65 years	66 (36.50)	25 (31.60)	91 (35)	7 (21.90)	55 (32.40)	15 (26.30)
≥ 65 years	115 (63.50)	54 (68.40)	169 (65)	25 (78.10)	115 (67.60)	42 (73.70)
Sex, n (%)						
Male	104 (57.50)	46 (58.20)	150 (57.70)	21 (65.60)	91 (53.50)	26 (45.60)
Female	77 (42.50)	33 (41.80)	110 (42.30)	11 (34.40)	79 (46.50)	31 (54.40)
Race, n (%)						
Asian	1 (0.60)	0	1 (0.40)	0	1 (0.60)	0
Black	0	0	0	0	1 (0.60)	0

	Prevalent users					
	Long Term N = 181	Short Term N = 79	Total N = 260	New users N = 32	Non-Exposed[1] N = 170	Switch to Ruxo[2] N = 57
Caucasian	134 (74)	57 (72.20)	191 (73.50)	23 (71.90)	106 (62.40)	40 (70.20)
Other	46 (25.40)	22 (27.80)	68 (26.20)	9 (28.10)	62 (36.50)	17 (29.80)
Weight (kg)						
n	137	50	187	21	115	31
Mean	75.05	69.65	73.61	69.29	73.57	66.53
SD	13.77	11.73	13.44	11.06	17.98	14.60
Median	75	68	73	68	71	64
Minimum	43	48	43	48	38	49
Maximum	110	104	110	90	134.7	120

- [1] N is the number of patients non-exposed to study drug at the time of enrollment (including switchers).
- [2] N is the number of patients who switched to ruxolitinib during the study. Baseline data provided for this group is the data at enrollment and not at start of ruxolitinib therapy.
Source: Table 14.1-3.1

Baseline disease characteristics

The majority (> 50%) of patients in all the cohorts except in the new users cohort (43.8%) were diagnosed with primary MF. A higher proportion of patients (70.6%) in the non-exposed to ruxolitinib cohort were diagnosed with primary MF. As expected, the median (range) time since diagnosis to Baseline was greater in the long-term users cohort, 37.65 months (2.4-282.2 months) compared to the short-term users cohort, 10.28 months (1.7-153.4 months); and was least in the new users cohort, 1.28 months (0-58.9 months). The median time since diagnosis was 32.16 months in the patients non-exposed to ruxolitinib cohort, however it was only 16.56 months in the patients switched to ruxolitinib cohort. The majority of patients were of MF severity intermediate-1 or 2 risk categories in all cohorts. A higher proportion of the patients were at high risk in the new users cohort (28.1%) while a higher proportion of patients in the non-exposed to ruxolitinib cohort were at low risk (24.1%) compared to the other cohorts. Whereas, patients in the switch to ruxolitinib cohort had a higher proportion of intermediate-2 risk (40.4%) compared to the patients in the non-exposed to ruxolitinib cohort (27.1%). The proportion of patients with a negative JAK2V617F mutation status was highest in the patients non-exposed to ruxolitinib cohort (40%) (Table 10-4).

Table 10-4 Baseline disease characteristics, by cohort (Full analysis set)

	Prevalent users					
	Long Term N = 181	Short Term N = 79	Total N = 260	New users N = 32	Non Exposed[1] N = 170	Switch to Ruxo[2] N = 57
MF primary diagnosis, n (%)						
Primary MF	92 (50.8)	41 (51.9)	133 (51.2)	14 (43.8)	120 (70.6)	40 (70.2)
Post PV-MF	53 (29.3)	17 (21.5)	70 (26.9)	10 (31.3)	18 (10.6)	7 (12.3)
Post ET-MF	35 (19.3)	20 (25.3)	55 (21.2)	7 (21.9)	30 (17.6)	10 (17.5)
Missing	1 (0.6)	1 (1.3)	2 (0.8)	1 (3.1)	2 (1.2)	0
Time from initial MF diag. to Baseline (months)						
n	110	61	171	25	135	43

[redacted]

	Prevalent users					
	Long Term N = 181	Short Term N = 79	Total N = 260	New users N = 32	Non Exposed[1] N = 170	Switch to Ruxo[2] N = 57
Mean	55.41	28.92	45.96	10.23	46.92	42.06
SD	52.855	35.527	48.976	17.493	53.650	61.025
Median	37.65	10.28	29.90	1.28	32.16	16.56
Minimum	2.4	1.7	1.7	0.0	0.0	1.2
Maximum	282.2	153.4	282.2	58.9	274.2	274.2
MF current risk group, n (%)						
DIPSS risk (previously diagnosed)	176 (97.2)	75 (94.9)	251 (96.5)	15 (46.9)	151 (88.8)	47 (82.5)
IPSS risk (newly diagnosed)	5 (2.8)	4 (5.1)	9 (3.5)	16 (50.0)	19 (11.2)	10 (17.5)
Missing	0	0	0	1 (3.1)	0	0
MF severity, n (%)						
Low risk	30 (16.6)	11 (13.9)	41 (15.8)	6 (18.8)	41 (24.1)	10 (17.5)
Intermediate -1 risk	59 (32.6)	24 (30.4)	83 (31.9)	8 (25.0)	63 (37.1)	18 (31.6)
Intermediate -2 risk	62 (34.3)	36 (45.6)	98 (37.7)	8 (25.0)	46 (27.1)	23 (40.4)
High risk	28 (15.5)	8 (10.1)	36 (13.8)	9 (28.1)	19 (11.2)	5 (8.8)
Missing	2 (1.1)	0	2 (0.8)	1 (3.1)	1 (0.6)	1 (1.8)
JAK2V617F mutation at Baseline, n (%)						
Positive	125 (69.1)	47 (59.5)	172 (66.2)	23 (71.9)	88 (51.8)	2 (3.5)
Negative	36 (19.9)	24 (30.4)	60 (23.1)	7 (21.9)	68 (40.0)	4 (7.0)
Not done	20 (11.0)	8 (10.1)	28 (10.8)	2 (6.3)	14 (8.2)	51 (89.5)

- [1] N is the number of patients non-exposed to study drug at the time of enrollment (including switchers).
- [2] N is the number of patients who switched to ruxolitinib during the study. Baseline data provided for this group is the data at enrollment and not at start of ruxolitinib therapy.
Source: Table 14.1-3.2

The median duration of the study was comparable across all the cohorts except in the new users cohort who had slightly lower duration. The study duration was less than 6 months in a lower proportion of the patients in all the cohorts (2% to 9% range in all cohorts). The median duration of exposure in the prevalent users cohort during the study was 33.38 months (range: 0.5-55.9 months). However, patients in this cohort had ruxolitinib therapy prior to entering the study. The median duration of exposure to ruxolitinib before study enrollment was 18.53 months in the long-term users and 2.69 months in the short term users (Table 14.3-1.1.1).

The median cumulative dose was highest in the prevalent users cohort (20477.5 mg) followed by the new users cohort (15755 mg) and in the switch to ruxolitinib cohort (12110 mg) (Table 10-5).

Table 10-5 Duration of study and exposure to ruxolitinib during the study, by cohort (Safety set modified)

	Prevalent users					
	Long Term N = 180	Short Term N = 79	Total N = 259	New users N = 32	Non-Exposed[1] N = 167	Switch to Ruxo[2] N = 57
Duration of study (months)						

	Prevalent users					
	Long Term N = 180	**Short Term N = 79**	**Total N = 259**	**New users N = 32**	**Non-Exposed[1] N = 167**	**Switch to Ruxo[2] N = 57**
n	180	79	259	32	167	57
Mean	32.51	29.62	31.63	26.11	28.90	32.47
SD	11.938	14.083	12.673	14.360	13.325	11.204
Median	35.71	33.05	35.22	30.09	34.99	36.04
Minimum	2.1	0.5	0.5	1.1	1.1	3.7
Maximum	55.9	55.0	55.9	49.3	53.2	53.2
Category of study duration, n (%)						
< 6 months	5 (2.8)	6 (7.6)	11 (4.2)	3 (9.4)	12 (7.2)	1 (1.8)
≥ 6 months	175 (97.2)	73 (92.4)	248 (95.8)	29 (90.6)	155 (92.8)	56 (98.2)
Duration of exposure (months)						
n	180	79	259	32	NA	57
Mean	30.91	26.26	29.49	25.29	NA	19.52
SD	12.861	15.594	13.889	14.082	NA	11.692
Median	33.81	27.79	33.38	26.14	NA	20.34
Minimum	0.9	0.5	0.5	1.1	NA	0.4
Maximum	55.9	55.0	55.9	49.0	NA	44.8
Category of exposure duration, n (%)						
< 6 months	11 (6.1)	13 (16.5)	24 (9.3)	3 (9.4)	NA	10 (17.5)
≥ 6 months	169 (93.9)	66 (83.5)	235 (90.7)	29 (90.6)	NA	47 (82.5)
Cumulative dose (mg)						
n	179	79	258	32	NA	57
Mean	23707.1	18489.2	22109.4	18327.3	NA	14925.4
SD	14922.03	15708.31	15326.98	14619.85	NA	11801.66
Median	22200.0	15160.0	20477.5	15755.0	NA	12110.0
Minimum	180	480	180	1020	NA	260
Maximum	78450	65450	78450	47440	NA	46530
Dose intensity (mg/day)						
n	179	79	258	32	NA	57
Mean	24.9	22.3	24.1	23.2	NA	25.2
SD	11.15	11.09	11.17	10.70	NA	11.51
Median	23.9	20.0	22.9	21.3	NA	26.1
Minimum	5	3	3	2	NA	5
Maximum	50	50	50	40	NA	50

- For patients who switched to ruxolitinib during the study, study duration before switch are presented in the 'Non-exposed' column and duration after switch are presented in the 'Switch to Ruxo' column.
- [1] N is the number of patients non-exposed to study drug at the time of enrollment (including switchers).
- [2] N is the number of patients who switched to ruxolitinib during the study.
- NA: Not applicable.
Source: Table 14.3-1.1.2

The dose of ruxolitinib was reduced in 51.4% of the patients in the prevalent users cohort, 53.1% of the patients in the new users cohort, and 45.6% of the patients in the switch to ruxolitinib

cohort. The ruxolitinib dose was interrupted in 33.2% of the patients in the prevalent users cohort, 21.9% of the patients in the new users cohort, and 29.8% of the patients in the switch to ruxolitinib cohort. The primary reasons for dose reductions and dose interruptions were medical decisions, followed by ADRs across all the cohorts. Dose reductions due to an ADR occurred in about 13% to 19% of the patients across all cohorts, slightly more often in the new users cohort and in the switch to ruxolitinib cohort than in the prevalent users cohort. Whereas, dose interruptions due to an ADR were observed in 9.7% of the patients in the prevalent users cohort, 6.3% of the patients in the new users cohort, and 8.8% of the patients in the switch to ruxolitinib cohort (Table 14.3-1.1.3).

10.4 Outcome data

The number of patients analyzed in each data set is provided in Section 10.1. The main summary measures and safety analyses are presented in Section 10.5.

10.5 Main results

10.5.1 Primary endpoints

10.5.1.1 Incidence of adverse drug reactions

Adverse drug reactions by system organ class

The most frequently reported ADRs in all cohorts were in the blood and lymphatic system disorders and infections. The most frequently reported ADRs by SOCs in each cohort (at least in 5%) are as follows:

Prevalent users cohort: Blood and lymphatic system disorders (22.8%), infections and infestations (20.8%), respiratory, thoracic and mediastinal disorders (7.7%), and gastrointestinal (GI) disorders (6.2%). No major differences were observed in the frequency of ADRs except in the infections and infestations (23.3% long-term users cohort vs 15.2% short-term users cohort) between the patients in the long-term users cohort and short-term users cohort (Table 10-6).

New users cohort: Blood and lymphatic system disorders (25%), infections and infestations (12.5%), investigations (9.4%), and neoplasms benign, malignant and unspecified (incl cysts and polyps) (6.3%) (Table 10-6).

Switch to ruxolitinib cohort: Blood and lymphatic system disorders (31.6%), infections and infestations (17.5%), respiratory, thoracic and mediastinal disorders (8.8%), vascular disorders (7%), general disorders and administration site conditions and investigations (each in 5.3%) (Table 10-6).

[redacted]

Table 10-6 Treatment-emergent adverse drug reactions, by system organ class and cohort (Safety set)

	Prevalent users				
System organ class	Long Term N = 180 n (%)	Short Term N = 79 n (%)	Total N = 259 n (%)	New users N = 32 n (%)	Switch to Ruxo[1] N = 57 n (%)
Patient with adverse drug reaction	**91 (50.6)**	**34 (43.0)**	**125 (48.3)**	**13 (40.6)**	**31 (54.4)**
Blood and lymphatic system disorders	44 (24.4)	15 (19.0)	59 (22.8)	8 (25.0)	18 (31.6)
Infections and infestations	42 (23.3)	12 (15.2)	54 (20.8)	4 (12.5)	10 (17.5)
Respiratory, thoracic and mediastinal disorders	11 (6.1)	9 (11.4)	20 (7.7)	1 (3.1)	5 (8.8)
Gastrointestinal disorders	11 (6.1)	5 (6.3)	16 (6.2)	0	2 (3.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (6.1)	1 (1.3)	12 (4.6)	2 (6.3)	1 (1.8)
General disorders and administration site conditions	7 (3.9)	3 (3.8)	10 (3.9)	0	3 (5.3)
Investigations	8 (4.4)	2 (2.5)	10 (3.9)	3 (9.4)	3 (5.3)
Skin and subcutaneous tissue disorders	6 (3.3)	2 (2.5)	8 (3.1)	1 (3.1)	1 (1.8)
Vascular disorders	6 (3.3)	2 (2.5)	8 (3.1)	0	4 (7.0)
Injury, poisoning and procedural complications	4 (2.2)	2 (2.5)	6 (2.3)	1 (3.1)	0
Nervous system disorders	4 (2.2)	2 (2.5)	6 (2.3)	1 (3.1)	1 (1.8)
Metabolism and nutrition disorders	3 (1.7)	1 (1.3)	4 (1.5)	0	2 (3.5)
Musculoskeletal and connective tissue disorders	1 (0.6)	3 (3.8)	4 (1.5)	0	2 (3.5)
Cardiac disorders	2 (1.1)	1 (1.3)	3 (1.2)	0	1 (1.8)
Reproductive system and breast disorders	3 (1.7)	0	3 (1.2)	0	0
Eye disorders	2 (1.1)	0	2 (0.8)	0	0
Renal and urinary disorders	2 (1.1)	0	2 (0.8)	0	1 (1.8)
Ear and labyrinth disorders	1 (0.6)	0	1 (0.4)	0	1 (1.8)
Hepatobiliary disorders	1 (0.6)	0	1 (0.4)	0	0
Psychiatric disorders	1 (0.6)	0	1 (0.4)	1 (3.1)	0

- System organ class are presented in descending frequency, as reported in the Prevalent users (Total) column.
- A patient with multiple occurrences of an ADR is counted only once in the ADR category.
- [1] N is the number of patients who switched to ruxolitinib during the study.

Source: Table 14.3.1-2.1.1

Adverse drug reactions by preferred term

Treatment-emergent ADRs were reported in 48.3% of the patients in the prevalent users cohort, 54.4% of the patients switch to ruxolitinib cohort, and 40.6% in the new users cohort. Thrombocytopenia and anemia were the most frequently reported ADRs in all cohorts.

The most frequently reported (at least in 3%) ADRs in each cohort are as follows:

Prevalent users cohort: thrombocytopenia (13.1%), anemia (9.3%), epistaxis (4.6%), urinary tract infection (3.5%), herpes zoster, and hematoma (each in 3.1%) (Table 10-7 and Table 14.3.1-2.1.1).

[redacted]

New users cohort: anemia (18.8%), thrombocytopenia (12.5%), pyoderma gangrenosum, dyspnoea, sleep disorder, epilepsy, metastases to lymph nodes, Bowen's disease, gamma glutamyl transferase increased, C-reactive protein increased, hemoglobin increased, platelet count decreased, subdural hematoma, subcutaneous abscess, bronchitis bacterial, upper respiratory tract infection, pneumonia, and herpes zoster (each in 1 patient, 3.1%) (Table 10-7 and Table 14.3.1-2.1.1).

Switch to ruxolitinib cohort: anemia and thrombocytopenia (each in 17.5%), epistaxis and herpes zoster (each in 5.3%), urinary tract infection, weight increased, dyspnoea, and hematoma (each in 3.5%) (Table 10-7 and Table 14.3.1-2.1.1).

Table 10-7 Treatment-emergent adverse drug reactions (at least 1% of the total prevalent users) by preferred term and cohort (Safety set)

	Prevalent users				
Preferred term	**Long Term N = 180 n (%)**	**Short Term N = 79 n (%)**	**Total N = 259 n (%)**	**New users N = 32 n (%)**	**Switch to Ruxo[1] N = 57 n (%)**
Patient with adverse drug reaction	**91 (50.6)**	**34 (43.0)**	**125 (48.3)**	**13 (40.6)**	**31 (54.4)**
Thrombocytopenia	25 (13.9)	9 (11.4)	34 (13.1)	4 (12.5)	10 (17.5)
Anaemia	19 (10.6)	5 (6.3)	24 (9.3)	6 (18.8)	10 (17.5)
Epistaxis	6 (3.3)	6 (7.6)	12 (4.6)	0	3 (5.3)
Urinary tract infection	6 (3.3)	3 (3.8)	9 (3.5)	0	2 (3.5)
Herpes zoster	6 (3.3)	2 (2.5)	8 (3.1)	1 (3.1)	3 (5.3)
Haematoma	6 (3.3)	2 (2.5)	8 (3.1)	0	2 (3.5)
Bronchitis	4 (2.2)	2 (2.5)	6 (2.3)	0	0
Pneumonia	5 (2.8)	1 (1.3)	6 (2.3)	1 (3.1)	1 (1.8)
Platelet count decreased	5 (2.8)	1 (1.3)	6 (2.3)	1 (3.1)	1 (1.8)
Diarrhoea	3 (1.7)	2 (2.5)	5 (1.9)	0	1 (1.8)
Sepsis	5 (2.8)	0	5 (1.9)	0	0
Contusion	3 (1.7)	2 (2.5)	5 (1.9)	0	0
Lung infection	2 (1.1)	2 (2.5)	4 (1.5)	0	0
Basal cell carcinoma	4 (2.2)	0	4 (1.5)	0	0
Squamous cell carcinoma	4 (2.2)	0	4 (1.5)	0	0
Pyrexia	2 (1.1)	2 (2.5)	4 (1.5)	0	1 (1.8)
Fatigue	2 (1.1)	1 (1.3)	3 (1.2)	0	0
Neutropenia	3 (1.7)	0	3 (1.2)	0	0
Lower respiratory tract infection	3 (1.7)	0	3 (1.2)	0	0
Nasopharyngitis	2 (1.1)	1 (1.3)	3 (1.2)	0	0
Oral candidiasis	3 (1.7)	0	3 (1.2)	0	0
Upper respiratory tract infection	3 (1.7)	0	3 (1.2)	1 (3.1)	0
Weight increased	2 (1.1)	1 (1.3)	3 (1.2)	0	2 (3.5)

-Preferred terms are sorted in descending frequency, as reported in the Prevalent users (Total) column.
- A patient with multiple occurrences of an ADR is counted only once in the ADR category.
- [1] N is the number of patients who switched to ruxolitinib during the study.
Source: Table 14.3.1-2.1.1

[redacted]

Incidence rates of treatment-emergent adverse drug reactions by preferred term

The incidence rates of ADRs were similar across all cohorts (approximately 20 /100 patient years (PY)) except for patients in the switch to ruxolitinib cohort who had slightly higher incidence rates (33.4). The higher incidence rates could be probably due to the shorter duration of exposure to ruxolitinib for the patients in the switch to ruxolitinib cohort (20.34 months) compared to the prevalent users cohort (33.38 months) (Table 10-5). A transient hematotoxicity is usually observed in the first few months of ruxolitinib therapy. Since the follow-up of the patients in the switch to ruxolitinib cohort was of shorter duration compared to the other cohorts, the toxicity of the first few months of therapy had higher prominence.

The majority of ADRs had an incidence rate of ≤ 1 per 100-PY in all cohorts. The most frequently reported ADRs (at least 1 per 100-PY) in the cohorts are as follows:

Prevalent users cohort: thrombocytopenia (5.3), anemia (3.8), epistaxis (1.9), UTI (1.4), herpes zoster, and hematoma (each in 1.3) (Table 10-8 and Table 14.3.1-2.2.1).

New users cohort: anemia (8.9), thrombocytopenia (5.9), herpes zoster, pneumonia, bronchitis bacterial, subcutaneous access, subdural hematoma, platelet count decreased, hemoglobin decreased, C-reactive protein increased, gamma glutamyl transferase increased, Bowen's disease, metastases to lymph nodes, epilepsy, sleep disorder, dyspnoea, URTIs, and pyoderma gangrenosum (each in 1.5) (Table 10-8 and Table 14.3.1-2.2.1).

Switch to ruxolitinib cohort: thrombocytopenia and anemia (each in 10.8), herpes zoster and epistaxis (each in 3.2), UTI, weight increased, dyspnoea and hematoma (each in 2.2), leukopenia, pancytopenia, hemorrhagic diathesis, cardiac arrest, vestibular disorder, diarrhoea, abdominal pain, flatulence, intestinal infarction, retroperitoneal hematoma, retroperitoneal hemorrhage, pyrexia, general physical health deterioration, hypothermia, pneumonia, clostridium difficile colitis, folliculitis, gastroenteritis, gingivitis, ophthalmic herpes zoster, pneumonia fungal, sinusitis, tonsillitis, viral infection, platelet count decreased, hypocalcemia, hypoglycemia, muscle hemorrhage, myalgia, ovarian cancer metastatic, dizziness, hydronephrosis, prerenal failure, hand dermatitis, aneurysm, aortic thrombosis, and hypotension (each in 1.1) (Table 10-8 and Table 14.3.1-2.2.1).

Table 10-8 Incidence rates (at least 0.5 per 100-patient years in total prevalent users) of treatment emergent-adverse drug reactions by preferred term and cohort (Safety set)

	Prevalent users				
Incidence rate (n/100 patient-years) Preferred term	**Long Term N = 180**	**Short Term N = 79**	**Total N = 259**	**New users N = 32**	**Switch to Ruxo[1] N = 57**
Patient-years	**463.6**	**172.9**	**636.5**	**67.4**	**92.7**
Any adverse drug reaction	**19.6**	**19.7**	**19.6**	**19.3**	**33.4**
Thrombocytopenia	5.4	5.2	5.3	5.9	10.8
Anaemia	4.1	2.9	3.8	8.9	10.8
Epistaxis	1.3	3.5	1.9	0	3.2
Urinary tract infection	1.3	1.7	1.4	0	2.2
Herpes zoster	1.3	1.2	1.3	1.5	3.2

[redacted]

Incidence rate (n/100 patient-years) Preferred term	Prevalent users Long Term N = 180	Short Term N = 79	Total N = 259	New users N = 32	Switch to Ruxo[1] N = 57
Haematoma	1.3	1.2	1.3	0	2.2
Bronchitis	0.9	1.2	0.9	0	0
Platelet count decreased	1.1	0.6	0.9	1.5	1.1
Pneumonia	1.1	0.6	0.9	1.5	1.1
Sepsis	1.1	0	0.8	0	0
Diarrhoea	0.6	1.2	0.8	0	1.1
Contusion	0.6	1.2	0.8	0	0
Pyrexia	0.4	1.2	0.6	0	1.1
Lung infection	0.4	1.2	0.6	0	0
Basal cell carcinoma	0.9	0	0.6	0	0
Squamous cell carcinoma	0.9	0	0.6	0	0
Neutropenia	0.6	0	0.5	0	0
Fatigue	0.4	0.6	0.5	0	0
Lower respiratory tract infection	0.6	0	0.5	0	0
Nasopharyngitis	0.4	0.6	0.5	0	0
Oral candidiasis	0.6	0	0.5	0	0
Upper respiratory tract infection	0.6	0	0.5	1.5	0
Weight increased	0.4	0.6	0.5	0	2.2

- Patient-years are derived as sum of individual durations exposed to ruxolitinib.
- Incidence rate is derived as number of patients who experienced a specific AE during the study dividing by associated patient-year*100.
Preferred terms are sorted in descending frequency, as reported in the Prevalent users (Total) column.
- A patient with multiple occurrences of an ADR is counted only once in the ADR category.
- [1] N is the number of patients who switched to ruxolitinib during the study.
Source: Table 14.3.1-2.2.1

10.5.1.2 Treatment-emergent serious adverse events

A slightly higher percentage of patients in the prevalent users cohort (61.4%) had treatment-emergent SAEs compared to the new users cohort (53.1%) or patients in the switch to ruxolitinib cohort (47.4%) (Table 10-9).

The most frequently reported treatment-emergent SAEs (at least 3%) in each cohort are as follows:

Prevalent users cohort: anemia (7.7%), pneumonia (6.9%), general physical health deterioration (5.4%), sepsis (5%), death and MF (each in 4.6%), dyspnoea, abdominal pain, UTI (each in 4.2%), cardiac failure (3.9%), pyrexia and renal failure (each in 3.5%), fall, basal cell carcinoma, and squamous cell carcinoma (each in 3.1%) (Table 10-9 and Table 14.3.1-2.1.2).

New users cohort: anemia (9.4%), febrile infection (6.3%), thrombocytopenia, cardiac failure, atrial fibrillation, cardiac arrest, cardiac failure chronic, ventricular tachycardia, ischemic enteritis, general physical health deterioration, multiple organ dysfunction syndrome, fatigue, pneumonia, UTI, bronchitis, herpes zoster, septic shock, gastroenteritis, lung infection, upper respiratory tract infection, anal abscess, campylobacter gastroenteritis, subcutaneous abscess, UTI enterococcal, urosepsis, subdural hematoma, neck injury, pulmonary function test, red

blood cell count decreased, dehydration, osteoarthritis, squamous cell carcinoma, acute myeloid leukemia (AML), lung adenocarcinoma, metastases to bone, metastases to lymph nodes, cerebral ischemia, epilepsy, renal failure, acute kidney injury, nephrolithiasis, renal colic, cough, pyoderma gangrenosum, and hematoma (each in 1 patient, 3.1%) (Table 10-9 and Table 14.3.1-2.1.2).

Switch to ruxolitinib cohort: general physical health deterioration, pneumonia and MF (each 7%), hematoma (5.3%), anemia, splenomegaly, abdominal pain, death, pyrexia, multiple organ dysfunction syndrome, gastroenteritis, influenza, and pleural effusion (3.5%) (Table 10-9 and Table 14.3.1-2.1.2).

Table 10-9 Treatment-emergent serious adverse events (at least in 1.5% in the total prevalent users), by preferred term and cohort (Safety set)

	Prevalent users				
Preferred term	**Long Term N = 180 n (%)**	**Short Term N = 79 n (%)**	**Total N = 259 n (%)**	**New users N = 32 n (%)**	**Switch to Ruxo[1] N = 57 n (%)**
Patient with serious adverse events	**115 (63.9)**	**44 (55.7)**	**159 (61.4)**	**17 (53.1)**	**27 (47.4)**
Anaemia	13 (7.2)	7 (8.9)	20 (7.7)	3 (9.4)	2 (3.5)
Pneumonia	15 (8.3)	3 (3.8)	18 (6.9)	1 (3.1)	4 (7.0)
General physical health deterioration	10 (5.6)	4 (5.1)	14 (5.4)	1 (3.1)	4 (7.0)
Sepsis	10 (5.6)	3 (3.8)	13 (5.0)	0	1 (1.8)
Death	8 (4.4)	4 (5.1)	12 (4.6)	0	2 (3.5)
Myelofibrosis	8 (4.4)	4 (5.1)	12 (4.6)	0	4 (7.0)
Dyspnoea	7 (3.9)	4 (5.1)	11 (4.2)	0	0
Abdominal pain	9 (5.0)	2 (2.5)	11 (4.2)	0	2 (3.5)
Urinary tract infection	8 (4.4)	3 (3.8)	11 (4.2)	1 (3.1)	1 (1.8)
Cardiac failure	10 (5.6)	0	10 (3.9)	1 (3.1)	0
Pyrexia	7 (3.9)	2 (2.5)	9 (3.5)	0	2 (3.5)
Renal failure	7 (3.9)	2 (2.5)	9 (3.5)	1 (3.1)	0
Fall	8 (4.4)	0	8 (3.1)	0	0
Basal cell carcinoma	6 (3.3)	2 (2.5)	8 (3.1)	0	1 (1.8)
Squamous cell carcinoma	6 (3.3)	2 (2.5)	8 (3.1)	1 (3.1)	1 (1.8)
Back pain	6 (3.3)	1 (1.3)	7 (2.7)	0	0
Acute kidney injury	6 (3.3)	1 (1.3)	7 (2.7)	1 (3.1)	0
Acute myeloid leukaemia	3 (1.7)	3 (3.8)	6 (2.3)	1 (3.1)	0
Pancytopenia	5 (2.8)	1 (1.3)	6 (2.3)	0	1 (1.8)
Atrial fibrillation	3 (1.7)	3 (3.8)	6 (2.3)	1 (3.1)	1 (1.8)
Ascites	2 (1.1)	3 (3.8)	5 (1.9)	0	0
Nausea	5 (2.8)	0	5 (1.9)	0	1 (1.8)
Vomiting	5 (2.8)	0	5 (1.9)	0	1 (1.8)
Thrombocytopenia	4 (2.2)	1 (1.3)	5 (1.9)	1 (3.1)	0
Bronchitis	3 (1.7)	2 (2.5)	5 (1.9)	1 (3.1)	0
Erysipelas	3 (1.7)	1 (1.3)	4 (1.5)	0	0
Herpes zoster	3 (1.7)	1 (1.3)	4 (1.5)	1 (3.1)	0
Septic shock	3 (1.7)	1 (1.3)	4 (1.5)	1 (3.1)	0
Epistaxis	1 (0.6)	3 (3.8)	4 (1.5)	0	0

[redacted]

Preferred term	Prevalent users: Long Term N = 180 n (%)	Prevalent users: Short Term N = 79 n (%)	Prevalent users: Total N = 259 n (%)	New users N = 32 n (%)	Switch to Ruxo[1] N = 57 n (%)
Dehydration	2 (1.1)	2 (2.5)	4 (1.5)	1 (3.1)	0
Malnutrition	4 (2.2)	0	4 (1.5)	0	0
Multiple organ dysfunction syndrome	2 (1.1)	2 (2.5)	4 (1.5)	1 (3.1)	2 (3.5)
Oedema peripheral	2 (1.1)	2 (2.5)	4 (1.5)	0	0
Myeloproliferative neoplasm	4 (2.2)	0	4 (1.5)	0	0
Transformation to acute myeloid leukaemia	4 (2.2)	0	4 (1.5)	0	1 (1.8)
Cardiopulmonary failure	2 (1.1)	2 (2.5)	4 (1.5)	0	0

- Preferred terms are sorted in descending frequency, as reported in the Prevalent users (Total) column.
- A patient with multiple occurrences of an SAE is counted only once in the SAE category.
- [1] N is the number of patients who switched to ruxolitinib during the study.
Source: Table 14.3.1-2.1.2

The incidence rate of treatment-emergent SAEs was similar across the prevalent users cohort and new users cohort (25 vs 25.2). Patients in the switch to the ruxolitinib cohort had slightly higher incidence rates (29.1/100 PY). The most frequently reported treatment-emergent SAEs with higher incidence rates were similar in the prevalent users cohort and in the switch to ruxolitinib cohort, while these were reported in lesser frequency in the new users cohort (Table 10-10 and Table 14.3.1-2.2.2).

The most frequently reported treatment-emergent SAEs with a higher incidence rate (≥ 1.5) in all the cohorts included:

Prevalent users cohort: anemia (3.1), pneumonia (2.8), general physical health deterioration (2.2), sepsis (2), death and MF (each in 1.9), UTI, abdominal pain, and dyspnoea (each in 1.7) and cardiac failure (1.6) (Table 10-10 and Table 14.3.1-2.2.2).

New users cohort: anemia (4.4), febrile infection (3), thrombocytopenia, cardiac failure, atrial fibrillation, cardiac arrest, cardiac failure chronic, ventricular tachycardia, ischemic enteritis, general physical health deterioration, multiple organ dysfunction syndrome, fatigue, pneumonia, UTI, bronchitis, herpes zoster, septic shock, gastroenteritis, lung infection, upper respiratory tract infection, anal abscess, campylobacter gastroenteritis, subcutaneous abscess, UTI enterococcal, urosepsis, subdural hematoma, neck injury, pulmonary function test, RBC decreased, dehydration, osteoarthritis, squamous cell carcinoma, AML, lung adenocarcinoma, metastases to bone, metastases to lymph nodes, cerebral ischemia, epilepsy, renal failure, acute kidney injury, nephrolithiasis, renal colic, cough, pyoderma gangrenosum, and hematoma, (each in 1.5%) (Table 10-10 and Table 14.3.1-2.2.2).

Switch to ruxolitinib cohort: pneumonia, general physical health deterioration, MF (each in 4.3), haematoma (3.2), anemia, death, abdominal pain, pyrexia, multiple organ dysfunction syndrome, pleural effusion, influenza, gastroenteritis, and splenomegaly (each in 2.2) (Table 10-10 and Table 14.3.1-2.2.2).

Table 10-10 Incidence rates (at least 0.5 per 100 patient-years in the total prevalent users) of serious treatment-emergent serious adverse events, by preferred term and cohort (Safety set)

	Prevalent users				
Incidence rate (n/100 patient-years) Preferred term	**Long Term N = 180**	**Short Term N = 79**	**Total N = 259**	**New users N = 32**	**Switch to Ruxo[1] N = 57**
Patient-years	**463.6**	**172.9**	**636.5**	**67.4**	**92.7**
Any serious adverse event	**24.8**	**25.5**	**25.0**	**25.2**	**29.1**
Anaemia	2.8	4.0	3.1	4.4	2.2
Pneumonia	3.2	1.7	2.8	1.5	4.3
General physical health deterioration	2.2	2.3	2.2	1.5	4.3
Sepsis	2.2	1.7	2.0	0	1.1
Death	1.7	2.3	1.9	0	2.2
Myelofibrosis	1.7	2.3	1.9	0	4.3
Urinary tract infection	1.7	1.7	1.7	1.5	1.1
Abdominal pain	1.9	1.2	1.7	0	2.2
Dyspnoea	1.5	2.3	1.7	0	0
Cardiac failure	2.2	0	1.6	1.5	0
Renal failure	1.5	1.2	1.4	1.5	0
Pyrexia	1.5	1.2	1.4	0	2.2
Fall	1.7	0	1.3	0	0
Basal cell carcinoma	1.3	1.2	1.3	0	1.1
Squamous cell carcinoma	1.3	1.2	1.3	1.5	1.1
Back pain	1.3	0.6	1.1	0	0
Acute kidney injury	1.3	0.6	1.1	1.5	0
Pancytopenia	1.1	0.6	0.9	0	1.1
Thrombocytopenia	0.9	0.6	0.8	1.5	0
Atrial fibrillation	0.6	1.7	0.9	1.5	1.1
Ascites	0.4	1.7	0.8	0	0
Nausea	1.1	0	0.8	0	1.1
Vomiting	1.1	0	0.8	0	1.1
Acute myeloid leukaemia	0.6	1.7	0.9	1.5	0
Bronchitis	0.6	1.2	0.8	1.5	0
Epistaxis	0.2	1.7	0.6	0	0
Erysipelas	0.6	0.6	0.6	0	0
Herpes zoster	0.6	0.6	0.6	1.5	0
Septic shock	0.6	0.6	0.6	1.5	0
Multiple organ dysfunction syndrome	0.4	1.2	0.6	1.5	2.2
Oedema peripheral	0.4	1.2	0.6	0	0
Myeloproliferative neoplasm	0.9	0	0.6	0	0
Transformation to acute myeloid leukaemia	0.9	0	0.6	0	1.1
Dehydration	0.4	1.2	0.6	1.5	0
Malnutrition	0.9	0	0.6	0	0
Cardiopulmonary failure	0.4	1.2	0.6	0	0
Acute coronary syndrome	0.6	0	0.5	0	0
Diverticular perforation	0.4	0.6	0.5	0	0
Intestinal perforation	0.2	1.2	0.5	0	0

[redacted]

Incidence rate (n/100 patient-years) Preferred term	Prevalent users: Long Term N = 180	Prevalent users: Short Term N = 79	Prevalent users: Total N = 259	New users N = 32	Switch to Ruxo[1] N = 57
Rectal haemorrhage	0.6	0	0.5	0	0
Acute myocardial infarction	0.6	0	0.5	0	0
Angina pectoris	0.4	0.6	0.5	0	0
Diffuse large B-cell lymphoma	0.2	1.2	0.5	0	0
Febrile neutropenia	0.4	0.6	0.5	0	0
Femur fracture	0.4	0.6	0.5	0	0
Asthenia	0.4	0.6	0.5	0	0
Pain	0.4	0.6	0.5	0	0
Infection	0.4	0.6	0.5	0	1.1
Syncope	0.6	0	0.5	0	0
Lung disorder	0.4	0.6	0.5	0	0
Pleural effusion	0.2	1.2	0.5	0	2.2
Pulmonary embolism	0.6	0	0.5	0	0
Respiratory failure	0.4	0.6	0.5	0	0
Haematoma	0.6	0	0.5	1.5	3.2
Hypertension	0.6	0	0.5	0	0

- Patient-years are derived as sum of individual durations exposed to ruxolitinib.
- Incidence rate is derived as number of patients who experienced a specific AE during the study dividing by associated patient-year*100.
- Preferred terms are sorted in descending frequency, as reported in the Prevalent users (Total) column.
- A patient with multiple occurrences of an SAE is counted only once in the SAE category for that treatment.
- [1] N is the number of patients who switched to ruxolitinib during the study.

Source: Table 14.3.1-2.2.2

10.5.2 Secondary endpoints

10.5.2.1 Management of myelofibrosis and co-morbidities

10.5.2.1.1 Medications for treatment and management of MF

A higher percentage of the patients in the non-exposed to ruxolitinib cohort (56.9%) and the patients in the switch to ruxolitinib cohort (47.4%) received concomitant medications to treat and manage MF compared to patients in the prevalent users cohort (25.9%), or in the new users cohort (28.1%). Hydroxycarbamide was the most frequently received medication in all the cohorts (Table 10-11).

The most frequently (at least 1.5%) used concomitant medications for MF in all the cohorts are as follows:

Prevalent users cohort: hydroxycarbamide (10.8%), darbepoetin alfa (4.2%), acetylsalicylic acid (1.9%), azacitidine, epoetin beta, and mercaptopurine (each in 1.5%).

New users cohort: hydroxycarbamide (12.5%), acetylsalicylate lysine, and prednisone (each in 6.3%), darbepoetin alfa, acetylsalicylic acid, anagrelide hydrochloride, erythropoietin, and valaciclovir hydrochloride (each in 3.1%) (Table 10-11).

Non-exposed to ruxolitinib cohort: hydroxycarbamide (36.5%), peginterferon alfa-2a, acetylsalicylate lysine, (each in 6.6%), and anagrelide hydrochloride (6%), darbapoetin alfa, and acetylsalicylic acid (each 3.6%), epoetin alfa (2.4%), anagrelide, mercaptopurine, and peginterferon alfa-2B (each in 1.8%) (Table 10-11).

Switch to ruxolitinib cohort: hydroxycarbamide (26.3%), anagrelide hydrochloride (8.8%), darbepoetin alfa (7%), acetylsalicylic acid, acetylsalicylate lysine (3.5%), azacitidine, epoetin beta, peginterferon alfa-2a, danazol, prednisone, ferrous sulfate, peginterferon alfa-2B, and pipobroman (each in 1.8%) (Table 10-11).

Table 10-11 Concomitant medication for myelofibrosis, by cohort (Safety set modified)

	Prevalent users					
Preferred term	Long Term N = 180 n (%)	Short Term N = 79 n (%)	Total N = 259 n (%)	New users N = 32 n (%)	Non-Exposed[1] N = 167 n (%)	Switch to Ruxo[2] N = 57 n (%)
Patient with concomitant medication for myelofibrosis	**43 (23.9)**	**24 (30.4)**	**67 (25.9)**	**9 (28.1)**	**95 (56.9)**	**27 (47.4)**
Hydroxycarbamide	19 (10.6)	9 (11.4)	28 (10.8)	4 (12.5)	61 (36.5)	15 (26.3)
Darbepoetin alfa	9 (5.0)	2 (2.5)	11 (4.2)	1 (3.1)	6 (3.6)	4 (7.0)
Acetylsalicylic acid	4 (2.2)	1 (1.3)	5 (1.9)	1 (3.1)	6 (3.6)	2 (3.5)
Azacitidine	4 (2.2)	0	4 (1.5)	0	0	1 (1.8)
Epoetin beta	2 (1.1)	2 (2.5)	4 (1.5)	0	2 (1.2)	1 (1.8)
Mercaptopurine	3 (1.7)	1 (1.3)	4 (1.5)	0	3 (1.8)	0
Acetylsalicylate lysine	2 (1.1)	1 (1.3)	3 (1.2)	2 (6.3)	11 (6.6)	2 (3.5)
Prednisolone	3 (1.7)	0	3 (1.2)	0	1 (0.6)	0
Anagrelide hydrochloride	0	2 (2.5)	2 (0.8)	1 (3.1)	10 (6.0)	5 (8.8)
Clopidogrel bisulfate	1 (0.6)	1 (1.3)	2 (0.8)	0	0	0
Cytarabine	2 (1.1)	0	2 (0.8)	0	0	0
Epoetin alfa	2 (1.1)	0	2 (0.8)	0	4 (2.4)	0
Erythropoietin	1 (0.6)	1 (1.3)	2 (0.8)	1 (3.1)	1 (0.6)	0
Peginterferon alfa-2a	1 (0.6)	1 (1.3)	2 (0.8)	0	11 (6.6)	1 (1.8)
Ruxolitinib	1 (0.6)	1 (1.3)	2 (0.8)	0	1 (0.6)	0
Anagrelide	1 (0.6)	0	1 (0.4)	0	3 (1.8)	0
Buparlisib	0	1 (1.3)	1 (0.4)	0	0	0
Calcitriol	0	1 (1.3)	1 (0.4)	0	0	0
Danazol	0	1 (1.3)	1 (0.4)	0	2 (1.2)	1 (1.8)
Eltrombopag olamine	1 (0.6)	0	1 (0.4)	0	0	0
Lenalidomide	0	1 (1.3)	1 (0.4)	0	0	0
Prednisone	1 (0.6)	0	1 (0.4)	2 (6.3)	1 (0.6)	1 (1.8)
Ruxolitinib phosphate	1 (0.6)	0	1 (0.4)	0	0	0
Busulfan	0	0	0	0	1 (0.6)	0
Deferasirox	0	0	0	0	1 (0.6)	0
Enoxaparin sodium	0	0	0	0	1 (0.6)	0
Ferrous sulfate	0	0	0	0	1 (0.6)	1 (1.8)
Imetelstat	0	0	0	0	1 (0.6)	0
Interferon	0	0	0	0	2 (1.2)	0

	Prevalent users					
Preferred term	Long Term N = 180 n (%)	Short Term N = 79 n (%)	Total N = 259 n (%)	New users N = 32 n (%)	Non-Exposed[1] N = 167 n (%)	Switch to Ruxo[2] N = 57 n (%)
Pacritinib	0	0	0	0	2 (1.2)	0
Peginterferon	0	0	0	0	1 (0.6)	0
Peginterferon alfa-2b	0	0	0	0	3 (1.8)	1 (1.8)
Pipobroman	0	0	0	0	1 (0.6)	1 (1.8)
Valaciclovir hydrochloride	0	0	0	1 (3.1)	0	0

- Preferred terms are sorted in descending frequency, as reported in the Prevalent users (Total) column.
- For patients who switched to ruxolitinib during the study, events before switch are presented in the 'Non-exposed' column and events after switch are presented in the 'Switch to Ruxo' column.
- [1] N is the number of patients non-exposed to study drug at the time of enrollment (including switchers).
- [2] N is the number of patients who switched to ruxolitinib during the study.
Source: Table 14.3-1.2.1

10.5.2.1.2 Non-pharmacologic treatment for MF

Prior and concomitant non-pharmacological treatment for MF in the majority of the patients across all the cohorts included splenectomy, allograft, venesection, bloodletting, allogenic stem cell transplantation (Listing 16.2.5-2.4).

10.5.2.1.3 Use of blood or platelet transfusions

At least 50% of the patients required concomitant PRBC transfusions across all cohorts except patients in the non-exposed to ruxolitinib cohort (34.1%). The median number of PRBC units required was highest in the non-exposed to ruxolitinib cohort (13.5 units) followed by the prevalent users cohort and the switch to ruxolitinib cohort (each 9.5 units) and was least in the new users cohort (6 units) (Table 10-12).

The proportion of patients who required concomitant platelet transfusion was comparable across all the cohorts with the exception of the new users cohort who did not require any platelet transfusion. The median units of platelets used was comparable in the prevalent users cohort and the non-exposed to ruxolitinib cohort (6 vs 8 units) (Table 10-12).

Table 10-12 Concomitant PRBC/platelet transfusion, by cohort (Safety set modified)

	Prevalent users					
	Long Term N = 180	Short Term N =79	Total N = 259	New users N = 32	Non-Exposed[1] N = 167	Switch to Ruxo[2] N = 57
Patient with concomitant PRBC transfusion, n (%)	**92 (51.1)**	**44 (55.7)**	**136 (52.5)**	**17 (53.1)**	**57 (34.1)**	**30 (52.6)**
Number of unit of PRBC						
n	92	42	134	17	54	30
Mean (SD)	30.9 (46.17)	26.8 (41.65)	29.6 (44.68)	13.2 (13.69)	22.6 (24.26)	18.9 (26.28)
Median	9.0	10.5	9.5	6.0	13.5	9.5
Min – Max	1 – 274	2 - 225	1 - 274	1 - 45	1 - 122	2 - 131

[redacted]

	Prevalent users					
	Long Term N = 180	Short Term N =79	Total N = 259	New users N = 32	Non-Exposed[1] N = 167	Switch to Ruxo[2] N = 57
Patient with concomitant platelet transfusion, n (%)	**23 (12.8)**	**8 (10.1)**	**31 (12.0)**	**0**	**13 (7.8)**	**6 (10.5)**
Number of unit of platelet						
n	22	7	29	0	13	6
Mean (SD)	16.4 (19.57)	4.9 (7.59)	13.6 (18.01)	NA	12.6 (15.07)	1.7 (0.52)
Median	8.0	2.0	6.0	NA	8.0	2.0
Min – Max	1 – 64	1 – 22	1 - 64	NA	1 – 58	1 - 2

- For patients who switched to ruxolitinib during the study, events before switch are presented in the 'Non-exposed' column and events after switch are presented in the 'Switch to Ruxo' column.
- [1] N is the number of patients non-exposed to study drug at the time of enrollment (including switchers).
- [2] N is the number of patients who switched to ruxolitinib during the study.
Source: Table 14.3-1.2.3

10.5.2.2 Constitutional symptoms and symptoms related to myelofibrosis

The proportion of patients with constitutional symptoms (night sweats, fever, and weight loss) was comparable in the prevalent users cohort (52.1%) and in the switch to ruxolitinib cohort (50.9%), with a lower proportion of patients in the new users cohort (40.6%) and in the non-exposed to ruxolitinib cohort (34.7%). Night sweats were the most frequently reported constitutional symptom in all the cohorts. Fever was reported by a lower proportion of patients in the non-exposed to ruxolitinib cohort. Weight loss was reported in a higher proportion of patients in the prevalent users cohort (22.8%) and in the new users cohort (21.9%); however, it was reported by a lower proportion of patients in the non-exposed to ruxolitinib cohort (13.2%) and in the switch to ruxolitinib cohort (15.8%) (Table 10-13).

Symptoms related to MF were reported by 84.6% of the patients in the prevalent users cohort, 75% in the new users cohort, 69.5% in the non-exposed to ruxolitinib cohort and 70.2% in the switch to ruxolitinib cohort. Fatigue was the most frequently reported, and chills was the least frequently reported MF symptom in all the cohorts. No consistent trend of a higher or lower frequency of symptoms related to MF was observed across all the cohorts (Table 10-13).

Table 10-13 Summary of constitutional symptoms and symptoms related to myelofibrosis, by cohort (Safety set modified)

	Prevalent users					
	Long Term N = 180	Short Term N = 79	Total N = 259	New users N = 32	Non-Exposed[1] N = 167	Switch to Ruxo[2] N = 57
Patients with constitutional symptoms, n (%)	**97 (53.9)**	**38 (48.1)**	**135 (52.1)**	**13 (40.6)**	**58 (34.7)**	**29 (50.9)**
Fever	28 (15.6)	14 (17.7)	42 (16.2)	4 (12.5)	13 (7.8)	9 (15.8)
Night Sweats	60 (33.3)	29 (36.7)	89 (34.4)	7 (21.9)	34 (20.4)	21 (36.8)
Weight Loss	49 (27.2)	10 (12.7)	59 (22.8)	7 (21.9)	22 (13.2)	9 (15.8)
Patients with symptoms related to myelofibrosis, n (%)	**155 (86.1)**	**64 (81.0)**	**219 (84.6)**	**24 (75.0)**	**116 (69.5)**	**40 (70.2)**

	Prevalent users					
	Long Term N = 180	Short Term N = 79	Total N = 259	New users N = 32	Non-Exposed[1] N = 167	Switch to Ruxo[2] N = 57
Abdominal Discomfort	56 (31.1)	27 (34.2)	83 (32.0)	6 (18.8)	28 (16.8)	12 (21.1)
Abdominal Pain	44 (24.4)	24 (30.4)	68 (26.3)	6 (18.8)	21 (12.6)	10 (17.5)
Bone Pain	51 (28.3)	19 (24.1)	70 (27.0)	4 (12.5)	28 (16.8)	10 (17.5)
Chills	20 (11.1)	9 (11.4)	29 (11.2)	2 (6.3)	13 (7.8)	4 (7.0)
Decreased Appetite	37 (20.6)	17 (21.5)	54 (20.8)	7 (21.9)	30 (18.0)	13 (22.8)
Early Satiety	32 (17.8)	17 (21.5)	49 (18.9)	4 (12.5)	17 (10.2)	10 (17.5)
Fatigue	116 (64.4)	48 (60.8)	164 (63.3)	19 (59.4)	80 (47.9)	33 (57.9)
Inactivity	62 (34.4)	22 (27.8)	84 (32.4)	3 (9.4)	24 (14.4)	14 (24.6)
Malaise	38 (21.1)	13 (16.5)	51 (19.7)	4 (12.5)	22 (13.2)	8 (14.0)
Pruritus	54 (30.0)	19 (24.1)	73 (28.2)	4 (12.5)	38 (22.8)	5 (8.8)
Other	73 (40.6)	23 (29.1)	96 (37.1)	11 (34.4)	48 (28.7)	16 (28.1)

- A patient may experience several symptoms.
- For patients who switched to ruxolitinib during the study, events before switch are presented in the'Non-exposed' column and events after switch are presented in the 'Switch to Ruxo' column.
- [1] N is the number of patients non-exposed to study drug at the time of enrollment (including switchers).
- [2] N is the number of patients who switched to ruxolitinib during the study.

Source: Table 14.3-1.3.1

10.5.2.3 Bone marrow biopsies

Bone marrow biopsies data could not be evaluated as the available data was limited to a very few patients.

10.5.2.4 Bone marrow blast percentage

A summary of bone marrow blast percentage by cohort is presented in Table 14.3-1.4.1. Due to the limited data available, no meaningful conclusion could be drawn.

10.5.2.5 Spleen length

Since this is a non-interventional study, the Baseline value of spleen length was not available for all patients. Among the patients who had spleen length values at Baseline and post-baseline, the majority of patients had a decrease in spleen length post-baseline. The median percentage decrease was 41.05% in the new users cohort, 37.72% in the switch to ruxolitinib cohort, 20% in the prevalent users cohort and was negligible in the non-exposed to ruxolitinib cohort (Table 10-14).

Table 10-14 Summary of change from Baseline in spleen length, by cohort (Safety set modified)

	Prevalent users					
Spleen length	Long Term N=180	Short Term N=79	Total N=259	New users N=32	Non-Exposed[1] N=167	Switch to Ruxo[2] N=57
Baseline(cm)						
n	77	41	118	15	53	18
Mean	9.47	9.56	9.50	9.80	9.43	10.88

	Prevalent users					
Spleen length	Long Term N=180	Short Term N=79	Total N=259	New users N=32	Non-Exposed[1] N=167	Switch to Ruxo[2] N=57
SD	6.48	5.85	6.24	5.80	5.89	6.02
Median	8.00	9.00	8.00	8.00	8.00	10.50
Minimum	0.00	1.00	0.00	2.00	1.00	3.00
Maximum	30.00	23.00	30.00	20.00	25.00	25.00
Maximum post-baseline (decrease, cm)						
n	119	52	171	21	61	29
Mean	7.22	8.28	7.54	7.57	8.24	7.64
SD	6.35	6.15	6.29	5.46	5.80	6.39
Median	5.00	6.25	6.00	8.00	6.50	6.00
Minimum	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	30.00	24.00	30.00	18.00	22.00	26.00
Maximum change from Baseline (decrease, cm)						
n	72	34	106	12	33	14
Mean	-2.83	-2.22	-2.64	-5.00	-0.41	-4.93
SD	4.19	5.68	4.70	4.67	5.22	4.18
Median	-1.00	-1.50	-1.00	-5.00	0.00	-4.50
Minimum	-18.00	-15.50	-18.00	-15.00	-17.00	-12.00
Maximum	5.00	10.00	10.00	2.00	16.00	1.00
Maximum percentage change from Baseline (decrease, %)						
n	70	34	104	12	33	14
Mean	-16.66	-3.58	-12.38	-46.51	9.27	-41.35
SD	71.71	75.26	72.79	38.63	65.96	25.04
Median	-21.36	-20.00	-20.00	-41.05	0.00	-37.72
Minimum	-100.00	-100.00	-100.00	-100.00	-77.27	-83.33
Maximum	500.00	200.00	500.00	33.33	266.67	8.33

- Baseline is defined as the last non-missing value prior to the reference start date.
- For patients who switched to ruxolitinib during the study, events before switch are presented in the 'Non-exposed' column and events after switch are presented in the 'Switch to Ruxo' column.
- [1] N is the number of patients non-exposed to study drug at the time of enrollment (including switchers).
- [2] N is the number of patients who switched to ruxolitinib during the study.

Source: Table 14.3-1.8.3

10.5.2.6 Body weight

The majority of patients had no change in body weight during the study compared to the Baseline weight.

A decrease in body weight of ≥ 20% compared to Baseline was reported in 1.2% of the patients in both the prevalent users cohort and in the non-exposed to ruxolitinib cohort, and 1.8% of the patients in the switch to ruxolitinib cohort. An increase in body weight of ≥ 20% compared to Baseline was reported in 1.5% of the patients in the prevalent users cohort, 3.1% in the new users cohort, and 5.3% in the switch to ruxolitinib cohort (Table 14.3-1.8.1).

Few patients had decreased weight compared to Baseline in all cohorts. A shift from normal to decreased (low) weight was observed in 8.2% of the patients in the prevalent users cohort, 6.3% in the new users cohort, 5.3% of the patients in the switch to ruxolitinib cohort and 4.8% in the

non-exposed to ruxolitinib cohort. None of the patients in any of the cohorts had increased weight compared to the Baseline except 2.4% of the patients in the non-exposed to ruxolitinib cohort (Table 14.3-1.8.2).

10.5.2.7 Events of special interest

The following EoSI were considered for the analysis:

- Bleeding events
- Serious and opportunistic infections
- Death due to any cause
- Secondary malignancy

Bleeding events

Bleeding events were reported in 40.2% in the prevalent users cohort, 31.3% in the new users cohort, 21.6% in the non-exposed to ruxolitinib cohort, and 35.1% in the switch to ruxolitinib cohort and (Table 10-15).

Further details on the different bleeding events are discussed below:

Bruising

- Bruising events were reported in 20.8% of the patients in the prevalent users cohort (22.2% of the long term users cohort; 17.7% in the short term users cohort), 15.6% in the new users cohort, 4.2% in the non-exposed to ruxolitinib cohort, and 15.8% in the switch to ruxolitinib cohort. The most frequently (at least 5% in any of the cohorts) reported bruising events in the prevalent users cohort, in the new users cohort, in the non-exposed to ruxolitinib cohort, and in the switch to ruxolitinib cohort included: hematoma (11.6% vs 9.4% vs 1.8% vs 12.3%) and contusion (5.4% vs 6.3% vs 0.6% vs 1.8%). All the other bruising events were reported in ≤ 3% of the patients in any of the cohorts (Table 10-15 and Table 14.3.1-2.1.3).

GI bleeding

- GI bleeding events were reported in 6.9% of the patients in the prevalent users cohort, 3.1% in the new users cohort, 4.2% in the non-exposed to ruxolitinib cohort, and 5.3% in the switch to ruxolitinib cohort. The most frequently reported GI bleeding events included GI haemorrhage (1.9%), and rectal haemorrhage (1.5%) in the prevalent users cohort (both in long term users cohort and none in short term users cohort), rectal haemorrhage (1.2%) in the non-exposed to ruxolitinib cohort and haematochezia (3.5%) in the switch to ruxolitinib cohort. Rectal haemorrhage (1 patient, 3.1%) was the only GI bleeding event reported in the new users cohort (Table 10-15 and Table 14.3.1-2.1.3).

Intracranial haemorrhage

- Among the bleeding events, intracranial haemorrhage events were reported in the lowest proportion of the patients in all the cohorts. These events were reported in 1.5% of the patients in the prevalent users cohort (2.2% long-term vs 0% short term), 3.1% in the new users cohort, 3% in the non-exposed to ruxolitinib cohort, and none in the switch to ruxolitinib cohort. Cerebral haemorrhage and subdural haematoma were the only events

[redacted]

reported in at least 1% of the patients in all the cohorts (Table 10-15 and Table 14.3.1-2.1.3).

Other haemorrhage events

- Hemorrhage-related events were reported in 29.3% of the patients in the prevalent users cohort (30% long-term; 27.8% short-term users), and 28.1% of the switch to ruxolitinib cohort. The most frequently (at least in 5% in any cohort) reported other haemorrhage-related event was epistaxis. None of the other haemorrhage events were reported in ≥ 4% of the patients in any cohort (Table 10-15 and Table 14.3.1-2.1.3).

Serious and opportunistic infections

Overall, infections were reported in 62.2% of the patients in the prevalent users cohort (67.8% long-term users and 49.4% short-term users), 65.6% in the new users cohort, 27.5% in the non-exposed to ruxolitinib cohort, and 56.1% in the switch to ruxolitinib cohort (Table 10-15).

Further details on different subgroups of infections are discussed below:

Herpes zoster

- Herper zoster related events were reported in 8.5% of the patients in the prevalent users cohort (9.4% long-term and 6.3% of the short-term), 12.5% in the new users cohort, 0.6% in the non-exposed to ruxolitinib cohort, 7% in the switch to ruxolitinib cohort. The most frequently reported herpes zoster-related event was ‘herpes zoster’ (7.7% of the patients in the prevalent users cohort, 12.5% in the new users cohort, 0.6% in the non-exposed to ruxolitinib cohort, and 5.3% in the switch to ruxolitinib cohort) (Table 10-15 and Table 14.3.1-2.1.3).

Urinary tract infections

- UTIs were reported in 15.4% of the patients in the prevalent users cohort (16.1% long-term users and 13.9% short-term users), 18.8% in the new users cohort, 4.8% in the non-exposed to ruxolitinib cohort, and 10.5% in the switch to ruxolitinib cohort. The most frequently reported UTI-related events in the prevalent users cohort, in the new users cohort, in the non-exposed to ruxolitinib cohort, and in the switch to ruxolitinib cohort was ‘urinary tract infection’ (13.1% vs 12.5% vs 3% vs 7%) and cystitis (1.9% vs 3.1 vs 1.2% vs 5.3%) (Table 10-15 and Table 14.3.1-2.1.3).

Tuberculosis

- Tuberculosis was reported in 1 patient (0.4%) in the prevalent users cohort (none in the long-term users and 1 patient (1.3%) in the short-term users) and in 1 patient (1.8%) in the switch to ruxolitinib cohort (Table 10-15).

Pneumonia

- 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

[redacted]

6.3% vs 0% vs 3.5%) and lower respiratory tract infection (2.3% vs 0% vs 0.6% vs 7%) (Table 10-15 and Table 14.3.1-2.1.3).

Sepsis and septic shock

- 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 sepsis and septic shock-related events in the prevalent users cohort, the new users cohort, the non-exposed to ruxolitinib cohort and the switch to ruxolitinib cohort was sepsis (5.4% vs 0% vs 1.8% vs 1.8%) and septic shock (1.5% vs 3.1% vs 1.8% vs 0%) (Table 10-15 and Table 14.3.1-2.1.3).

Opportunistic infections

- 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 (Table 10-15).

Other infections

- 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 (Table 10-15).
- 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% 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 (Table 10-15 and Table 14.3.1-2.1.3).

Death due to any cause

Sixty-seven deaths in the prevalent users cohort (49 in the long-term users and 18 in the short-term users), 7 deaths were reported in the new users cohort, 32 deaths in the non-exposed to ruxolitinib cohort, and 12 deaths in the switch to ruxolitinib cohort (Table 10-15).

Table 10-15 Summary of treatment-emergent adverse events by category of special interest and cohort (Safety set modified)

	Prevalent users					
Category of events of special interest Sub-category	**Long Term N = 180 n (%)**	**Short Term N = 79 n (%)**	**Total N = 259 n (%)**	**New users N = 32 n (%)**	**Non-Exposed[1] N = 167 n (%)**	**Switch to Ruxo[2] N = 57 n (%)**
Patients with any event of special interest	**144 (80.0)**	**51 (64.6)**	**195 (75.3)**	**25 (78.1)**	**72 (43.1)**	**40 (70.2)**
Bleeding event	**74 (41.1)**	**30 (38.0)**	**104 (40.2)**	**10 (31.3)**	**36 (21.6)**	**20 (35.1)**
Bruising	40 (22.2)	14 (17.7)	54 (20.8)	5 (15.6)	7 (4.2)	9 (15.8)

[redacted]

	Prevalent users					
Category of events of special interest **Sub-category**	**Long Term N = 180 n (%)**	**Short Term N = 79 n (%)**	**Total N = 259 n (%)**	**New users N = 32 n (%)**	**Non-Exposed[1] N = 167 n (%)**	**Switch to Ruxo[2] N = 57 n (%)**
GI bleeding	15 (8.3)	3 (3.8)	18 (6.9)	1 (3.1)	7 (4.2)	3 (5.3)
Intracranial haemorrhage	4 (2.2)	0	4 (1.5)	1 (3.1)	5 (3.0)	0
Other haemorrhage events	54 (30.0)	22 (27.8)	76 (29.3)	4 (12.5)	24 (14.4)	16 (28.1)
Serious and opportunistic infection[3]	**122 (67.8)**	**39 (49.4)**	**161 (62.2)**	**21 (65.6)**	**46 (27.5)**	**32 (56.1)**
Herpes zoster	17 (9.4)	5 (6.3)	22 (8.5)	4 (12.5)	1 (0.6)	4 (7.0)
Urinary tract infections	29 (16.1)	11 (13.9)	40 (15.4)	6 (18.8)	8 (4.8)	6 (10.5)
Tuberculosis	0	1 (1.3)	1 (0.4)	0	0	1 (1.8)
Pneumonia	32 (17.8)	12 (15.2)	44 (17.0)	3 (9.4)	16 (9.6)	12 (21.1)
Sepsis and septic shock	22 (12.2)	6 (7.6)	28 (10.8)	2 (6.3)	11 (6.6)	1 (1.8)
Opportunistic infections	7 (3.9)	0	7 (2.7)	0	0	1 (1.8)
Other infections	86 (47.8)	30 (38.0)	116 (44.8)	13 (40.6)	29 (17.4)	21 (36.8)
Malignancies	49 (27.2)	15 (19.0)	64 (24.7)	5 (15.6)	11 (6.6)	8 (14.0)
Non melanoma skin cancer	20 (11.1)	5 (6.3)	25 (9.7)	3 (9.4)	0	3 (5.3)
Death due to any cause	**49 (27.2)**	**18 (22.8)**	**67 (25.9)**	**7 (21.9)**	**32 (19.2)**	**12 (21.1)**

- For patients who switched to ruxolitinib during the study, events before switch are presented in the 'Non- exposed' column and events after switch are presented in the 'Switch to Ruxo' column.
- A patient with multiple occurrences of an EOSI is counted only once in the EOSI category or sub-category.
- [1] N is the number of patients non-exposed to study drug at the time of enrollment (including switchers).
- [2] N is the number of patients who switched to ruxolitinib during the study.
- [3] includes all infections

Source: Table 14.3.1-2.1.3

Secondary malignancy

Any malignancy event reported during the study was considered as secondary malignancy. Secondary malignancies were reported in a higher proportion of patients in the prevalent users cohort, followed by the new users cohort, switch to ruxolitinib cohort, and non-exposed to ruxolitinib cohort (24.7% vs 15.6% vs 14% vs 6.6%) (Table 10-16).

These secondary malignancies were sub-classified into solid tumors (non-melanoma skin cancers (NMSCs) and other solid tumors) and hematological malignancies (AML and other hematological malignancies) and analysed below. Since NMSC is a documented potential risk with ruxolitinib and AML related events are considered progression of the underlying MF, they were separately analysed. In addition, lymphomas seen only in the prevalent cohort were further evaluated.

Secondary malignancy subcategories of events are discussed below:

Non-melanoma skin cancers

- Non-melanoma skin cancers were reported in 9.7% of the patients in the prevalent users cohort (11.1% long-term users and 6.3% short-term users), 9.4% in the new users cohort, 5.3% in the switch to ruxolitinib cohort, and none in the non-exposed to ruxolitinib cohort. The most frequently reported NMSC-related malignancies (at least 5% of the patients in

[redacted]

any of the cohort) in the prevalent users cohort, new users cohort, non-exposed to ruxolitinib cohort, and switch to ruxolitinib cohort included: basal cell carcinoma (6.6% vs 3.1% vs 0% vs 1.8%) and squamous cell carcinoma (4.2% vs 3.1% vs 0% vs 5.3%) (Table 10-16 and Table 14.3.1-2.1.3a).

Other solid tumors (solid tumors excluding NMSCs)

- Other solid tumors were reported in 6.9% of the patients in the prevalent users cohort (8.9% long-term users and 2.5% short-term users), 3.1% in the new users cohort, 3% in the non-exposed to ruxolitinib cohort, and 3.5% in the switch to ruxolitinib cohort. Except squamous cell carcinoma of the tongue (reported in 3 prevalent users), colon cancer (reported in 2 prevalent users), no other solid tumor malignancy was reported in more than 1 patient in any cohort (Table 10-16 and Table 14.3.1-2.1.3a).

Acute myeloid leukaemia

- AML-related events or events suggestive of leukemic transformation were reported in 6.6% of the patients in the prevalent users cohort (6.1% long-term users and 7.6% short term users), 3.1% in the new users cohort, 2.4% in the non-exposed to ruxolitinib cohort and 5.3% in the switch to ruxolitinib cohort (Table 10-16 and Table 14.3.1-2.1.3a).

Other hematological malignancies (hematological malignancies excluding AML)

- Other hematological malignancies were reported in 3.1% of the patients in the prevalent users cohort (3.3% long-term users and 2.5% short-term users), 3.1% of the new users cohort, 1.2% of the non-exposed to ruxolitinib cohort, and none in the switch to ruxolitinib cohort (Table 10-16 and Table 14.3.1-2.1.3a).

Lymphomas

- Lymphomas (subgroup of other hematological malignancies) were reported in 5 patients in the prevalent users cohort (3 patients in long term users and 2 patients in short term users). Lymphomas were not reported for patients in the other cohorts. Diffuse large B-cell lymphoma was reported in 2 patients in the short-term users cohort and in 1 patient in long-term users Cohort, while B-cell small lymphocytic lymphoma, and mycosis fungoides were each reported in 1 patient in the long-term users cohort (Table 10-16 and Table 14.3.1-2.1.3a).

Table 10-16 Summary of secondary malignancy by cohort (Safety set modified)

	Prevalent users					
Category of malignant tumor Sub-category	Long Term N = 180 n (%)	Short Term N = 79 n (%)	Total N = 259 n (%)	New users N = 32 n (%)	Non-Exposed[1] N = 167 n (%)	Switch to Ruxo[2] N = 57 n (%)
Patient with any malignant tumor	**49 (27.2)**	**15 (19.0)**	**64 (24.7)**	**5 (15.6)**	**11 (6.6)**	**8 (14.0)**
Solid tumors	**34 (18.9)**	**7 (8.9)**	**41 (15.8)**	**4 (12.5)**	**5 (3.0)**	**5 (8.8)**
Non melanoma skin cancers (NMSC)	20 (11.1)	5 (6.3)	25 (9.7)	3 (9.4)	0	3 (5.3)
Other solid tumors	16 (8.9)	2 (2.5)	18 (6.9)	1 (3.1)	5 (3.0)	2 (3.5)
Hematological malignancies	**16 (8.9)**	**8 (10.1)**	**24 (9.3)**	**2 (6.3)**	**6 (3.6)**	**3 (5.3)**

[redacted]

Category of malignant tumor Sub-category	Prevalent users: Long Term N = 180 n (%)	Prevalent users: Short Term N = 79 n (%)	Prevalent users: Total N = 259 n (%)	New users N = 32 n (%)	Non-Exposed[1] N = 167 n (%)	Switch to Ruxo[2] N = 57 n (%)
Acute myeloid leukaemia (AML)	11 (6.1)	6 (7.6)	17 (6.6)	1 (3.1)	4 (2.4)	3 (5.3)
Other hematological malignancies	6 (3.3)	2 (2.5)	8 (3.1)	1 (3.1)	2 (1.2)	0
Lymphomas	3 (1.7)	2 (2.5)	5 (1.9)	0	0	0

- For patients who switched to ruxolitinib during the study, events before switch are presented in the 'Non- exposed' column and events after switch are presented in the 'Switch to Ruxo' column.
- A patient with multiple occurrences of an EOSI is counted only once in the EOSI category or sub-category.
- [1] N is the number of patients non-exposed to study drug at the time of enrollment (including switchers).
- [2] N is the number of patients who switched to ruxolitinib during the study.
Source: Table 14.3.1-2.1.3a

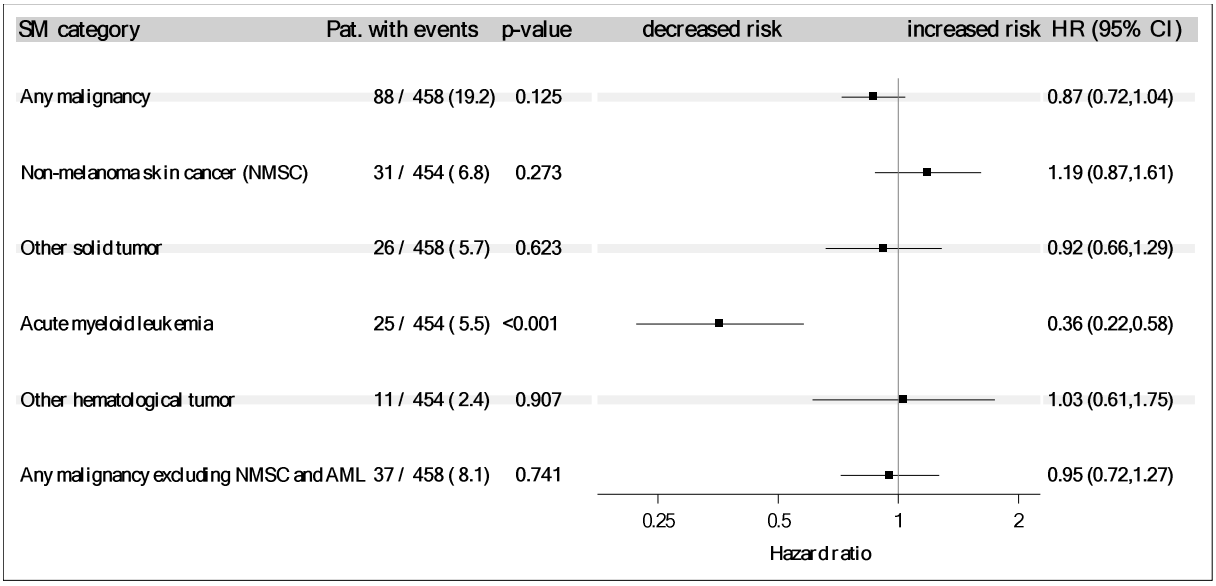
Considering the lower rates of secondary malignancies in some cohorts such as the non-exposed cohort and to evaluate the role of ruxolitinib in these events, an exploratory analyses (not planned in the SAP) was carried out using multivariate cox-regression model.

An exploratory multivariate cox regression models of time to first secondary malignancy event was carried out including variables to adjust for differences in duration of ruxolitinib treatment and imbalances in the Baseline characteristics or other risk factors (e.g. prior malignant tumors) that might impact secondary malignancies. The overall exposure to ruxolitinib prior and during the study has been considered in the model. Separate cox regression models have been done for the different subcategories of secondary malignancies. The hazard ratios for the overall duration of ruxolitinib therapy from the cox regression models for these different subcategories are displayed in Figure 10-1.

Differences in duration of ruxolitinib treatment

Patients treated with ruxolitinib were at a lower risk for AML (HR: 0.36; 95% CI: 0.22 to 0.58; $p < 0.001$) and tended to be at a higher risk for NMSCs (HR: 1.19 (95% CI: 0.87 to 1.61; $p = 0.273$). Ruxolitinib did not appear to have an impact on other malignancies such as other solid tumors, or other hematological tumors (Figure 10-1). For these categories of secondary malignancies the analyses showed a correlation between both longer prior or concomitant hydroxyurea (HU) exposure and history of malignancies and increased risk of secondary malignancies.

Figure 10-1 Forest plot on the impact of duration of ruxolitinib therapy on different categories of secondary malignancy (Safety set modified)



Displayed are the hazard ratios for the risk of malignancy associated with each additional year of treatment with ruxolitinib (based on total duration of exposure to prior and during the study)

Source: Figure 14.3.1-1

Prior malignant tumors

Prior malignant tumors were reported already in a substantial number of patients: in higher percentage of patients in the new users (21.9%) followed by the long term prevalent users (20.0%), short term prevalent users (16.5%), non-exposed to ruxolitinib cohort (13.6%), and switch to ruxolitinib cohort (12.3%). The most frequent prior malignancies included prostate cancer, basal cell carcinoma, and squamous cell carcinoma (Table 14.3.1-3.1.2).

Prior or concomitant therapies that may cause malignant tumors

The number of patients with secondary malignancies was higher in patients who had prior HU exposure than those without prior HU exposure in the prevalent users (33.6 vs 15.2%) and non-exposed to ruxolitinib cohort (8% vs. 5%). However, in the new users cohort (10% vs 18.2%) and switch to ruxolitinib cohort (12.9% vs 15.4%), patients who had prior exposure to HU reported fewer malignancy events compared to those who did not have prior exposure to HU (Table 14.3.1-2.1.3b). Similar results were reported with respect to the exposure-adjusted incidence rates (Table 14.3.1-2.2.3b).

Separate cox regression models have been used for the different subcategories of secondary malignancies.

Non-melanoma skin cancers

- Cox-regression model analysis revealed that apart from age and gender, type of MF (increased risk for post PV-MF), prior history of malignancy especially prior NMSC were important risk factors for secondary malignancies of NMSC (Table 14.3.1-3.2.2).

Other solid tumors

[redacted]

- From the Cox-regression model analysis, prior exposure to HU and prior history of malignancies were the primary risk factors which were considered to be significant. Exposure to ruxolitinib was not a significant risk factor for the cause of other solid tumors (Table 14.3.1-3.2.3).

Acute myeloid leukaemia

- From the Cox-regression model analysis, prior or concomitant exposure to HU was the significant risk factor. Male patients also seems to have an increased risk of AML (Table 14.3.1-3.2.4).

Other hematological malignancies

- In the cox regression model analysis, prior or concomitant exposure to HU was one of the important risk factors for other hematological malignancies but it was not statistically significant. No other parameter was statistically significant probably due to the low number (only 11) of events (Table 14.3.1-3.2.5).

Lymphomas:

- Lymphoma events (subset of other hematological malignancies) were too few for a reasonable cox regression model. No parameter was significant in the model.

The interpretation of the exploratory cox-regression models should be performed with caution as the number of patients and events are very few and the collection of the data is different in non-interventional studies (NIS) than in Phase 3 trials. There may be also a selection bias in regards to risk for AML, since in the prevalent users cohort only those patients were enrolled who were on ruxolitinib treatment for a while without developing an AML.

The 5 lymphoma cases are discussed below:

- Patient [redacted], a [redacted]-year old [redacted] was diagnosed with diffuse large B-cell lymphoma of right [redacted] (grade 3) during the study. Relevant medical history included hysterectomy, [redacted] conserving surgery, mass excision, varicose vein operation, and splenomegaly. Prior medications for MF included fedratinib, hydroxycarbamide, and ruxolitinib phosphate. The patient was exposed to the study drug for a duration of 21 months. Diffuse large B-cell lymphoma resolved on Day 288. The investigator did not suspect a relationship between the event and the study medication.
- Patient [redacted] entered the study on [redacted] (Day 1) with primary MF diagnosed in [redacted]. Prior medication for MF included ruxolitinib phosphate. No relevant malignancy medical history was reported. The patient was exposed to the study drug for a duration of 39 months. The patient developed diffuse large B cell lymphoma in oral cavity (grade 2) and was treated with rituximab and combinations of antineoplastic agents. No action was taken with the study medication and the event resolved on Day 472. The investigator did not suspect a relationship between the event and the study medication.
- Patient [redacted] entered the study on [redacted] (Day 1) with primary MF diagnosed in [redacted]. No relevant malignancy medical history was reported. Prior medications for MF included ruxolitinib phosphate, hydroxycarbamide, and anagrelide hydrochloride. The patient was exposed to the

[redacted]

study drug for a duration of 47.2 months. The patient developed diffuse large B-cell lymphoma (grade 3), which led to hospitalization. The patient was treated with cyclophosphamide doxorubicin and no action was taken with the study medication. The Investigator suspected a relationship between the event and the study medication.

- Patient [redacted] entered the study on [redacted] (Day 1) with primary MF diagnosed in [redacted]. Relevant malignancy medical history included chronic lymphocytic leukemia, neoplasm prostate, and lymphoma. Prior medications for MF included hydroxycarbamide and ruxolitinib. On Day 658, the patient was hospitalized with the diagnosis of small B cell lymphocytic lymphoma (grade 3) and was treated with clindamycin hydrochloride. No action was taken with the study medication due to the event. The event (B cell small lymphocytic lymphoma) resolved with sequelae on Day 1240. The Investigator did not suspect a relationship between the event and study medication.
- The patient [redacted] entered the study on [redacted] (Day 1) with primary MF diagnosed in [redacted]. Prior medications for MF included ruxolitinib. No relevant malignancy medical history was reported for this patient. The patient was exposed to the study drug for 34.1 months. The patient developed cutaneous T cell lymphoma (grade 2) on Day 291 and was treated with mometasone furoate and received radiotherapy to skin. No action was taken with the study medication and the event resolved on Day 939. The Investigator did not suspect a relationship between the event and the study medication. This case did not meet the criteria for narratives.

Please refer to Section 14.3.3 for detailed narratives on EoSI.

10.5.3 Laboratory data

10.5.3.1 Hematology

Notable shifts in the hematology parameters reported across all the cohorts are provided below:

- **Decreased hemoglobin (anemia)**: A shift from grade 1 to grade 3 was observed in 15% of the patients in the prevalent users cohort (13% long-term users and 20% short-term users), 20% in the new users cohort, and 15.4% in the switch to ruxolitinib cohort. A shift from grade 2 to grade 3 was observed in 47.1% of the patients in the prevalent users cohort (48.3% long-term users and 44.8% short-term users), 54.5% in the switch to ruxolitinib cohort, and 28.6% in the new users cohort (Table 14.3-1.6.1).
- **Decreased lymphocyte count**: A shift from grade 0 to grade 4 was observed in 10.3% of the patients in the prevalent users cohort (10.2% long-term users and 10.4% short-term users) and 12.5% in the new users cohort. A shift from grade 2 to grade 4 was observed in 22.2% in the prevalent users cohort (26.7% long-term users) and 25% in the switch to ruxolitinib cohort (Table 14.3-1.6.1).
- **Decreased neutrophil count**: A shift from grade 0 to grade 4 was observed in 10.6% of the patients in the prevalent users cohort (10% long-term users and 12.1% short-term users). A shift from grade 1 to grade 4 was observed in 15.4% of the patients in the prevalent users cohort (12.5% long-term users and 20% short-term users), and 33.3% of the patients in the switch to ruxolitinib cohort (Table 14.3-1.6.1).

[redacted]

- **Decreased platelet count**: A shift from grade 0 to grade 4 was observed in 7.9% of the patients in the prevalent users cohort (6.9% long-term users and 10.8% short-term users), and 6.7% in the switch to ruxolitinib cohort. A shift from grade 2 to grade 4 was observed in 26.9% of the patients in the prevalent users (26.7% long-term users and 27.3% short term users) (Table 14.3-1.6.1).
- **Decreased white blood cell count**: A shift from grade 0 grade 4 was observed in 5.8% of the patients in the prevalent users cohort (4.5% long-term users and 8.6% short-term users), 3.2% in the new users cohort, and 2.7% in the switch to ruxolitinib cohort. A shift from grade 1 to grade 4 was observed in 17.6% of the patients in the prevalent users cohort (23.1% long-term users) (Table 14.3-1.6.1).

Notable shifts in the following hematology parameters had a positive impact on patients' health:

- **Hemoglobin increased**: A shift from grade 0 to grade 3 was observed in 1.6% of the patients in the prevalent users cohort (1.1% long-term users and 2.6% short term users). None of the patients in other cohorts had a shift from grade 0 to grade 2 and above (Table 14.3-1.6.1).
- **Increased lymphocyte count**: A shift from grade 0 to grade 3 was observed in 2.4% of the patients in the prevalent users cohort (1.3% long-term users and 4.9% short-term users), and 7.4% in the new users cohort (Table 14.3-1.6.1).

10.5.3.2 Biochemistry

For majority of the biochemistry parameters, no patient had a shift from grade 0 to grade 4. However, 1 patient in the short-term users cohort had a worst shift from grade 0 to grade 4 in increased alanine aminotransferase, and increased aspartate aminotransferase; whereas 2 patients in the short-term users cohort, 1 patient in the new users cohort, and 1 patient in the switch to ruxolitinib cohort had a shift from grade 0 to grade 4 in increased creatinine (Table 14.3-1.6.2).

In the prevalent users cohort, 1.3% of the patients (1.9% long-term users) had increased alanine aminotransferase, 0.8% (2.7% short-term users) had increased aspartate aminotransferase, 1.4% (3.9% short-term users) had creatinine increased and 0.6% (1% long-term users) had increased total bilirubin. All these increases were a shift from grade 0 to grade 3. For majority of the patients, the Baseline alkaline phosphatase was grade 0. Increased alkaline phosphatase had a shift from grade 0 to grade 3 in 1.2% of the patients in the prevalent users cohort (4.3% short-term users) and 4.3% of the patients in the switch to ruxolitinib cohort (Table 14.3-1.6.2).

10.6 Other analyses

Not applicable.

10.7 Adverse events/adverse reactions

10.7.1 Overview of treatment-emergent adverse events

The frequency of treatment-emergent AEs and other AE categories (EoSI, ADRs, SAEs, and grade 3/4 AEs) were comparable across all ruxolitinib exposed cohorts. Grade 3/4 ADRs were reported in a slightly higher proportion in the switch to ruxolitinib cohort (31.6%) than in other

[redacted]

cohorts. Study treatment discontinuation due to AE was seen in few patients across all cohorts except in the switch to ruxolitinib cohort (12.3%) where it was slightly increased compared to other cohorts (Table 10-17).

In patients in the non-exposed to ruxolitinib cohort, where only EoSI were collected, the frequency of AEs were reported in a lower frequency. It should be noted that these patients had a lower risk MF compared to other cohorts. This may be explained due to the fact that the majority of adverse effects due to ruxolitinib treatment tend to occur at a higher frequency during the initial period of exposure. Patients who switched to ruxolitinib had shorter duration of exposure to ruxolitinib in the study and might have experienced greater frequency of ADRs.

As expected, a lower proportion of the patients in the non-exposed cohort reported EoSI, compared to the patients in the other cohorts as they did not receive ruxolitinib during the study. According to the protocol only EoSI had to be reported for the patients in the non-exposed to ruxolitinib cohort. However, other events were also reported and are displayed here for reasons of completeness.

Table 10-17 Summary of treatment-emergent adverse events by cohort (safety set modified)

	Prevalent users					
Patients with at least one	**Long Term N = 180 n (%)**	**Short Term N = 79 n (%)**	**Total N = 259 n (%)**	**New users N = 32 n (%)**	**Non-Exposed[1] N = 167 n (%)**	**Switch to Ruxo[2] N = 57 n (%)**
Adverse event[3]	161 (89.4)	65 (82.3)	226 (87.3)	29 (90.6)	93 (55.7)	50 (87.7)
Event of special interest	144 (80.0)	51 (64.6)	195 (75.3)	25 (78.1)	72 (43.1)	40 (70.2)
Adverse drug reaction	91 (50.6)	34 (43.0)	125 (48.3)	13 (40.6)	1 (0.6)	31 (54.4)
Serious adverse event	115 (63.9)	44 (55.7)	159 (61.4)	17 (53.1)	8 (4.8)	27 (47.4)
Grade 3/4 adverse event[3]	113 (62.8)	45 (57.0)	158 (61.0)	17 (53.1)	53 (31.7)	38 (66.7)
Grade 3/4 adverse drug reaction	44 (24.4)	18 (22.8)	62 (23.9)	7 (21.9)	-	18 (31.6)
Adverse event leading to study treatment discontinuation[3]	12 (6.7)	6 (7.6)	18 (6.9)	2 (6.3)	-	7 (12.3)
Adverse event leading to dose adjustment[3]	44 (24.4)	18 (22.8)	62 (23.9)	8 (25.0)	2 (1.2)	16 (28.1)

Two patients ([redacted]) who switched to ruxolitinib had events that started before, but continued under ruxolitinib therapy and led finally to a dose administration.
- For patients who switched to ruxolitinib during the study, events before switch are presented in the Non-exposed' column and events after switch are presented in the 'Switch to ruxolitinib' column.
- [1] N is the number of patients non-exposed to study drug at the time of enrollment (including switchers). Two patients ([redacted]) who switched to Ruxo had events that started before, but continued under ruxolitinib therapy and led finally to a dose adjustment.
- [2] N is the number of patients who switched to ruxolitinib during the study.
- [3] Only EoSI, ADRs, SAEs were collected acc. to protocol, whereas for non-exposed, only AEs of special interest were collected.
Source: Table 14.3.1-1.1.1

[redacted]

10.7.2 Deaths

10.7.2.1 All deaths

Ninety-two patients (35.5%) in the prevalent users cohort (61 in the long-term users, 33.9% and 31 in the short-term users, 39.2%), 32 patients (19.2%) in the non-exposed to ruxolitinib cohort, 16 patients (28.1%) in the switch to ruxolitinib cohort, and 9 patients (28.1%) in the new user cohort died (Table 14.3.1-2.4.1).

In some cases, no cause of death was provided. The most frequently reported reasons that led to the death of the patients in all the cohorts are as follows:

Prevalent users cohort: Death due to unspecified cause (13 patients, 5%), MF (12 patients, 4.6%), MPN (7 patients, 2.7%), sepsis (6 patients, 2.3%), multiple organ dysfunction syndrome (5 patients, 1.9%), and pneumonia (3 patients, 1.2%).

New users cohort: cardiac arrest, ventricular tachycardia, pneumonia, septic shock, enteritis infectious, subdural hematoma, neck injury, squamous cell carcinoma, and acute respiratory distress syndrome (each 1 patient, 3.1%) (Table 14.3.1-2.4.1).

Non-exposed to ruxolitinib cohort: Sepsis (3 patients, 1.8%), death due to unspecified cause, multiple organ dysfunction syndrome, graft versus host disease, and AML (each 2 patients, 1.2%), and MF (1 patient, 0.6%).

Switch to ruxolitinib cohort: MF (5 patients, 8.8%), death due to unspecified cause, and AML (each in 2 patients, 3.5%).

Please refer to Section 14.3.3 for detailed narratives on deaths.

10.7.2.2 On-treatment deaths

On-treatment deaths were reported in 67 patients in the prevalent users cohort (25.9%) (49 long-term users, 27.2% and 18 short-term users, 22.8%), 12 patients (21.1%) in the switch to ruxolitinib cohort and 7 patients (21.9%) in the new users cohort (Table 10-18).

The most frequently reported reasons that led to the death of the patients included:

Prevalent users cohort (for at least 3 patients): death due to unspecified cause (9 patients, 3.5%), MF and MPN (6 patients each, 2.3%), sepsis (5 patients, 1.9%), and multiple organ dysfunction syndrome (3 patients, 1.2%).

New users cohort (for at least 1 patient): pneumonia, septic shock, subdural hematoma, neck injury, cardiac arrest, ventricular tachycardia and squamous cell carcinoma (each 3.1%).

Switch to ruxolitinib cohort (for at least one patient): Three deaths (5.3%) due to MF, 2 deaths (3.5%) due to unspecified cause, 2 deaths (3.5%) due to AML, and 1 death (1.8%) each due to sepsis, pneumonia, general physical health deterioration, intestinal infarction, and squamous cell carcinoma (Table 10-18).

Please refer to Section 14.3.3 for detailed narratives on deaths.

[redacted]

Table 10-18 On-treatment deaths, by preferred term and cohort (Safety set)

	Prevalent users				
Preferred term	Long term N=180 n (%)	Short term N=79 n (%)	Total N=259 n (%)	New users N=32 n (%)	Switch to Ruxo* N=57 n (%)
All on-treatment deaths	**49 (27.2)**	**18 (22.8)**	**67 (25.9)**	**7 (21.9)**	**12 (21.1)**
Death	6 (3.3)	3 (3.8)	9 (3.5)	0	2 (3.5)
Myelofibrosis	3 (1.7)	3 (3.8)	6 (2.3)	0	3 (5.3)
Myeloproliferative neoplasm	6 (3.3)	0	6 (2.3)	0	0
Sepsis	3 (1.7)	2 (2.5)	5 (1.9)	0	1 (1.8)
Multiple organ dysfunction syndrome	2 (1.1)	1 (1.3)	3 (1.2)	0	0
Cardiopulmonary failure	1 (0.6)	1 (1.3)	2 (0.8)	0	0
Pneumonia	2 (1.1)	0	2 (0.8)	1 (3.1)	1 (1.8)
Sudden death	1 (0.6)	1 (1.3)	2 (0.8)	0	0
Septic shock	1 (0.6)	1 (1.3)	2 (0.8)	1 (3.1)	0
Transformation to acute myeloid leukaemia	2 (1.1)	0	2 (0.8)	0	0
Myocardial infarction	1 (0.6)	0	1 (0.4)	0	0
Disseminated intravascular coagulation	1 (0.6)	0	1 (0.4)	0	0
Gastrointestinal haemorrhage	1 (0.6)	0	1 (0.4)	0	0
Intestinal perforation	0	1 (1.3)	1 (0.4)	0	0
General physical health deterioration	0	1 (1.3)	1 (0.4)	0	1 (1.8)
Graft versus host disease	1 (0.6)	0	1 (0.4)	0	0
Mycobacterium avium complex infection	1 (0.6)	0	1 (0.4)	0	0
Neutropenic sepsis	1 (0.6)	0	1 (0.4)	0	0
Pneumococcal sepsis	1 (0.6)	0	1 (0.4)	0	0
Pneumonia respiratory syncytial viral	1 (0.6)	0	1 (0.4)	0	0
Subdural haematoma	1 (0.6)	0	1 (0.4)	1 (3.1)	0
Transfusion-related acute lung injury	1 (0.6)	0	1 (0.4)	0	0
Traumatic intracranial haemorrhage	1 (0.6)	0	1 (0.4)	0	0
Acute leukaemia	1 (0.6)	0	1 (0.4)	0	0
Blast cell crisis	0	1 (1.3)	1 (0.4)	0	0
Bronchial carcinoma	1 (0.6)	0	1 (0.4)	0	0
Endometrial cancer	1 (0.6)	0	1 (0.4)	0	0
Gastrointestinal cancer metastatic	1 (0.6)	0	1 (0.4)	0	0
Leukaemia	1 (0.6)	0	1 (0.4)	0	0
Metastases to lymph nodes	1 (0.6)	0	1 (0.4)	0	0
Myelodysplastic syndrome transformation	1 (0.6)	0	1 (0.4)	0	0
Pancreatic carcinoma metastatic	0	1 (1.3)	1 (0.4)	0	0
Primary myelofibrosis	1 (0.6)	0	1 (0.4)	0	0
Dementia	0	1 (1.3)	1 (0.4)	0	0
End stage renal disease	1 (0.6)	0	1 (0.4)	0	0
Acute pulmonary oedema	1 (0.6)	0	1 (0.4)	0	0
Lung disorder	0	1 (1.3)	1 (0.4)	0	0
Pulmonary oedema	1 (0.6)	0	1 (0.4)	0	0
Acute myeloid leukaemia	0	0	0	0	2 (3.5)
Neck injury	0	0	0	1 (3.1)	0
Intestinal infarction	0	0	0	0	1 (1.8)

	Prevalent users				
Preferred term	Long term N=180 n (%)	Short term N=79 n (%)	Total N=259 n (%)	New users N=32 n (%)	Switch to Ruxo* N=57 n (%)
Intestinal infarction	0	0	0	0	1 (1.8)
Cardiac arrest	0	0	0	1 (3.1)	0
Ventricular tachycardia	0	0	0	1 (3.1)	0
Squamous cell carcinoma	0	0	0	1 (3.1)	1 (1.8)

Preferred terms are sorted in descending frequency, as reported in the Prevalent users (Total) column.
- * N is the number of patients who switched to ruxolitinib during the study.
Source: Table 14.3.1-2.4.2

11 Discussion

11.1 Key results

This was a non-interventional, observational study conducted to provide real-world safety data of patients with MF exposed and non-exposed to ruxolitinib within 2 years, and followed for at least 3 years, and thereby to provide insights on the disease management and long-term safety profile of ruxolitinib. According to the protocol only EoSI were to be collected for the patients in the non-exposed to ruxolitinib cohort. In general, ADRs and SAEs were collected regularly in all the other cohorts.

Patient demographics and Baseline disease characteristics were representative of a population of patients with MF, the majority of them with primary MF. The median age ranged between 68 and 72.5 among all the cohorts (range: 21 to 92 years). The risk stratification of MF in most of the patients in all the cohorts was intermediate -1 or -2 risk. A higher proportion of the patients in the new users cohort were in the high risk category while a higher proportion of the patients in the non-exposed cohort were in the lower risk category compared to the other cohorts. A higher proportion of the patients in the switch to ruxolitinib cohort were at intermediate-2 risk category compared to the patients in the non-exposed cohort.

Deaths and administrative problems were the primary reasons for a majority of the patients to discontinue from the study. The most common reasons that led to death included the progression of the underlying MF disease, sepsis, AML, pneumonia, and general disorder death. Deaths were reported in a slightly higher proportion in the prevalent users cohort compared to the other cohorts and this might be attributed to the progression of the underlying long standing disease condition, MF and several other contributing factors such as increased age and other comorbid conditions.

The most frequently reported ADRs across all types of cohorts included: anemia, thrombocytopenia, herpes zoster, epistaxis, and UTIs. No considerable differences were observed in the frequency of ADRs within the prevalent users cohort with the exception of epistaxis and UTI. The new users cohort had less frequency of ADRs compared to the prevalent users cohort and switch to ruxolitinib cohort. As expected, anemia was reported in a higher frequency in the new users cohort and in the switch to ruxolitinib cohort compared to the prevalent users cohort. There was no pattern of worsening of this event with long-term exposure. It is a well-known fact that ruxolitinib causes transient hematotoxicity in the first few months

of its administration. Hence, anemia was reported in a higher frequency in the new users cohort and the switch to ruxolitinib cohort. Although some of the patients who switched to ruxolitinib had ruxolitinib therapy before the study, they may also be considered similar to the new users as these patients did not have exposure to ruxolitinib for a significant period.

The incidence rate of ADRs was similar across all cohorts (approximately 20 /100 PY) except in the switch to ruxolitinib cohort, who had slightly higher incidence rate (33.4/100 PY). The majority of ADRs had an incidence rate of ≤ 1 per 100-PY in all cohorts. The incidence rates of thrombocytopenia and anemia were higher in the patients who switched to ruxolitinib cohort compared to patients in the prevalent users cohort and the new users cohort. The incidence rate of anemia was higher in the new users cohort compared to the prevalent users cohort.

Higher ADR incidence rates in the switch to ruxolitinib cohort compared to the prevalent users cohort is likely due to the initial toxicity associated with ruxolitinib use and the shorter duration of exposure to ruxolitinib for the switch to ruxolitinib cohort. A transient hematotoxicity is usually observed in the first few months of ruxolitinib therapy and since the follow-up of the patients who switched to ruxolitinib cohort was of shorter duration compared to the other cohorts, the toxicity of the first few months of therapy had higher prominence.

The incidence of treatment-emergent SAEs was reported at a higher frequency in the prevalent users cohort compared to all the other cohorts (61.4% vs < 54% in all the other cohorts). The most frequently reported (at least 3%) treatment-emergent SAEs in the prevalent users cohort included anemia, pneumonia, general physical health deterioration, sepsis, death, MF, dyspnoea, abdominal pain, UTI, cardiac failure, pyrexia, renal failure, fall, basal cell carcinoma, and squamous cell carcinoma. The incidence rate of treatment-emergent SAEs was similar in the prevalent users cohort and in the new users cohort, whereas they were slightly higher in the switch to ruxolitinib cohort. A higher incidence rate of treatment-emergent SAEs (≥ 1.5) in the prevalent users cohort included anemia, pneumonia, general physical health deterioration, sepsis, death, MF, UTI, abdominal pain, and dyspnea.

A higher proportion of patients in the non-exposed to ruxolitinib cohort and patients in the switched to ruxolitinib cohort received concomitant medications to treat and manage MF compared to the other cohorts. Hydroxycarbamide was the most frequently used concomitant medication across all types of cohorts.

Non-pharmacological treatment for MF in the majority of patients included splenectomy, allograft, venesection, bloodletting, and allogenic stem cell transplantation. At least half of the patients across all cohorts except for those in the non-exposed to ruxolitinib cohort (34.1%) required PRBC transfusions. The mean number of PRBC units required was highest in the prevalent users cohort compared to the other cohorts. Concomitant platelet transfusion was required in a comparable percentage of patients across all cohorts with the exception of the new users cohorts.

Constitutional symptoms were reported in at least 50% of the patients in the prevalent users cohorts and in the switch to ruxolitinib cohort and in a lower percentage of patients in the new users cohort and the non-exposed to ruxolitinib cohort. Night sweats were the most frequently reported symptom in all cohorts. Symptoms related to MF were reported in a slightly higher percentage of patients in the prevalent users cohort compared to the other cohorts. This might

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be due to the length of the MF disease in the prevalent users cohort compared to the other cohorts.

A decrease in spleen length was observed in the new users cohort and the switch to ruxolitinib cohort, with a decrease of approximately 40%. However, the majority of patients had no post-Baseline measurement. In the prevalent users cohort, the decrease in spleen length was well maintained over the period of data collection.

A decrease in body weight over time was observed in very few patients compared to the body weight at Baseline across all cohorts.

Bleeding events were reported in a higher percentage of patients in the prevalent users cohort followed by patients in the switch to ruxolitinib cohort and new users cohort; while patients non-exposed to ruxolitinib cohort had the lowest percentage of bleeding events. With regards to bleeding events, bruising and other haemorrhage events were most frequently reported in the majority of patients across all cohorts. Serious and opportunistic infections were reported in a higher percentage of patients in the new users cohort followed by the prevalent users cohort and the switch to ruxolitinib cohort.

Prior malignant tumors were reported in higher percentage of patients in the new users cohort (21.9%) and prevalent users cohort (18.9%). During the study, secondary malignancies were reported in higher proportion of the patients in the prevalent users cohort followed by the new users cohort, switch to ruxolitinib cohort, and non-exposed to ruxolitinib cohort (24.7% vs 15.6% vs 14% vs 6.6%, respectively). In order to evaluate the role of ruxolitinib and other factors in occurrence of secondary malignancies, exploratory analyses were carried out using multivariate cox-regression models. Patients treated with ruxolitinib were at a lower risk for AML (HR: 0.36; 95% CI: 0.22 to 0.58; $p < 0.001$) and tended to be at a higher risk for NMSCs (HR: 1.19 (95% CI: 0.87 to 1.61; $p = 0.273$). Ruxolitinib did not appear to have an impact on other malignancies such as other solid tumors, or other hematological tumors.

Based on the cox regression model, it was evident that having adjusted for ruxolitinib exposure, prior HU exposure and history of malignancies were correlated with the risk of secondary malignancies. Cox-regression model analyses revealed that apart from age and gender, type of MF (increased risk for post PV-MF patients), prior history of malignancies especially prior NMSC were significant risk factors for secondary malignancies of NMSC.

No patient had a shift from grade 0 to grade 4 in the following hematology parameters: decreased hemoglobin, increased hemoglobin, increased lymphocyte count and increased white blood cell count. Decreased hemoglobin was the most frequently observed hematology abnormality with at least 15% of patients in all cohorts having a shift from grade 1 to grade 3. Decreased lymphocyte count with a shift from grade 0 to grade 4 was reported in at least 10% of the patients in the prevalent users cohort and new users cohort. A decreased neutrophil count with a shift from grade 0 to grade 4 was reported in at least 10% of patients in the prevalent users cohort. For majority of the biochemistry parameters, no patient had a shift from grade 0 to grade 4 with few exceptions.

11.2 Limitations

A direct comparison or hypothesis testing between patients exposed to ruxolitinib and those that were not exposed to ruxolitinib was not possible due to several reasons: patients were not randomized, there were differences noted in the exposure to ruxolitinib prior to study start for the prevalent users, and due to other confounding factors; i.e., patients with fewer manifestations of MF might be managed differently from those with more serious manifestations such as splenomegaly and pronounced disease symptoms. Nevertheless, the limited data received from patients non-exposed to ruxolitinib provided valuable contextual information supporting the interpretation of the observations that were made, even if some of these patients had previous exposure to ruxolitinib. Potential or identified risks related to ruxolitinib drug treatment have been characterized and quantified in (interventional) Phase III clinical studies and therefore represent an important reference. It was therefore possible to review solicited safety observations from this NIS in the context of the safety profile of ruxolitinib established from MF clinical studies.

11.3 Interpretation

The long-term safety of ruxolitinib as assessed in this real world PASS study was consistent with the previous findings (COMFORT I/II). Of note, the study comprised of a broader population including patients at lower risk and elderly patients. No new or unexpected safety signals were identified with long-term treatment. Overall, the safety profile was supportive of long-term treatment with ruxolitinib in patients with MF. The common AEs that led to death included the progression of the underlying MF disease, sepsis, AML, pneumonia, and general disorder death. Most of these are similar to the findings in the COMFORT-I study.

The incidence rates of treatment-emergent ADRs did not show any major differences between the prevalent users cohort and the new users cohort. Most of the treatment-emergent ADRs were reported in less than 1 per 100 PY. Ruxolitinib use may not predispose a patient to an increased risk of infection, and patients who benefit in terms of spleen response may actually have a lower probability of developing an infection. However, because patients with MF are already predisposed to infections, additional precautions such as antiviral prophylaxis, may be considered. The non-hematologic AE rates generally remained stable or decreased with prolonged ruxolitinib treatment duration and were consistent with those reported in previous analyses of the COMFORT-I study.

Secondary malignancies were reported in higher percentage of patients in the prevalent users cohort, followed by the new users cohort, switch to ruxolitinib cohort, and non-exposed to ruxolitinib cohort. An exploratory multivariate cox regression models of time to first secondary malignancy event was carried out including variables to adjust for differences in duration of ruxolitinib treatment and imbalances in the Baseline characteristics or other risk factors (prior malignant tumors and prior HU exposure) that might impact secondary malignancies. Ruxolitinib did not appear to have an impact on other malignancies such as other solid tumors, or other hematological tumors. Based on the cox regression models, apart from age and gender, type of MF (increased risk for post PV-MF), prior history of malignancy especially prior NMSC were important risk factors for secondary malignancy of NMSC. The previous history of malignancies and prior exposure to HU were observed to be the most relevant risk factors associated with the probability of developing secondary malignancies. However, it should be

noted that the interpretation of cox-regression models should be performed with caution as the number of patients and events are very few and the collection of the data is different in the NIS than in Phase 3 trials.

Few patients who had long-term exposure to ruxolitinib had decreased hemoglobin with a shift from grade 1 to grade 3. A few of the patients in the prevalent users cohort had a worst shift from grade 0 to grade 4 with decreased lymphocyte count, and decreased neutrophil count. However, all these laboratory abnormalities are expected to occur in the MF population.

As expected, given the mechanism of action of ruxolitinib as a JAK1/JAK2 inhibitor, the most common hematologic AEs were anemia and thrombocytopenia, but these rarely led to treatment discontinuation. No unexpected increased incidences of AEs were reported in the patients who had long-term exposure to ruxolitinib.

Overall, the safety profile was supportive of long-term treatment with ruxolitinib, with no unexpected safety signals.

Spleen length reductions indicated the benefits of ruxolitinib in MF patients. Spleen length decrease was observed in the new users cohort and in the switch to ruxolitinib cohort with a decrease of approximately 40%. Also, the decrease in spleen length was well maintained in the prevalent users cohort. However, it should be noted that the majority of patients had no post-baseline measurement. These benefits of ruxolitinib are very much in agreement with the findings in the COMFORT studies. Due to the limited number of bone marrow biopsies performed, the bone marrow fibrosis and bone marrow blast percentage could not be evaluated. Hence, no meaningful conclusion could be drawn.

Transfusions of PRBCs are a relatively common occurrence for MF patients. At least 50% of patients in all the cohorts except the non-exposed to ruxolitinib cohort required PRBC transfusion. Increased rates of anemia might have led to the transfusion of PRBCs reported in a majority of the users. These results are in agreement with the results of the COMFORT studies which demonstrated that an increased frequency of patients required transfusion of one or more units of PRBCs while on treatment with ruxolitinib compared to placebo or best available therapy. Concomitant platelet transfusions were required in a higher percentage of total patients in the prevalent users cohort and patients who switched to ruxolitinib as clinically indicated.

11.4 Generalizability

To date, few trial-based assessments of ruxolitinib in patients with low and intermediate-risk MF have been conducted, and no studies have made such assessments in a real-world setting. Very few studies have been conducted in patients who are at intermediate-1 risk category compared to patients in the intermediate-2 or high risk category (per the COMFORT I and COMFORT II studies). The COMFORT I and COMFORT II studies have shown that the safety profile of ruxolitinib remained consistent with no new unexpected AEs identified with long-term treatment. These studies also supported ruxolitinib as an effective long-term treatment option for patients with intermediate-2 or high risk MF. It was agreed with the EMA to collect data from patients with MF treated with ruxolitinib or with other treatments outside of a clinical trial setting in normal clinical practice as a PASS.

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The long-term safety of ruxolitinib in the real world setting as reported in this study was very much consistent with the findings from clinical studies although a broader population were included (population at lower risk and elderly patients). However, with regards to efficacy it should be noted that there was some missing or unavailable data in terms of spleen length, bone biopsy and bone marrow blast percentage.

12 Other information

Not applicable

13 Conclusion

This was a non-interventional, observational study conducted to provide real-world safety data on patients with MF exposed and non-exposed to ruxolitinib and thereby to provide insights on the disease management and safety profile of ruxolitinib.

The safety profile of ruxolitinib is consistent with previous studies, although a broader population including patients at lower risk and elderly patients were included. There were no new or unexpected ADRs identified with long-term treatment.